Antiarrhythmic Drug Therapy for Atrial Fibrillation

Muhammad Rizwan Sardar, MD[a,b,c,*], Wajeeha Saeed, MD[d], Peter R. Kowey, MD[c,e]

KEYWORDS

• Atrial fibrillation • Cardioversion • Antiarrhythmic • Pharmacologic therapy • Rhythm control • Rate control • Upstream therapy • Prevention

KEY POINTS

- Atrial fibrillation (AF) is a complex disease, requiring better understanding in a multifaceted approach.
- Better research is needed to develop, subclassify, and identify new therapeutic targets, which hold the promise that precise therapies aimed at preventing or reversing AF will be developed.
- Antiarrhythmic therapeutic strategies for AF should be focused on controlling pathophysiologic remodeling, with better prevention and disease-modifying strategies.

Atrial fibrillation (AF) is the most common arrhythmia, and its incidence increases with advanced age. About 1% of patients with AF are younger than 60 years, 12% are between 75 and 85 years, and one-third of patients with AF are older than 80 years.[1–3] It is estimated that there are 3 million AF cases, and prevalence is expected to reach 7 million by 2050.[4,5] Incidence rates of AF vary among different races. Individuals of European descent have lifetime risk of 20% to 25% of developing AF after the 40 years of age.[6] Although risk factors for developing AF are more prevalent in African Americans, their incidence seems to be lower than whites.[7]

AF is associated with a 3-fold to 5-fold increased risk of stroke, and stroke caused by AF has significantly higher mortality and morbidity than without AF. There is a 3-fold increase in the risk of heart failure (HF),[8] 2-fold increased risk of dementia, and higher mortality associated with AF. There are more than 470,000 hospitalizations in the United States with the primary diagnosis of AF, and it is estimated to cause 100,000 deaths per year. AF, besides being one of the leading causes of mortality and morbidity, adds $26 billion to costs in the US health system annually.[9]

Treatment of AF is multifold but revolves around 1 essential consideration: whether or not to attempt to restore sinus rhythm or to treat AF by controlling ventricular rate only. This decision depends on symptom severity, age of the patient, underlying heart disease, and other comorbidities, which may limit therapeutic options.

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[a] Department of Cardiology, Cooper University Hospital, 3rd Floor Dorrance, One Cooper Plaza, Camden, NJ 08103, USA; [b] Lankenau Institute for Medical Research (LIMR), Wynnewood, PA 19096, USA; [c] Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA; [d] Albert Einstein College of Medicine, Bronx Lebanon Hospital Center, Bronx, NY 10457, USA; [e] Lankenau Institute for Medical Research (LIMR), Lankenau Medical Center, Wynnewood, PA 19096, USA

* Corresponding author. Department of Cardiology, Cooper University Hospital, 3rd Floor Dorrance, One Cooper Plaza, Camden, NJ 08103.

E-mail address: rizwansardar@hotmail.com

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AF can be classified as paroxysmal, persistent, and permanent. The term lone AF refers to the finding of AF in patients without obvious structural heart disease. Paroxysmal AF terminates spontaneously or with intervention within 7 days of onset. Persistent AF lasts longer than 7 days, requiring electrical or chemical cardioversion. Long-standing persistent AF is continuous AF for longer than 12 months. Permanent AF describes continuous AF that has failed cardioversion, and the patient and clinician have jointly decided to not pursue restoring or maintaining sinus rhythm. Nonvalvular AF is AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.[10]

Symptoms of AF can vary and are individual. They range from fatigue, shortness of breath, palpitations, syncope, hypotension, and HF, with the most common symptom being fatigue. Some of the symptoms may abate with slowing of the heart rate with the use of atrioventricular (AV) nodal blocking agents. Symptom resolution may not be achieved in some patients, who continue to feel fatigued and have exercise intolerance despite adequate heart rate control, which is attributed to the loss of atrial mechanical function. Patients with underlying diastolic dysfunction and left ventricular hypertrophy are particularly sensitive to the loss of AV synchrony. For patients with no deterioration of functional status in AF, rate control may be sufficient. On the other hand, patients with clear functional decline and exacerbation of symptoms may benefit from the rhythm control strategy.

RHYTHM VERSUS RATE CONTROL

Several studies have assessed rhythm versus rate control strategies. The 2 largest trials, AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation), failed to show any significant benefit in choosing the rhythm control strategy.[11,12] Similar findings were seen in the PIAF (Pharmacological Intervention in Atrial Fibrillation) and STAF (Strategies of Treatment of Atrial Fibrillation) trials.[13,14]

The AFFIRM trial enrolled patients with persistent and paroxysmal AF randomly assigned to rate or rhythm control strategy. There were no significant differences in overall mortality, with a trend toward increase mortality in the rhythm control group. There was also a trend toward more ischemic strokes in rhythm control groups; however, this was mainly in patients who were not adequately anticoagulated.[12]

An AFFIRM substudy analyzing on-treatment analysis[15] showed that the presence of sinus rhythm was associated with a lower risk of mortality, suggesting that adverse effect of antiarrhythmic drugs (AAD) overcomes the potential benefit of sinus rhythm restoration.

The RACE trial[11] randomized only patients with persistent AF, and all patients were anticoagulated irrespective of previous electric cardioversion efforts into rate or rhythm control groups. After a mean follow-up of 2.3 years, the rate control strategy was noninferior to rhythm control for the prevention of death or morbidity. A substudy of the AFFIRM trial[16] looked at exercise tolerance within the rhythm control and rate control strategies for AF and performed serial 6-minute walk tests on 245 patients. There was improvement in walking distance in both groups. Roy and colleagues[17] in 2008 analyzed rhythm versus rate controlled strategy for AF with patients with HF in the AF-CHF trial. This trial enrolled 1376 patients with left ventricular ejection fraction (LVEF) of 35% or less and found no clinically significant differences between the 2 groups in terms of cardiovascular death, all-cause death, stroke, or worsening HF.

Most of the studies evaluating issue of rhythm versus rate control treatment of AF are applicable to patient's age older than 60 years and younger than 80 years but still failed to show mortality benefit with the rhythm control strategy.[11–14,18] This lack of superiority is partly linked to AAD side effects as well as excess stroke risk in patients in whom anticoagulation was discontinued. Although younger (<60 years) and older (>80 years) are not well represented in these studies, the results are still applicable. In the last decade, there has been an increase in the use of rhythm control strategies, which is largely driven by an increase in AF ablations.[19] For younger symptomatic patients with AF without significant underlying heart disease, who are not adequately represented in the earlier studies, restoration of sinus rhythm is still considered a valid approach, because the long-term implications of permanent AF are unknown.

RHYTHM CONTROL

AAD have been available for nearly 100 years and remain a cornerstone in AF therapy.[20] The role of AAD is not only to reduce the arrhythmia burden (frequency and duration of AF) but also to reduce hospitalization associated with AF. Despite the side effects associated with most of the antiarrhythmic pharmacotherapy for AF, AAD are still widely prescribed medications for AF.

Pharmacologic Cardioversion

Chemical cardioversion can be achieved with oral as well as intravenous (IV) AAD. Once the decision