Controlling the ventricular rate during both paroxysmal and persistent atrial fibrillation (AF), initially with digitalis preparations and subsequently with β-blockers and calcium channel blockers, has been a mainstay for the management of this arrhythmia for many years. With the advent of a wide range of pharmacological and nonpharmacological approaches for maintaining sinus rhythm, rhythm control strategies have entered widespread clinical use in selected subsets of symptomatic patients. Despite the availability of these rhythm control strategies, however, rate control of AF remains an important and useful approach for a large number of patients, especially those with little or no symptoms from the arrhythmia once the ventricular rate has been controlled. This review discusses the relative risks and benefits of rate versus rhythm control strategies, describes the targets and available methods for rate control, and highlights special considerations for ventricular rate control when cardiac resynchronization therapy (CRT) is used in patients with AF.

Rate versus Rhythm Control
Among the most important decisions that must be made by a patient and care provider when choosing a treatment plan for AF is the choice between rate and rhythm control. Rate control is typically a simpler strategy than rhythm control, involving the use of generally less toxic medications and fewer medical procedures, although rate control strategies can result in adverse drug side effects and toxicities and, in some cases, may require interventions such as pacemaker implantation and atrioventricular (AV) nodal ablation. Rhythm control strategies typically involve potentially riskier antiarrhythmic medications or invasive procedures such as catheter ablation or surgery, but, when successful, provide the benefits of sinus rhythm.

Randomized Trials of Rate versus Rhythm Control
Several large randomized, controlled clinical trials have been performed to compare the risks and benefits of rate versus pharmacological rhythm control strategies in patients with AF. Among these are the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM), Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation Study (RACE), Pharmacological Intervention in Atrial Fibrillation (PIAF), Strategies of Treatment of Atrial Fibrillation (STAF), and How to Treat Chronic Atrial Fibrillation (HOT CAFE´) trials, and the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial in patients with congestive heart failure (CHF). The primary end points of the trials varied considerably, ranging from a composite end point in 3 of the studies (RACE, STAF, HOT CAFE´) to improvement in AF symptoms in PIAF, cardiovascular mortality in AF-CHF, and all-cause mortality in AFFIRM. Despite substantial differences in trial design, these 6 studies, which in total randomly selected 6615 patients to rate versus (primarily) pharmacological rhythm control strategies, uniformly concluded that rate control was not inferior to rhythm control for the primary end points of the trials (Table). It should be noted, however, that these trials generally included only patients able to tolerate AF, and so younger patients and those with severe symptoms from AF were underrepresented in these trials. AFFIRM, the largest of these studies, demonstrated a statistical trend toward increased overall mortality in the rhythm control arm compared with the rate control arm (hazard ratio 1.18, P = 0.08) (Figure 1). Interestingly, there was no reduction in the rate of stroke with rhythm control in comparison with rate control in these studies, and it was noted that most strokes occurred among patients who were either not taking warfarin, or who were taking warfarin but had subtherapeutic international normalized ratio values at the time of the stroke. A meta-analysis suggested that the recently approved antiarrhythmic drug dronedarone may reduce stroke in comparison with other antiarrhythmic drugs, but it should be noted that dronedarone was not available for use in the rate versus rhythm control trials described above and that reduction in stroke was not the primary end point of the dronedarone trials included in the meta-analysis. In addition, dronedarone has a relatively modest antiarrhythmic effect in maintaining sinus rhythm and is less effective than amiodarone in this regard.

