The historically known debate between the rate control strategy and the rhythm control strategy is now over. Several major studies, completed during the past 10 years, uniformly concluded that both strategies are equivalent in patients with persistent or paroxysmal AF [1-6]. Comparison of rate control versus rhythm control trials in AF is shown in Table I.

Despite the fact that patients with AF have a worse prognosis than those in sinus rhythm, it was not possible to prove any survival advantage of reversing every AF episode and maintaining sinus rhythm on the long term. This is mainly due to two factors: first, limitations and side effects of current available antiarrhythmic agents [7], and second, underuse of antithrombotic drugs after restoration of sinus rhythm (preventing thromboembolic complications is better achieved by using an antithrombotic drug rather than by reversing AF to sinus rhythm).

In daily practice, the choice between rate and rhythm control in patients with AF will depend on some AF characteristics as well as on patient and physician preferences (Table II).

Achieving normal sinus rhythm (rhythm control strategy) is preferred in patients with moderate or severe symptoms associated with AF episodes (palpitations, dyspnea, and fatigue). Many post hoc analyses and sub-studies from major rhythm- versus rate-control trials have demonstrated that restoration and maintenance of sinus rhythm is associated with important benefits on quality of life, functional status, and exercise tolerance [8-10]. On the other hand, an initial rate-control strategy is recommended in asymptomatic or minimally symptomatic AF patients.

The rhythm control strategy is also advocated in younger and active patients with less comorbidities. These patients were not well represented in trials comparing rate

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>TRIALS COMPARING RATE and RHYTHM CONTROL STRATEGIES in PATIENTS with ATRIAL FIBRILLATION (AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>Patients (n)</td>
</tr>
<tr>
<td>AFFIRM [1]</td>
<td>4060</td>
</tr>
<tr>
<td>RACE [2]</td>
<td>522</td>
</tr>
<tr>
<td>PIAF [3]</td>
<td>252</td>
</tr>
<tr>
<td>HOT CAFE [4]</td>
<td>205</td>
</tr>
<tr>
<td>STAF [5]</td>
<td>200</td>
</tr>
<tr>
<td>AF-CHF [6]</td>
<td>1376</td>
</tr>
</tbody>
</table>

AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management  
RACE: Rate Control vs Electrical Cardioversion  
PIAF: Pharmacological Intervention in Atrial Fibrillation  
HOT CAFE: How to Treat Chronic Atrial Fibrillation  
STAF: Strategies of Treatment of Atrial Fibrillation  
AF-CHF: Atrial Fibrillation/Congestive Heart Failure  
CHF: congestive heart failure  
PM: pace maker  
CPR: cardiopulmonary resuscitation

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and rhythm control strategies (the average age of patients enrolled in these trials ranged from 61 to 70 years). The results of these trials may therefore not be applicable to younger patients.

Patients presenting for the first episode of AF will benefit from a pharmacological or electrical cardioversion. An initial rhythm control strategy is most appropriate in these patients. Some authors recommend an immediate, aggressive and permanent treatment of initial AF episodes in order to prevent early atrial remodelling [11], but this approach still needs to be tested and validated.

AF patients with structural heart disease, left ventricular hypertrophy, coronary artery disease or depressed left ventricular function are less likely to remain in sinus rhythm on the long term and are more likely to have serious side effects from antiarrhythmic drugs (old and new agents). A rate control strategy is preferred in these cases, particularly when AF is recurrent. The Atrial Fibrillation and Congestive Heart Failure trial (AF-CHF) compared the rate control strategy versus the rhythm control strategy in AF patients with heart failure [6]. Cardiovascular mortality was similar in the two treatment arms, whereas the rate-control strategy was associated with fewer hospitalizations and cardiac procedures. Even more, neither the presence of sinus rhythm nor the maintenance of sinus rhythm were associated with better outcomes [12].

