



■ FEATURE

# When to Consider Rate Control, Rhythm Control, and Catheter Ablation for AF

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State-of-the-art management of atrial fibrillation (AF) requires an understanding of the general therapeutic strategies, limitations of each approach, and the factors involved in the selection of a strategy.

Richard I. Fogel, MD, St. Vincent Hospital, Indianapolis, Indiana, USA, discussed the merits of a rate control versus a rhythm control strategy using antiarrhythmic drugs. The presumed benefits of rhythm control over rate control were not realized in 2 large clinical trials of older patients with AF [Wyse DG et al. *N Engl J Med* 2002; Van Gelder IC et al. *N Engl J Med* 2002]. Outcomes including all-cause mortality, hospitalization, and stroke were not significantly different between the 2 strategies, validating rate control as a management strategy for older patients with AF. According to Dr. Fogel, these results do not pertain to younger patients, especially those with “lone” AF. In addition, in an observational study of routine clinical practice that used population-based claims data, initiation of a rhythm control strategy seemed to be superior to rate control for the endpoint of mortality, with the superiority noted after Year 4 [Ionescu-Ittu R et al. *Arch Intern Med* 2012].

Dr. Fogel recommended that a reasonable approach for strategy selection is attempted rhythm control in patients with 1 of the following: age <70 years; significant symptoms despite rate control; congestive heart failure that is exacerbated during AF; lone AF; left atrium (LA) <4.0 cm; and first episode of AF. Rate control is the preferred approach in patients who are aged >70 years, have symptoms that are well regulated with rate control, have failed prior antiarrhythmic drug therapy, or have an LA >4.5 cm.

Assessment of heart rate (HR) response should include a period of prolonged monitoring, ideally with an assessment during moderate activity. A lenient resting HR goal of <110 bpm during activity seems reasonable and noninferior to a stricter target resting HR goal of <80 bpm [Van Gelder IC et al. *N Engl J Med* 2010].

Peter R. Kowey, MD, Jefferson Medical College, Philadelphia, Pennsylvania, USA, spoke about optimal approaches to anticoagulation in patients with AF. Although warfarin anticoagulation reduces rates of stroke and mortality in patients with nonvalvular AF, a number of limitations have impeded its use, including its narrow therapeutic window [Hart RG et al. *Ann Intern Med* 2007]. Patients who cannot be maintained in the therapeutic range on warfarin are candidates for switching to a novel oral anticoagulant (NOAC; dabigatran, apixaban, or rivaroxaban).

Dabigatran performed better than warfarin in reducing the risk of ischemic stroke and was associated with less bleeding [Connolly SJ et al. *N Engl J Med* 2009]. Rivaroxaban showed superiority to warfarin in both the primary and secondary prevention of stroke in patients with AF and  $\geq 2$  risk factors for stroke [Patel MR et al. *N Engl J Med* 2011]. Apixaban was superior to warfarin on the primary outcome of stroke or systemic embolism [Granger CB et al. *N Engl J Med* 2011].

NOACs have a wide therapeutic range. Although no reversal agents exist at present, the number of fatal bleeding events is not higher than with warfarin, in part because they are short acting. Trial data demonstrate that the reduction in stroke observed with NOACs is mostly attributed to a substantial reduction in the rate of hemorrhagic stroke, more so than ischemic stroke. Nonetheless, longer-term safety and efficacy data are required, especially in older patients, those with severe renal dysfunction, and in African Americans.

Persistent AF may be harmful in the long term, exposing patients to an increased risk of mortality and other complications including vascular dementia, said Eric N. Prystowsky, MD, St. Vincent Hospital, Indianapolis, Indiana, USA. For this reason, he agreed that rhythm control is favored in younger patients who may be facing decades of AF, as well as in patients with conditions predisposing to left ventricular (LV) diastolic dysfunction.

Consistent with the 2006 Guideline for the Management of Patients With Atrial Fibrillation and its 2011 update [Fuster V et al. *Circulation* 2006; Fuster V et al. *Circulation* 2011], Dr. Prystowsky said that selection of an appropriate agent for maintaining sinus rhythm should be based on safety. When making this selection, patient’s LV ejection fraction and size of the LA should be taken into consideration.

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Dr. Prystowsky said that drugs other than amiodarone perform poorly in controlling rhythm when LA size is >5 cm. With minimal to no heart disease, or hypertension with minimal LV hypertrophy, flecainide, propafenone, sotalol, and dronedarone are first-line choices; with amiodarone and dofetilide as second-line; and catheter ablation performed in the event of failure of drug therapy.