Possible Benefits of Rhythm Control
These studies of rate versus rhythm control did not demonstrate any significant benefit of a rhythm control strategy over rate control among the primary trial end points. This raises the question of whether the maintenance of sinus rhythm is
truly beneficial and should be sought in minimally symptomatic AF patients, or whether sinus rhythm is simply a marker for patients with a better prognosis. If sinus rhythm is simply a marker for better prognosis, there may be no benefit to achieving sinus rhythm in AF patients. There are several important caveats to the widespread application of this conclusion to patients with AF; however. Young patients with AF were not well represented in these trials (the average age of patients enrolled in the trials ranged from 61–70 years), and only the PIAF trial used AF symptoms as a primary end point. The results of these trials may therefore not be applicable to younger patients or to patients who experience severe symptoms from their AF despite adequate rate control. In support of this, the PIAF and HOT CAFÉ studies demonstrated improved exercise tolerance in the rhythm control group, and the success rate of this therapy in these trials was relatively modest, with sinus rhythm maintenance ranging from 10% to 35% in the rate control arms in comparison with 26% to 63% in the rhythm control arms. Therefore, the difference in successful maintenance of sinus rhythm was not large when comparing the rate versus rhythm control arms, and it is possible that a more effective rhythm control therapy might have resulted in greater benefit. Amiodarone in the AF-CHF trial was considerably more effective than placebo at maintaining sinus rhythm, but analysis of this study showed no benefit in regard to cardiovascular mortality or worsening heart failure either for the rhythm control strategy or for presence of sinus rhythm versus AF (regardless of rate/rhythm control strategy). Currently available antiarrhythmic drugs all carry some risk for toxicity, including the potential for causing ventricular proarhythmia. It is possible that, for patients with few or no symptoms attributable to their AF, the risks of currently available antiarrhythmic drugs outweigh the modest effectiveness of these agents in the maintenance of sinus rhythm. Comparison between antiarrhythmic agents suggests that amiodarone is both the most effective agent for maintenance of sinus rhythm and also the most potentially toxic with long-term use.

Several lines of evidence support the hypothesis that maintenance of sinus rhythm could result in better patient outcomes in comparison with rate control for AF, if sinus rhythm could be maintained with a high success rate and with a therapy that has a better safety profile than currently available antiarrhythmic drugs. Observational studies have demonstrated higher morbidity and mortality among patients with a history of AF, in particular, if they have coexistent CHF, in comparison with those without AF. Second, among patients with symptomatic paroxysmal AF, symptoms are worse during periods of AF in comparison with sinus rhythm. Third, analyses of the AFFIRM database demonstrated that patients who maintained sinus rhythm in the study (regardless of rate versus rhythm control strategy) had reduced mortality and heart failure symptoms compared with patients who remained in AF, and that CHF symptoms were worse in the rate control arm in comparison with the rhythm control arm. Fourth, the PABA-CHF study, a small trial that compared a strategy of catheter ablation of AF

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**Table. Rate vs Rhythm Control Trials for AF**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>Primary End Point</th>
<th>HR (Rate vs Rhythm Control)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIAF</td>
<td>2000</td>
<td>252</td>
<td>Improvement AF symptoms</td>
<td>1.10</td>
<td>0.31</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>2002</td>
<td>4060</td>
<td>Overall mortality</td>
<td>0.87</td>
<td>0.08</td>
</tr>
<tr>
<td>RACE</td>
<td>2002</td>
<td>522</td>
<td>Composite</td>
<td>0.73</td>
<td>0.11</td>
</tr>
<tr>
<td>STAF</td>
<td>2003</td>
<td>200</td>
<td>Composite</td>
<td>1.09</td>
<td>0.99</td>
</tr>
<tr>
<td>HOT CAFÉ</td>
<td>2004</td>
<td>205</td>
<td>Composite</td>
<td>1.98</td>
<td>&gt;0.71</td>
</tr>
<tr>
<td>AF-CHF</td>
<td>2005</td>
<td>1376</td>
<td>Cardiovascular mortality</td>
<td>0.94</td>
<td>0.59</td>
</tr>
<tr>
<td>PABA-CHF</td>
<td>2008</td>
<td>81</td>
<td>Composite</td>
<td>Multiple (see below)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AF-CHF and PABA-CHF Trials enrolled only patients with congestive heart failure. PABA-CHF compared rate control via AV nodal ablation with biventricular pacing versus rhythm control via AF ablation (≥ antiarrhythmic medication). All other trials compared predominantly pharmacological rate control with pharmacological rhythm control. Composite primary outcomes are as follows: RACE (death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, pacemaker implantation, severe adverse drug effects), STAF (death, cardiopulmonary resuscitation, cerebrovascular event, and systemic embolism), HOT CAFÉ (all-cause mortality, thromboembolic events, major bleeding), PABA-CHF (Minnesota Living with Heart Failure Questionnaire score, left ventricular ejection fraction at 6 months, 6-minute walk distance—note that all 3 individual components of the composite end point in PABA-CHF favored AF ablation over AV nodal ablation with biventricular pacing with P<0.001). HR indicates hazard ratio for primary end point, comparing rate versus rhythm control strategies.

