Congestive heart failure (CHF) and atrial fibrillation (AF) often coexist, and each increase the morbidity and mortality associated with the other. Until now, many studies have reported that a strategy of rate control, in combination with anticoagulation in patients at risk of thromboembolic events, appears to be at least equivalent to a strategy of maintaining sinus rhythm with currently available pharmacological therapeutic options. As compared to rhythm control therapy, rate control treatment is simple and relatively easy. Therefore, pharmacological rate control should be considered initially in patients with AF associated with CHF. However, cardiac symptoms associated with AF may continue after achieving reasonable ventricular rate control. Either pharmacological or non-pharmacological rhythm control needs to be considered at that time. Amiodarone is the only recommended antiarrhythmic drug in the recent therapeutic guidelines for CHF, and can be used for both rhythm and rate control of AF. However, there is no question that some patients require early non-pharmacological rhythm control instead of long-lasting rate control. Catheter ablation (CA) can be applicable even in AF associated with CHF, but the results of CA are closely associated with the clinical and electrophysiological characteristics in each patient, as well as with the experience with this procedure in each institution. Indications for and the appropriate period of CA need to be carefully examined in each individual. (Circ J 2011; 75: 970–978)

Key Words: Amiodarone; Atrial fibrillation; Catheter ablation; Rate control therapy; Rhythm control therapy
Until now, many studies have reported that a strategy of rate control, in combination with anticoagulation in patients at risk of thromboembolic events, appears to be at least equivalent to a strategy of maintaining sinus rhythm with currently available therapeutic strategies (Table). Therefore, we will discuss the limitations of pharmacological and non-pharmacological rhythm control therapy, and describe why rhythm control therapy is not suitable as an initial treatment of AF associated with CHF.

### Table. Rhythm vs. Rate in Non-Selected Patients

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Age (year)</th>
<th>Follow (month)</th>
<th>CHF (%)</th>
<th>Sinus rhythm (%)</th>
<th>Anti-coagulation (%)</th>
<th>Embolism (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM</td>
<td>Rate control</td>
<td>2,027</td>
<td>70</td>
<td>42</td>
<td>23.1</td>
<td>35</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Rhythm control</td>
<td>2,033</td>
<td>70</td>
<td>42</td>
<td>23.4</td>
<td>63</td>
<td>70</td>
<td>7.5</td>
</tr>
<tr>
<td>RACE</td>
<td>Rate control</td>
<td>256</td>
<td>68</td>
<td>27</td>
<td>51</td>
<td>10</td>
<td>96–99</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Rhythm control</td>
<td>266</td>
<td>68</td>
<td>27</td>
<td>49</td>
<td>39</td>
<td>86–99</td>
<td>7.9</td>
</tr>
<tr>
<td>STAF</td>
<td>Rate control</td>
<td>100</td>
<td>65</td>
<td>22</td>
<td>55.5</td>
<td>0</td>
<td>Not reported</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Rhythm control</td>
<td>100</td>
<td>66</td>
<td>22</td>
<td>55.5</td>
<td>Not reported</td>
<td>Not reported</td>
<td>3.1</td>
</tr>
<tr>
<td>PIAF</td>
<td>Rate control</td>
<td>125</td>
<td>61</td>
<td>12</td>
<td>–</td>
<td>10</td>
<td>100</td>
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<td>127</td>
<td>60</td>
<td>12</td>
<td>–</td>
<td>56</td>
<td>100</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; AFFIRM, atrial fibrillation follow-up investigation of rhythm management; RACE, rate control vs. electrical cardioversion; STAF, strategies of treatment of atrial fibrillation; PIAF, pharmacological intervention in atrial fibrillation. (Modified from Zimetbaum P. Circulation 2005; 111: 3150–3156 with permission.)

### Figure 1. Twelve-lead electrocardiogram. Amiodarone (200mg/day) was administered to a 39-year-old woman with persistent atrial fibrillation (AF) associated with congestive heart failure due to dilated-phase hypertrophic cardiomyopathy. The AF converted to sinus rhythm 5 days after treatment, and the level of B-type natriuretic peptide decreased from 1,650 to 600 pg/dl.

