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REVIEW

Pharmacological Therapy for Rate and Rhythm Control for Atrial Fibrillation in 2017

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In spite of the emergence of non-pharmacological approaches, medical therapy remains the primary modality of treatment for most patients with atrial fibrillation (AF). This review will look at evidence for rate and rhythm control approaches, and at factors that would help in choosing the appropriate treatment strategy for individual patients.

Keywords Atrial fibrillation • Pharmacological therapy

Introduction

Atrial fibrillation (AF) is one of the commonest arrhythmias encountered in adult cardiology practice. The incidence and prevalence of AF increases with age. Atrial fibrillation is associated with an increase in morbidity and mortality. Atrial fibrillation also affects the quality of life [1].

The treating physician needs to make two main decisions when seeing a patient with AF. The first is to assess thromboembolic risk and evaluate whether the patient needs anticoagulation. The CHA_2DS_2VASc score helps with this decision-making, and the HAS-BLED score may help to assess the risk of anticoagulation therapy.

The next decision is whether to embark on a rhythm control strategy or primary rate control strategy. Even patients with a primary objective of obtaining and maintaining sinus rhythm (SR) will require rate control until SR is achieved. Many factors influence whether one should aim for rhythm control or rate control, and it may be necessary to change from one approach to other due to changing clinical circumstances.

The main factors that influence this decision would include the patient's symptoms, type of AF (paroxysmal, persistent or long standing persistent) and the likelihood of maintaining SR. Patient age, co-morbidities and left atrial size also need to be factored into this decision.

This review will examine the available clinical trial data for each of these approaches and look at specific patient groups that may benefit from each approach. This review will focus on pharmacological therapies, however rhythm control and rate control may also be achieved by non-pharmacological means (such as ablation and device therapies).

Reappraisal of the Traditional Approach

Traditionally rhythm control was looked at as the first option and only when rhythm control failed were patients delegated to rate control strategy. However, the results of the AF Follow-up Investigation of Rhythm Management (AFFIRM) and the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trials have led to a reconsideration of this approach.

In the AFFIRM trial, 4,060 patients who were thought to be at risk of recurrent AF were enrolled and had a mean follow-

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up of 3.5 years [2]. In this group with mean age of 69.7 years, rhythm control strategy was mostly with amiodarone or sotalol and rate control was mainly with a beta blocker (BB), calcium channel blocker (CCB) — diltiazem or verapamil, or with digoxin. In the rhythm control group, the prevalence of SR was 82.4%, 73.3% and 62.6% at one-, three- and five-year follow-up, respectively. In this study, a rhythm control strategy did not offer a survival advantage over the rate control strategy. In the rate control group there were less drug-related side effects. There was no difference in stroke rates. Most strokes occurred after anticoagulation withdrawal or in patients with sub-therapeutic INR. In the rate control strategy group, about one third were in SR on follow-up.

In the RACE trial, 522 patients with persistent AF were randomised to rhythm control or rate control after cardioversion [3]. Both groups received anticoagulation. The rhythm control group had serial cardioversions and antiarrhythmic (AA) medications. After a mean follow-up of 2.3+/− 0.6 years, 39% in the rhythm control strategy group and 10% in the rate control strategy group were in SR. The endpoints of death, heart failure, thromboembolic complications were similar in both groups.

These two trials were pivotal in establishing that a strategy of rate control is not inferior to a strategy of pharmacological rhythm control in patients with mean age of 68–69 years. The results of these trials should not be interpreted as showing an equivalence of SR and AF with respect to stroke risk and mortality. Rather, they show that with available antiarrhythmic drug therapies, the ability to maintain SR is modest and their potential benefits may be counterbalanced by significant cardiac and non-cardiac side effects including proarrhythmia [4]. There is great interest awaiting the results of ongoing large randomised trials of catheter ablation for AF such as the CABANA study (Clinicaltrials. gov. NCT00911508) to determine whether a non-pharmacological approach to rhythm control will decrease stroke risk and mortality.

Rate Control for AF – How Strict Should We Be?

An important question to consider when implementing rate control for AF is how strictly to reduce the ventricular rate. Fast ventricular rates may be associated with palpitations, fatigue, chest discomfort and dyspnoea and may truncate diastolic filling and reduce cardiac output. A proportion of patients with sustained fast ventricular rates have also been documented to have a poor ejection fraction (tachycardia-induced cardiomyopathy), which has been noted to improve with better rate control or rhythm control.

In the RACE II trial, 610 patients with permanent AF were randomiaed to strict rate control (resting heart rate less than 80 beats per minute (bpm) and with moderate exercise <110 bpm) or lenient rate control (resting HR <110 bpm) [5]. At three-year follow-up, there was no difference in death, stroke and heart failure hospitalisations. At the end of a three-year period, the resting heart rate of the aggressive rate control group was 76+/− 14 bpm, and in the lenient rate control group it was 85+/− 14 bpm. Resting heart rate target was achieved in 98% of the lenient group and only in 75% of strict rate control group. As expected, the number of medications required and the dosage used were higher in the strict rate control group, and they had a higher incidence of drug related side effects. However, it is important to note that the observed mean heart rate difference between the groups was small (9 bpm).

A subsequent combined analysis of the AFFIRM and RACE cohorts showed that the AFFIRM patients with a resting heart rate in AF of less than 80 bpm and the RACE patients with a heart rate <100 bpm had better outcomes compared with patients with a resting heart rate greater than 100 bpm, with odds ratios of 0.7 and 0.66, respectively [6].

A meta-analysis of all rate control and rhythm control studies showed similar long-term outcomes, including all-cause mortality, cardiac mortality and stroke with either approach [7].

The current ESC guidelines recommend targeting a resting heart rate of <110 bpm then adjusting therapy if the patient remains symptomatic. They emphasise the importance of trying to avoid excessive bradycardia (Figure 1, from ESC guidelines [8]). However, as the lenient rate control group in RACE II had a mean heart rate of 85 bpm, in clinical practice it would be reasonable to aim for a resting heart rate of 80–90 bpm.

Pharmacological Agents for Rate Control

The main agents used for rate control are BB, non-dihydropyridine CCB, and digoxin. Most of the evidence for effectiveness of these drugs come from small studies. The choice of drugs depends on patient co-morbidities, symptoms, ejection fraction, lifestyle and the target heart rate.

Beta Blockers

The common BBs used are metoprolol, atenolol and, to a lesser extent, carvedilol and bisoprolol. Beta blockers may have additional benefit in patients with hypertension, ischaemia, and heart failure. The side effects of BBs include fatigue, sexual dysfunction, bronchospasm, vivid dreams and altered mood. Commonly used BBs and dosages are listed in Table 1.

Calcium Channel Blockers

The non-dihydropyridine CCBs are used for rate control (Table 2). They may have negative inotropic effect, and are best avoided in patients with systolic dysfunction. The CCBs can cause vasodilation, oedema, headache and constipation.

Digoxin

Cardiac glycosides like digoxin have been used for more than 200 years for the treatment of AF. Despite lack of clinical trial evidence, digoxin is still used widely for rate control in AF. Although digoxin can control ventricular rate at rest, it is less effective when there is higher sympathetic tone (that is, with exercise). Recently, the safety of digoxin for rate control in AF has been called into question.