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**Figure 1.** A comparison of cumulative mortality from any cause in the rhythm control group and the rate control group in the AFFIRM study. Reproduced from Wyse et al with permission from the publisher. Copyright © Elsevier, 2009.
directed at restoration and maintenance of sinus rhythm with rate control by means of AV nodal ablation and biventricular pacing, demonstrated superiority of AF ablation in comparison with AV nodal ablation/biventricular pacing with regard to heart failure symptoms, 6-minute walk distance, and left ventricular ejection fraction (LVEF). It should be noted that sinus rhythm was maintained after catheter ablation of AF in 88% of patients receiving antiarrhythmic drug therapy and 71% of patients not receiving antiarrhythmic drugs in PABA-CHF, which are considerably higher success rates of sinus rhythm maintenance than were achieved in the pharmacological arms of the rate versus rhythm control trials described above (Table).

It is clear from the published trials of rate versus rhythm control that, for patients similar to those enrolled in the trials (especially older patients and those with minimally symptomatic or asymptomatic AF), rate control is not inferior to pharmacological rhythm control with currently available antiarrhythmic agents with regard to clinically relevant end points, and may be associated with a lower risk for drug-related adverse effects and toxicity. It is also clear that, for patients with symptomatic AF despite attempts at rate control, rhythm control (either via pharmacological therapy or catheter ablation) can significantly improve symptoms related to AF. Important questions remain unanswered with regard to rate versus rhythm control strategies, however. Whether catheter ablation can improve clinical outcomes such as stroke, heart failure, and death in a diverse group of patients with AF in comparison with pharmacological strategies will await the results of large ongoing studies such as CABANA. Newer antiarrhythmic agents, including dronedarone, and a variety of investigational agents, as well, may result in different outcomes compared with rate control strategies, but this will require new rate versus rhythm studies with these agents before conclusions can be drawn. Until data from these studies become available, rate control should remain the treatment of choice for the majority of patients with asymptomatic or minimally symptomatic AF.

Methods of Achieving Rate Control in AF
Pharmacological Rate Control
In the absence of preexcitation, the AV node is the only electric pathway available for transmission of rapid fibrillatory activity from the atrium to the ventricles. Therefore, pharmacological rate control strategies are directed at increasing the refractoriness of the AV node to reduce the ventricular rate during AF. Drugs that prolong AV nodal refractoriness include β-adrenergic receptor blockers, nondihydropyridine calcium channel blockers, and digitalis glycosides. In an analysis of the AFFIRM study, β-blockers were more successful than calcium channel blockers in achieving rate control (70% versus 54%, respectively) when used either alone or in combination with digitalis. Digitalis alone is moderately effective in controlling the ventricular rate at rest, but generally ineffective during exertion and other states of high adrenergic tone, and it is, therefore, not recommended as monotherapy for most patients. When combined with carvedilol, digitalis does improve ventricular rate control and left ventricular (LV) function (in comparison with carvedilol alone) in patients with AF and CHF. In the acute setting, intravenous drugs are favored for rate control, with conversion to oral agents for long-term maintenance. The onset of action of intravenous digitalis is much slower than intravenous β-blockers or calcium blockers, and digitalis is therefore not widely used for acute rate control. It should also be noted that some drugs intended primarily for rhythm control, including amiodarone and dronedarone (via multiple mechanisms) and sotalol (via its β-blocking properties) can also reduce the ventricular rate during AF. Amiodarone may be particularly helpful in slowing the ventricular rate in patients with AF and CHF who are intolerant to high-dose β-blockade in combination with digitalis and in whom calcium channel blockers are contraindicated. In contrast, other antiarrhythmic agents with relatively pure sodium or potassium channel-blocking properties, such as flecainide, ibutilide, and dofetilide, are generally not effective rate control agents during AF. Class I agents such as flecainide may also paradoxically lead to very high ventricular rates by converting AF to atrial flutter and slowing the flutter rate sufficiently to allow 1:1 A:V conduction. For these reasons, class I antiarrhythmic agents should be given with AV nodal slowing agents such as β-blockers. Propafenone has mild β-blocking properties that can exert a modest rate-controlling effect. Intravenous amiodarone can be useful for acute rate control with minimal hemodynamic effects when administered slowly in severely ill patients with AF or other atrial tachyarrhythmias.