### Pharmacological Therapy

Among patients with CHF, maintaining sinus rhythm with the use of antiarrhythmic drugs is challenging, because of the limited efficacy and potentially proarrhythmic effects of the drugs. Furthermore, the prognosis of patients with AF and appropriate anticoagulation therapy is relatively good, as reported in the J-rhythm study (0.9% mortality of the subjects).

### Drug Selection

The Japanese Circulation Society (JCS) guideline suggests...
various types of class I antiarrhythmic drugs for pharmacological rhythm control treatment of paroxysmal lone AF. On the other hand, class III/IV antiarrhythmic drugs such as amiodarone, sotalol, and bepridil with/without aprindine are recommended for pharmacological rhythm control of persistent lone AF. Similarly, in AF associated with systemic heart disease (hypertrophic, ischemic and/or failing heart), the JCS guideline suggests aprindine, amiodarone, sotalol and bepridil for pharmacological rhythm control treatment. This is because class I antiarrhythmic drugs have limited efficacy and a potential risk of proarrhythmic effects in AF associated with systemic heart diseases. Indeed, antiarrhythmic drug therapy and cardiac mortality in AF (SPAF) study reported that class I antiarrhythmic drugs worsened the survival rate of patients with CHF. Therefore, it is reasonable that the American College of Cardiology/American Heart Association (ACC/AHA) therapeutic guideline for CHF recommends that drugs known to adversely affect the clinical status of patients with current or prior symptoms of CHF and reduced left ventricular ejection fraction (LVEF) should be avoided or withdrawn whenever possible. Furthermore, the European Society of Cardiology (ESC) guideline of arrhythmias in heart failure recommends that, in patients with AF and CHF or depressed left ventricular (LV) function, the use of antiarrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone. The recent JCS guideline also has the same suggestion; that is, except for amiodarone, none of the antiarrhythmic drugs are recommended for the treatment of AF associated with CHF. As shown in these recent guidelines, physicians need to consider amiodarone for pharmacological rhythm control in patients with AF associated with CHF, but due to its unique electrophysiological and cardiopharmacological characteristics, amiodarone is most commonly prescribed by experienced cardiologists.

**Amiodarone and Sotalol** Amiodarone is the most powerful of the antiarrhythmic drugs and can be used for patients with CHF or cardiac dysfunction (Figure 1). Sotalol, on the other hand, inhibits rapid components of the delayed rectifier potassium current (I\(\text{Kr}\)) and \(\beta\)-adrenergic receptor, thus it should be carefully used in patients with cardiac dysfunction. Although these drugs are useful in some patients, previous studies demonstrated limited efficacy of them in maintaining sinus rhythm. The Canadian Trial of Atrial Fibrillation (CTAF) study included 403 patients with persistent AF and compared the antiarrhythmic effects of amiodarone (201 patients), sotalol (101 patients) and propafenone (101 patients). The results showed that recurrence rate of AF was significantly lower in the amiodarone group than in the sotalol and propafenone groups, but the patients without recurrence of AF in the amiodarone group were limited to 65% during a follow-up period of 16 months. In other small trials, the proportion of patients assigned to the rhythm control group (who mostly used amiodarone) who were in sinus rhythm at the end of the study varied greatly, from 38% to 63.5%. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study included a large number of AF patients, and a substudy showed that recurrence of AF was lower in the amiodarone group as compared to other groups; namely, class I antiarrhythmic drugs and sotalol. However, in the rhythm control group, after 3 and 5 years, 73.3% and 62.6% of patients, respectively, were in sinus rhythm, which was maintained by antiarrhythmic drugs. However, large clinical trials, including this AFFIRM study, have consistently shown that ventricular rate control is as equally effective as rhythm control in terms of survival, quality of life, and multiple other endpoints (Table). Nevertheless, a number of physicians believe that pharmacological rhythm control therapy is superior to rate control therapy in patients with CHF because maintenance of sinus rhythm can help improve cardiac dysfunction. However, the results of the rhythm control vs. rate control for atrial fibrillation and heart failure (AF-CHF) study did not support this hypothesis. The study included 1,376 patients with LVEF <35% (average LVEF 27%), symptoms of CHF (NYHA II–IV), and a history of AF. The patients were divided into a rhythm control (682 patients) or rate control (694 patients) group. In the rhythm control group, amiodarone (or sotalol or dofetilide) were prescribed after electrical cardioversion, and \(\beta\)-blockers and digitalis were used in the rate control group. During the mean follow-up period of 37 months, there was no difference in the survival rate of the 2 groups. This study demonstrated that even in the patients with CHF, pharmacological rhythm control was equivalent to ventricular rate control.