**HOW TO CONTROL THE VENTRICULAR RATE?**

**Medical treatment**
Pharmacological control of the ventricular rate during AF is obtained by using drugs that prolong AV nodal refractoriness. In comparison to antiarrhythmic agents, drugs used to control ventricular rate are generally considered safer. Three major classes of drugs may be used in this indication: β-adrenergic receptor blockers, nondihydropyridine calcium channel blockers, and digitalis glycosides. In rare specific cases, amiodarone can also be used.

In permanent AF, patients often require combinations of two drugs for rate control. Table III shows how to choose between rate-control drugs according to the clinical conditions associated with AF.

In the rate-control arm of the AFFIRM study, initial treatment included a β-blocker alone in 24%, a calcium channel blocker alone in 17%, digoxin alone in 16%, a β-blocker and digoxin in 14% of patients [13].

The most effective drug when used alone for controlling ventricular rate is a β-blocker [13], and the most potent combination is a β-blocker plus digoxin [14-15].

Digoxin is a poor rate-control agent by itself, moderately effective in controlling the ventricular rate at rest, but generally ineffective during exertion and other states of high adrenergic tone. It is mainly indicated in elderly and sedentary patients or in heart failure patients.

Non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are used alone or in combination with other drugs to control the heart rate during both normal activities and exercise. They are contraindicated in congestive heart failure and in patients with old myocardial infarction.

In some cases, β-blockers, calcium antagonists or digoxin may be contraindicated, ineffective or not well tolerated. Amiodarone may be helpful in these situations in slowing the ventricular rate.

**Electrical treatment: AV nodal ablation and pacing**
In some cases, effective rate control of AF is difficult to achieve despite adequate AV nodal blocking treatment. In these situations, AV block induced by radiofrequency ablation of the AV node combined with permanent pacemaker implantation can be performed as a definitive strategy for rate control.

In a meta-analysis of 21 trials (1181 patients), clinical outcomes and survival were studied after ablation and pacing in medically refractory AF patients [16]. This meta-analysis showed that patients with refractory atrial tachyarrhythmia, ablation and pacing therapy significantly reduces cardiac symptoms and healthcare use while improving exercise duration, quality of life, and ejection fraction.

In congestive heart failure (CHF), the “ablate and pace” approach must be always associated with a cardiac

**TABLE II**
**PREFERRED STRATEGIES in MANAGING PATIENTS with ATRIAL FIBRILLATION (AF)**

<table>
<thead>
<tr>
<th>Clinical conditions</th>
<th>Rate control preferred</th>
<th>Rhythm control preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic / Minimal symptoms</td>
<td>Moderate / Severe symptoms</td>
<td>First episode</td>
</tr>
<tr>
<td>Recurrent AF</td>
<td>First episode</td>
<td>Rate control inefficient</td>
</tr>
<tr>
<td>Younger patients</td>
<td>Active patients</td>
<td></td>
</tr>
<tr>
<td>Sedentary patients</td>
<td>Active patients</td>
<td></td>
</tr>
<tr>
<td>Risk of proarrhythmia</td>
<td>Rate control inefficient</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE III**
**HOW TO CHOOSE BETWEEN RATE-CONTROL DRUGS IN ATRIAL FIBRILLATION (AF)**

<table>
<thead>
<tr>
<th>Clinical conditions associated with AF</th>
<th>Preferred drugs</th>
<th>Drugs to avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>BB, DIG</td>
<td>CCB</td>
</tr>
<tr>
<td>CAD - angina</td>
<td>BB, CCB</td>
<td>DIG</td>
</tr>
<tr>
<td>CAD - old MI</td>
<td>BB</td>
<td>DIG, CCB</td>
</tr>
<tr>
<td>HCM (obstructive)</td>
<td>BB, CCB</td>
<td>DIG</td>
</tr>
<tr>
<td>Asthma / COPD</td>
<td>CCB, DIG</td>
<td>BB</td>
</tr>
<tr>
<td>Renal failure</td>
<td>BB, CCB</td>
<td>DIG</td>
</tr>
<tr>
<td>Active patients</td>
<td>BB, CCB</td>
<td></td>
</tr>
<tr>
<td>Elderly, sedentary</td>
<td>DIG</td>
<td></td>
</tr>
</tbody>
</table>