The selection of specific drugs for rate control is often based on physician preference, but can be tailored on the basis of patient comorbidities. For example, patients with CHF or coronary artery disease have an indication for β-blocker therapy, and a β-blocker would typically be the agent of first choice for rate control in these patients provided the drug is well tolerated. Combinations of β-blockers and digitalis may be particularly useful in patients with AF and CHF. Calcium channel blockers are contraindicated in most patients with significant LV systolic dysfunction. β-Blockers may also be particularly effective in situations associated with high adrenergic tone such as exercise-induced AF in postoperative patients, and also in the setting of hyperthyroidism. Conversely, β-blockers may exacerbate conditions such as asthma or depression, and other agents may be preferred in patients with these conditions. In many cases, even high doses of a single agent may be insufficient to achieve adequate rate control, and combinations of agents are frequently required. In a crossover study, combinations of digitalis with β-blockers were found to be more effective than combinations of digitalis with calcium blockers in achieving rate control. When combinations of agents are used, in particular, combinations of β-blockers and nondihydropyridine calcium channel blockers, there is an elevated risk of bradycardia and hypotension, and close monitoring is warranted.

Management of Preexcited Atrial Fibrillation
Patients with preexicted AF represent a special case in that AF and other atrial tachyarrhythmias can be conducted to the
ventricles both via the AV node and via the accessory pathway (Figure 2). Drugs such as β-blockers, calcium channel blockers, and digitalis are not effective in slowing conduction through the accessory pathway, and some drugs such as the digitalis glycosides may paradoxically increase the preexcited ventricular rate by shortening accessory pathway refractoriness and facilitating conduction over the accessory pathway. This can lead to hemodynamic instability and, in some cases, to ventricular fibrillation. Digitals glycosides, and diltiazem and verapamil, as well, are therefore contraindicated in patients with preexcited AF. When a patient with preexcited AF is hemodynamically unstable, permanent pacing is often required to prevent severe drug-induced bradycardia while allowing aggressive titration of rate- and/or rhythm-controlling medications for control of AF. Patients with AV block observed with the use of AV nodal-blocking drugs

Figure 2. Management of a patient with preexcited atrial fibrillation. A, A 38-year-old man presented with acute onset of palpitations and dyspnea. A 12-lead ECG demonstrated an irregular, wide-complex tachycardia most consistent with preexcited AF. He was given 1 g of intravenous procainamide over 20 minutes in an attempt to control his heart rate. Only minimal heart rate slowing was evident after procainamide infusion. He then developed chest pain and was promptly sedated and electrically cardioverted to sinus rhythm. B, After cardioversion to sinus rhythm, a delta wave is present. The patient underwent successful catheter ablation of a left lateral accessory pathway. Since ablation, he has had no further documented arrhythmia.

Pacing and AV Nodal Ablation

One of the limitations of both pharmacological rate and rhythm control strategies is the possibility that the drugs used might result in symptomatic bradycardia or pauses, either during AF or at the time of conversion of AF to sinus rhythm (conversion pauses). It is common for AF to coexist with sinus node dysfunction, which is known as the brady-tachy variant of sick sinus syndrome. When symptomatic bradycardia occurs in these situations, permanent pacing is often required to prevent severe drug-induced bradycardia while allowing aggressive titration of rate- and/or rhythm-controlling medications for control of AF. Patients with AV block observed with the use of AV nodal-blocking drugs
often are noted to have subsequent recurrence of AV block after the drugs are discontinued, and this can also be an indication for pacing.\textsuperscript{24} In many patients, effective rate control during AF is not possible in the absence of a pacemaker because of coexisting symptomatic pauses during AF or at the time of conversion of paroxysmal AF to sinus rhythm. In addition, pacing at a rate similar to the rate of conducted AF may help to regularize the ventricular response during AF without substantially increasing the overall ventricular rate. This may improve AF-related symptoms, in particular, in patients with paroxysmal AF.\textsuperscript{25,26} AF may contribute directly to sinus node dysfunction, and successful catheter ablation of AF has been shown to reduce the occurrence of sinus node dysfunction, obviating the need for permanent pacemaker implantation in some patients.\textsuperscript{27,28}