**Bepridil** In Japan, bepridil is also available for the treatment of AF. Besides the sodium and calcium currents, bepridil, like amiodarone, inhibits many other myocardial ionic currents, including the rapid and slow components of the delayed rectifier potassium current (I\(\text{Kr}\) and I\(\text{k1}\)), the transient outward potassium current, and the inward rectifying potassium current, etc. Although there are studies reporting excellent effects of bepridil for converting AF to sinus rhythm, maintenance of sinus rhythm by bepridil is limited and this drug may increase the risk of cardiovascular events. In the J-BAP study, 90 patients were randomly administered either a placebo, or 100 or 200 mg/day of bepridil for 12 weeks. Although there was a clear dose–response relationship between the bepridil dosage and the rate of conversion from persistent AF to sinus rhythm (38% in the 100 mg/day and 69% in the 200 mg/day group), AF recurrence after conversion, however, was high irrespective of continued treatment (92% in the 100 mg/day and 75% in the 200 mg/day group). Furthermore, sudden cardiac death due to ventricular tachycardia (1 patient) and remarkable QT prolongation (4 patients: 14%) occurred among the 29 patients who were under the 200 mg/day treatment. Therefore, the results of this study suggest a limited role for of bepridil in the pharmacological treatment of AF.

**Dronedarone** New antiarrhythmic drugs may have reasonable efficacy and less adverse effects in AF treatment of CHF patients. In the recent ESC guidelines, dronedarone is approved as a first-line therapy in AF patients with or without structural heart disease. A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter study (ATHENA) included 4,623 patients with paroxysmal or persistent AF, and 21% of the patients had a history of CHF (NYHA II–III) and 12% of the patients had cardiac dysfunction (LVEF <45%). In this study, dronedarone (800 mg/day) reduced the primary endpoints of cardiovascular death and first hospitalization for a cardiovascular event as compared to placebo group. An interesting finding from ATHENA is that in the post hoc analysis the benefit of the new drug was not limited to only those who converted to sinus rhythm. However, results of the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) study were not consistent with the ATHENA study. The ANDROMEDA study includes 627 patients with more severe CHF (NYHA III–IV) and cardiac dysfunction (LVEF <35%). Primary outcome was
death from any cause and hospitalization for worsening CHF. Although the same dose of dronedarone (800 mg/day) as used in ATHENA study was prescribed in the ANDROMEDA study, its results showed that, in the patients with severe CHF and cardiac dysfunction, treatment with dronedarone was associated with increased early mortality related to the worsening of cardiac function. Therefore, the new drug can be effectively used in patients with moderate cardiac dysfunction, but may not be considered as a true substitute for amiodarone, particularly in patients with severe heart failure. The efficacy of dronedarone in maintaining sinus rhythm may be lower than that of amiodarone, but the favorable side-effect profile will certainly make it the drug of choice in those with LV hypertrophy, coronary artery disease and mild heart failure, as stated in the new ESC guidelines.

**Torsades de Pointes (Tdp)**
Several adverse effects have been reported during antiarrhythmic drugs treatment. Since class III/IV antiarrhythmic drugs are usually prescribed in patients with CHF, it seems less likely that cardiac dysfunction is further worsened by the use of drugs, because class III/IV antiarrhythmic drugs (except for sotalol) have a weaker negative inotropic effect. On the other hand, Tdp arrhythmia associated with marked QT interval prolongation can develop as a serious proarrhythmic effect of these drugs.