In the presence of LV hypertrophy exceeding 1.4 cm, amiodarone is recommended for maintenance of sinus rhythm. For patients with coronary artery disease, safety data support the use of dofetilide, dronedarone, and sotalol as initial choices. No antiarrhythmic drug has been shown to be safe in the setting of heart failure, but amiodarone appears to be the safest choice.

#### CATHETER ABLATION TECHNIQUES STILL EVOLVING

Evidence of rapid firing of the pulmonary veins (PV) as a trigger of AF has led to the introduction of various catheter ablation techniques targeting the PV, said Hugh Calkins, MD, Johns Hopkins University, Baltimore, Maryland, USA.

Catheter-based techniques are still evolving. The most commonly employed ablation strategy today involves the electrical isolation of the PV by creation of circumferential lesions around the right and the left PV ostia.

A meta-analysis of 4 randomized trials demonstrated an approximately 4-fold improvement in atrial tachyarrhythmia recurrence-free survival with circumferential catheter ablation of AF compared with antiarrhythmic drug therapy [Noheria A et al. *Arch Intern Med* 2008]. Results with the cryoballoon ablation system are nearly identical to those with catheter ablation. Because repeat procedures are required in a significant number of patients, catheter ablation probably should not be used first-line, depending on patient preference, said Dr. Calkins.

Current indications for catheter ablation of AF [Calkins H et al. *J Interv Card Electrophysiol* 2012]:

- Symptomatic AF that is refractory to ≥1 Class I or a total of 3 antiarrhythmic drugs
  - » Paroxysmal AF – catheter ablation recommended (Class IA, level of evidence A)
- Symptomatic AF prior to initiation of drug therapy
  - » Paroxysmal AF – catheter ablation reasonable (Class IIA, level of evidence B; Table 1)

Age is a consideration in the management of AF, said Win-Kuang Shen, MD, Mayo Clinic, Scottsdale, Arizona, USA. Age-related structural changes in the heart that lead to functional changes such as prolonged contraction, prolonged action potential, and diminished velocity [Lakatta EG. *Hurst's The Heart* 2001], and age-mediated changes in the pharmacokinetics of drugs [Lee HC et al. *J Geriatric Cardiol* 2011], can affect the success of the management strategy. For example, there is an increase in the volume of distribution

of fat-soluble drugs as people age, prolonging elimination half-life, and a decrease in the volume of distribution of water-soluble drugs [Cusack B et al. *Clin Pharmacol Ther* 1979; Lee HC et al. *J Geriatric Cardiol* 2011].

**Table 1. Patient Selection for Ablation**

Variable	Highly symptomatic	Minimally symptomatic
Symptoms	Highly symptomatic	Minimally symptomatic
Class I and III drugs failed	≥1	0
AF type	Paroxysmal	Long-standing persistent
Age	Younger (<70 years)	Older (≥70 years)
LA size	Smaller (<5.0 cm)	Larger (≥5.0 cm)
Ejection fraction	Normal	Reduced
Congestive heart failure	No	Yes
Other cardiac disease	No	Yes
Pulmonary disease	No	Yes
Sleep apnea	No	Yes
Obesity	No	Yes
Prior stroke/TIA	No	Yes

AF=atrial fibrillation; LA=left atrium; TIA=transient ischemic attack.

Many antiarrhythmic drugs are metabolized by the cytochrome P450 P2D6 and 3A4 isoenzymes (Table 2) [Trujillo TC, Nolan PE. *Drug Saf* 2000], and when used concomitantly with other drugs metabolized by these pathways, the antiarrhythmic drugs can cause prolongation of the QT interval.

**Table 2. Antiarrhythmic Agents Metabolized by P2D6 and 3A4**

CYP Enzyme	Substrate	Inhibitor
CYP2D6	Flecainide	Amiodarone
	Mexiletine	Flecainide
	Propafenone	Propafenone Quinidine
CYP3A4	Amiodarone Disopyramide Lidocaine Propafenone Quinidine	Quinidine

CYP=cytochrome P450.

The elderly, who tend to have diffuse substrate and in whom maintenance of sinus rhythm is more difficult, have not been well represented in studies of left atrial ablation for AF [Calkins H et al. *J Interv Card Electrophysiol* 2012]. Most studies of atrioventricular (AV) nodal ablation in older patients have been conducted in patients refractory to medical therapy. Compared with drug therapy, AV nodal ablation plus permanent pacing has been shown to reduce symptoms and rates of hospital admission with comparable survival, but most studies of this approach are observational in nature, and this procedure should be reserved for severely symptomatic patients refractory to medical therapy [Chatterjee NA et al. *Circ Arrhythm Electrophysiol* 2012].