For some patients with AF, effective rate control is difficult to achieve even in the presence of a permanent pacemaker. This may be due either to the ineffectiveness of rate-controlling drugs used in combination and at high doses, or to intolerance to the drugs at doses that result in adequate rate control. 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 experienced hands, AV nodal ablation is typically a relatively simple procedure with a high success rate. AV nodal ablation with pacemaker implantation has been shown to result in improvements in both symptoms and LVEF.\textsuperscript{29,30} However, because this procedure is irreversible, frequently associated with pacemaker dependency and commits patients to permanent AF and lifelong anticoagulation, it should be performed only as a last resort when other rate and/or rhythm control strategies have been unsuccessful or are contraindicated. AV nodal ablation and pacing for patients with AF have not been found to worsen survival in comparison with drug therapy for AF.\textsuperscript{31} A therapeutic trial of medication with monitoring for symptoms and ventricular rate control can be performed within a period of weeks to months. If this approach proves ineffective, AV nodal ablation and pacing for appropriately selected patients is reasonable and should be considered.

Techniques directed at selective ablation of the slow pathway inputs to the AV node have been used in an attempt to slow the ventricular rate while preserving AV conduction.\textsuperscript{32,33} However, when this strategy is attempted, the ventricular rate may rise over time, resulting in incomplete rate control, and it is therefore seldom used. A more effective strategy involves ablation of both the slow- and fast-pathway inputs to the AV node, producing complete AV block with a greater likelihood of a junctional escape rhythm in comparison with more distal ablation of the AV node or His bundle.\textsuperscript{34}

In addition to pacemaker dependence, AV nodal ablation and pacemaker implantation is associated with a sudden death risk of \textasciitilde 2\% in the early to intermediate postprocedure period.\textsuperscript{35} It is postulated, but not proven, that this risk may be related to a transient state of heightened susceptibility to ventricular proarrhythmia present soon after the ablation, possibly because of a failure of cardiac repolarization to adapt to the combination of a sudden rate change and the effects of newly instituted chronic ventricular pacing. This risk may be significantly reduced by pacing at a higher rate (90 bpm has been recommended) for the first month after AV junctional ablation.\textsuperscript{19,36} In addition, AV nodal ablation typically results in nearly 100\% right ventricular (RV) pacing, which can induce ventricular dyssynchrony and worsen systolic function. Biventricular pacing may be useful in this situation, as will be discussed in greater detail in the section on Resynchronization Considerations.