CHF: congestive heart failure; BB: beta-blockers; DIG: digoxine; CCB: calcium channel blockers (nondihydropyridine); CAD: coronary artery disease; MI: myocardial infarction; HCM: hypertrophic cardiomyopathy; COPD: chronic obstructive pulmonary disease.
resynchronization therapy. Many studies have demonstrated the deleterious effect of right ventricular pacing in CHF patients, and the superiority of biventricular pacing on hospitalization rate, NYHA status, worsening of CHF, total death and cardiovascular mortality [17-18].

HOW TO MONITOR VENTRICULAR RATE IN PERMANENT ATRIAL FIBRILLATION?

Assessment of long term efficacy of ventricular rate control in permanent AF is based mainly on resting ECG and clinical symptoms.

Marked acceleration in ventricular rate during exertion may provoke palpitations and/or dyspnea in permanent AF patients, even when resting heart rate is adequate. Excessive deceleration of ventricular rate, or long pauses, may lead to dizziness and syncope.

Asymptomatic patients with adequate heart rate during regular office visit do not need further evaluation. In patients suffering from exercise dyspnea, palpitations, dizziness or syncope, ventricular rate must be studied during 24-hour Holter monitoring and during exertion (6-minute walk test, stress test, etc.).

A correlation between symptoms and excessive acceleration or deceleration of ventricular rate must be always obtained before adjusting doses of rate control drugs since the degree of symptoms during AF is more strongly related to severity of the underlying cardiac disease than it is to heart rate itself [19].

HOW STRICT SHOULD BE THE CONTROL OF VENTRICULAR RATE?

In permanent AF, attempting to achieve ventricular rates similar to those present during sinus rhythm is not considered a reasonable option anymore. Retrospective sub-studies from AFFIRM and RACE trials have already shown no advantage of “tight” versus “less tight” rate control in permanent AF.

The prospective randomized trial Rate Control Efficacy in Permanent Atrial Fibrillation (RACE-II) was conducted to compare strict versus lenient rate control strategies for patients with AF [20]. Permanent AF patients (n = 614) aged < 80 years with a mean resting heart rate > 80 bpm were randomized in two groups: strict rate control (resting heart-rate goal < 80 bpm; heart rate goal during moderate exercise < 110 bpm) and lenient rate control (resting heart-rate goal < 80 bpm). The mean (± SD) resting heart rate at the end of the dose-adjustment phase was 93 ± 9 beats per minute in the lenient control group, as compared with 76 ± 12 beats per minute in the strict-control group (p < 0.001).

At three years, the lenient rate control was as effective as strict rate control. The cumulative incidence of the composite primary outcome (cardiovascular death, heart failure hospitalization, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events) was 12.9% in the lenient rate control and 14.9% in the strict rate control (hazard ratio 0.8, p < 0.001 for noninferiority of lenient rate control).

Therefore, based on current available data, heart-rate goal < 110 bpm at rest can be advocated as a first-choice strategy. If the patient remains symptomatic or develops heart failure, a more strict rate-control approach can be adopted.

CONCLUSION

The rhythm control strategy has not been proved superior to rate control strategy in managing persistent or paroxysmal AF. An individualized approach is usually used in daily clinical practice. When adopting a ventricular rate control strategy, the choice between a β-blocker, a calcium channel blocker or digoxin depends on clinical conditions associated with AF. Patients often require combinations of two drugs for rate control; especially a β-blocker plus digoxin which is the most potent combination. As a first-choice approach, a “very tight” ventricular rate control is not recommended since it is not associated with any clinical advantage, in comparison with a “lenient” rate control.

REFERENCES