**Targets for Rate Control**

Uncontrolled rapid ventricular rates during AF may cause severe symptoms and, in some cases, can lead to the development of a tachycardia-induced cardiomyopathy and CHF.\textsuperscript{37} For these reasons, rate control sufficient to improve symptoms during AF and prevent the development of left ventricular dysfunction and CHF is of paramount importance. Despite universal recognition of the importance of rate control, precise targets for optimal ventricular rates during AF remain controversial. The 2006 consensus guidelines for AF management recommended target heart rates of 60 to 80 bpm at rest and 90 to 115 bpm during moderate exercise.\textsuperscript{19} In the AFFIRM trial, recommended targets for rate control were no higher than 80 bpm at rest and no higher than 110 bpm during a 6-minute walk test, and an average heart rate no higher than 100 bpm over 18+ hours of Holter monitoring with no rates \textasciitilde 100\% of maximal age-predicted heart rate, as well.\textsuperscript{1,18} The goal for rate control in the RACE trial was more lenient than AFFIRM, with a target resting heart rate \textasciitilde 100 bpm.\textsuperscript{2} It should be noted, however, that these criteria for rate control were not based on strong clinical evidence, and, when the recommendations were made, it was not clear whether achieving these rate control targets would translate to clinical benefit. Retrospective analysis of the AFFIRM study suggested that a variety of outcomes including overall and event-free survival, quality of life, and functional status were similar between patients divided into quartiles based on achieved heart rates at rest and during exercise.\textsuperscript{38} A similar retrospective analysis of the RACE study showed no differences in cardiovascular morbidity, mortality, and quality of life between patients with achieved resting heart rates \textasciitilde 80 bpm versus \textasciitilde 80 bpm.\textsuperscript{39} Although strict rate control was not beneficial in these retrospective analyses, an analysis of both RACE and AFFIRM did suggest a benefit to moderate rate control, because patients with resting heart rates \textasciitilde 100 bpm were more likely to reach a composite end point of mortality, cardiovascular hospitalization, or myocardial infarction in comparison with patients with resting rates \textasciitilde 100 bpm.\textsuperscript{40}

**The RACE II Study**

On the basis of these data, the RACE II study was performed to prospectively compare strict versus lenient rate control strategies for patients with AF. In RACE II, 614 patients with permanent AF were randomly assigned to lenient (resting heart rate \textasciitilde 110 bpm) or strict (resting heart rate \textasciitilde 80 bpm and heart rate during moderate exercise \textasciitilde 110 bpm) rate control. Achieved resting heart rates in the study were 93\pm9 bpm in the lenient rate control group and 76\pm12 bpm in the strict rate control group (P<0.001). Over 2 to 3 years of follow-up, the primary composite outcome of cardiovascular
death, CHF hospitalization, stroke, systemic embolism, bleeding, and life-threatening arrhythmia occurred in 12.9% of patients randomly assigned to strict rate control and 14.9% of patients randomly assigned to strict rate control (hazard ratio 0.8, P<0.001 for noninferiority of lenient rate control) (Figure 3).41 Symptoms related to AF including dyspnea, palpitations, and fatigue were similar between the groups, as were New York Heart Association (NYHA) CHF class, frequency of hospitalizations, and adverse events. Not surprisingly, more medical visits were required to achieve strict rate control in comparison with lenient rate control (684 versus 75 total visits, P<0.001). Based on RACE II, and subanalyses of RACE and AFFIRM, as well, the consensus guidelines for rate control were changed in the 2011 update. Specifically, strict rate control as defined in RACE II was given a class III (no benefit) rating in comparison with lenient rate control strategy. Reproduced from Van Gelder et al41 with permission from the publisher. Copyright © Elsevier, 2009.

Rate Control for Patients With CHF

Important questions remain about the optimal intensity of rate control during AF. RACE II monitored patients for only 2 to 3 years, and it is possible that detrimental effects of chronically higher heart rates may take longer than 2 to 3 years to become clinically manifest. In addition, the effect of higher heart rates may be different in patients with systolic dysfunction and CHF. The SHIFT study analyzed the effect of the If blocker ivabradine versus placebo in patients in sinus rhythm with a resting heart rate ≥70 bpm and symptomatic CHF and LVEF ≥35% on good medical therapy including a β-blocker if tolerated. In this study, higher sinus rates were associated with worse outcomes: every 5-bpm increase in the baseline heart rate was associated with a 16% increase in the composite end point of cardiovascular death or hospital admission for worsening CHF.43 Ivabradine, which selectively slows the sinus rate, produced a modest slowing of the resting heart rate in SHIFT (average resting heart rates: 75 bpm in the control group, 64–67 bpm in the ivabradine group). Ivabradine was associated with a significant decrease in CHF admissions (16% versus 21%, P<0.0001) and in deaths due to CHF (3% versus 5%, P=0.014) in comparison with placebo.44 Presumably, these benefits of ivabradine are due to slowing of the sinus rate, although it is possible that the drug could benefit patients with CHF by other unknown mechanisms. Assuming that the beneficial effect of the drug is directly related to heart rate slowing, it is reasonable to hypothesize that lowering the ventricular rates of patients with AF and CHF would also be beneficial, although ivabradine would not be expected to be effective in AF because its primary effect is on the sinus node. Whether stringent rate control is superior to lenient rate control (and if so, what the rate control targets should be) for patients with AF and CHF lacks definitive proof, however, and further studies will be required to answer these important questions. Until further studies become available, it is the current clinical practice of the authors to target resting heart rates in the range of 60 to 70 bpm for patients with AF and CHF, with attention paid to avoiding excessively slow heart rates during rest/sleep and avoiding extremely high rates (above the maximal age-predicted heart rate) during exertion.

Resynchronization Considerations

CRT has emerged as an important treatment for patients with CHF due to systolic LV dysfunction and ventricular dyssynchrony, as evidenced by a wide QRS complex.45,46 It should be noted, however, that most of the landmark CRT trials either excluded patients with AF, or enrolled primarily patients in sinus rhythm, and so the effect of CRT in patients with AF cannot be directly extrapolated from the overall results of these trials. A recent meta-analysis suggests that the beneficial effects of CRT are comparable between patients in AF and those in sinus rhythm with respect to improvements in LVEF and NYHA CHF class.47 Based on these observations, CRT should be offered to patients with AF and CHF who would otherwise qualify for this therapy. Interestingly, CRT in patients with permanent AF was noted to result in spontaneous return of sinus rhythm in ~10% of these patients in a retrospective multicenter study.48

Rate Control and Pacing Goals in CRT Patients

During sinus rhythm, CRT is achieved by biventricular pacing with an A-V interval shorter than the patient’s intrinsic A-V interval. During AF, there is no A-V interval and, therefore, it is necessary to pace the ventricles faster than the patient’s underlying ventricular rate to deliver effective CRT. Because many patients with AF have rapid ventricular rates, it is necessary to slow the intrinsic ventricular rate sufficiently to allow for a high percentage of biventricular pacing, which studies have shown to be important for patients with AF receiving CRT. In one study, patients who received <92% biventricular pacing as detected by their implanted devices had worse clinical outcomes in comparison with patients who received >92% biventricular pacing (Figure 4A). Another study showed that, even for patients with >90% biventricular pacing recorded by the device, those

![Kaplan-Meier estimates of the cumulative incidence of the primary outcome (composite of: death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events) comparing strict versus lenient rate control strategies in the RACE II trial. P<0.001 for noninferiority of the lenient rate control strategy. Reproduced from Van Gelder et al41 with permission from the publisher. Copyright © Elsevier, 2009.](http://circ.ahajournals.org/lookup/doi/10.1161/CIRCULATIONAHA.108.784612)
with a larger percentage of QRS complexes with fusion or pseudofusion of paced beats with intrinsic complexes identified on Holter monitoring experienced a lower response rate to CRT in comparison with patients with less fusion and pseudofusion50 (Figure 4B). Device-based algorithms have been developed to attempt to pace the ventricles faster than the rate of intrinsic conduction during AF and thereby regularize the ventricular rate and increase the percentage of biventricular pacing. Other algorithms have been developed to pace the left ventricular lead immediately when an intrinsic beat is sensed by the right ventricular lead, but the clinical benefit of these algorithms remains unproven. It is also unclear whether biventricular pacing at relatively rapid rates to overdrive conducted AF and increase the percentage of biventricular pacing is helpful or harmful.

**Rate Control Methods in CRT Patients**

AV nodal-blocking agents, in particular, β-blockers and digitalis, may be useful in patients with AF and CHF receiving CRT, both to control the ventricular rate and thereby increase the percentage of biventricular pacing, and also as primary treatment for CHF. For some patients, however, it is not possible to pharmacologically control the ventricular rate during AF to a sufficient degree to allow a high percentage of biventricular pacing. For these patients, AV nodal ablation is almost always effective in controlling the ventricular rate and in allowing for a very high percentage of biventricular pacing. It should be noted, however, that other arrhythmias that are not corrected by AV nodal ablation, such as frequent premature ventricular contractions, can also lower the percentage of biventricular pacing. Among patients undergoing AV nodal ablation for refractory atrial arrhythmias, the PAVE study demonstrated greater benefit in the 6-minute walk distance and LVEF for patients randomly assigned to CRT in comparison with those randomly assigned to RV pacing. This difference was particularly prominent among patients with baseline LV systolic dysfunction or CHF.51 In PAVE, among patients with an LVEF ≤45% at baseline, the 6-minute walk test improvement was significant and 73% greater in patients who received CRT in comparison with those who received RV pacing after AV nodal ablation. For patients with LVEF >45%, there were no significant differences in 6-minute walk tests between patients receiving CRT versus RV pacing. Similarly, 6-minute hall walk significantly favored CRT versus RV pacing (by 53%) for patients with NYHA class II or III symptoms at baseline, but not for those with NYHA class I symptoms.51 On the basis these data, we believe that CRT (as opposed to RV pacing) is indicated for patients undergoing AV nodal ablation who have significant LV dysfunction at baseline and/or symptomatic CHF. If an RV pacemaker is placed at the time of AV nodal ablation and CHF with LV dysfunction develops subsequently, then upgrade to a CRT device should be considered. Studies have also suggested larger benefits from CRT for patients with AF who undergo AV nodal ablation in comparison with those whose ventricular rates are controlled pharmacologically, and some studies have even suggested that CRT only benefits those patients with AF who also undergo AV nodal ablation.52–54 Given the risks of pacemaker dependence in patients who undergo AV nodal ablation, it seems premature in the absence of randomized controlled trials to recommend AV nodal ablation for AF patients undergoing CRT who can be effectively rate controlled with β-blockers and/or digitalis and in whom a high percentage of biventricular pacing can be achieved. For those patients with AF and CHF in whom adequate rate control cannot be achieved with pharmacological means, however, AV nodal ablation is an
effective strategy to ensure a high percentage of biventricular pacing.

Conclusions and Recommendations

Despite the availability of numerous pharmacological options for the maintenance of sinus rhythm, acceptance of AF with control of the ventricular rate (using either AV nodal blocking drugs or, less commonly, AV nodal ablation and pacing) remains a viable option that may be preferable to a rhythm control strategy with currently available antiarrhythmic drugs for some subgroups of patients. In particular, patients with minimal or no symptoms attributable to AF, and in whom there is no evidence of AF-related left ventricular dysfunction, may be well suited to a rate control strategy. The targets for rate control remain controversial: very high ventricular rates are clearly harmful and can result in symptoms and, in some patients, the development of a tachycardia-induced cardiomyopathy and CHF. Strict rate control was not demonstrated to be superior to more lenient rate control over 2 to 3 years of follow-up in RACE II and in post hoc subanalyses of RACE and AFFIRM. Therefore, based on available data, strict rate control cannot be advocated over lenient rate control for patients with no or minimal symptoms and normal LV function. Strict rate control may offer clinical benefit in patients with AF and coexisting CHF, but this remains to be proven in prospective studies. CRT is beneficial for patients with AF and CHF who meet other criteria for CRT. When CRT is offered to patients with AF, ventricular rate control with AV nodal-blocking drugs (or AV nodal ablation when drugs are ineffective) is important to ensure a high percentage of biventricular pacing (in general, >90% pacing). Finally, the question of whether rate control is truly equivalent to rhythm control in patients with AF must be considered in light of the risks and limited efficacy of currently available antiarrhythmic drugs. The potential benefits of rhythm over rate control will continue to be tested as newer, safer, and more effective treatment options for AF become available.

Many important questions remain unanswered, awaiting the results of ongoing and future clinical trials. There are significant differences in expert recommendations for AF management even when comparing recent consensus documents from the American College of Cardiology Foundation/ American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS), the Canadian Cardiovascular Society (CCS), and the European Society of Cardiology (ESC). Among the differences between these consensus documents are the heart rate targets during rate control of AF, the indications for AV nodal ablation, and the indications for catheter ablation of AF. Ongoing clinical trials such as CABANA will provide much needed information about the role of catheter ablation versus pharmacological therapies for AF management both with regard to rhythm and rate control strategies.

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References


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