Heterogeneous distribution of ventricular repolarization and triggering premature beats most likely due to early depolarization are 2 key factors in the initiation of Tdp. Since amiodarone, sotalol and bepridil inhibit potassium channels (I_{Kr} and I_{Ks} etc), decreasing the net repolarization current of the myocardium results in the prolongation of both myocardial repolarization and the QT interval. In patients with cardiac dysfunction, drug-induced prolongation of the QT interval often manifests because of electrical and structural myocardial remodeling, electrolyte imbalance (hypokalemia, hypomagnesemia etc), augmentation of sympathetic nerve activity and/or renal and/or liver dysfunction etc. Among the currently available class III/IV antiarrhythmic drugs, the incidence of drug-induced Tdp is lower for amiodarone as compared to sotalol and bepridil, probably due to the fact that amiodarone homogeneously increases ventricular repolarization through the inhibition of both I_{Kr} and I_{Ks}, whereas sotalol and bepridil can induce heterogeneous distribution of

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**Figure 2.** Twelve-lead electrocardiogram. Bepridil (150 mg/day) was administered to a 35-year-old man who suffered from persistent atrial fibrillation (AF). The QT/QTc interval was 370/453 ms during treatment with bepridil (A), but was prolonged to 500/521 ms when the AF converted to sinus rhythm (B).
ventricular repolarization because of their predominant inhibition of $I_{Kr}$. To predict and prevent the occurrence of Tdp, monitoring of both the QT interval and serum drug concentration are important during antiarrhythmic drug treatment. However, class III/IV antiarrhythmic drugs have reverse use-dependent characteristics,\(^\text{38,39}\) so it is possible that marked QT interval prolongation becomes obvious when AF resumes sinus rhythm with a slower heart rate (Figure 2). Marked QT interval prolongation (or Tdp arrhythmia) induced by class III/IV antiarrhythmic drugs can be abbreviated (or treated) by temporary pacing, intravenous isoproterenol or magnesium infusion, and/or potassium supplementation.\(^\text{40,41}\) However, the effects of such therapeutic interventions can differ according to the type of antiarrhythmic drug that was prescribed. Thus, the therapeutic strategy for drug-induced QT interval prolongation may need to be clarified for each class III/IV antiarrhythmic drug.

**Rhythm Control Therapy (From Pharmacological to Non-Pharmacological Approach)**

It is still possible that maintaining sinus rhythm without the accompanying adverse effects of the drugs can provide a better rate of survival, quality of life and cardiac function.\(^\text{42}\) However, of the currently available antiarrhythmic drugs, the beneficial effects of antiarrhythmic therapy will be observed only in a limited number of patients with AF and CHF. Furthermore, these responders to pharmacological therapy are, unfortunately, unable to be selected before prescribing the antiarrhythmic drugs.

As described earlier, several important studies that included a large number of patients have suggested an equivalent outcome for strategies involving pharmacological rhythm and rate control.\(^\text{20}\) Therefore, there are no reasons for pharmacological rhythm control therapy (which showed a low rate of success and potential risk of adverse effects) to be initially recommended for all patients with AF associated with CHF. On the other hand, pharmacological rhythm control is simply applicable for most patients and should be considered a reasonable initial therapy in patients with AF associated with CHF. However, catheter ablation (CA) may maintain sinus rhythm without accompanying adverse effects and may provide beneficial effects to patients with AF and CHF.

**Results of CA for AF**

CA of paroxysmal lone AF is considered to be effective and safe (Figure 3).\(^\text{43-45}\) In most patients with paroxysmal lone AF, the size of the atria is within normal, and simple pulmo-
nary vein (PV) isolation is highly effective. Furthermore, recent advances in medical technology in this area (3-dimensional mapping systems, irrigation catheters, guiding catheters etc) greatly assist in completing the electrical isolation of the PVs from the left atrium (Figure 4). In a randomized trial of circumferential PV ablation vs. antiarrhythmic drug therapy in Paroxysmal Atrial Fibrillation (the APAF study; 198 patients), Paponne et al compared the efficacy of CA and antiarrhythmic drug therapy in patients with paroxysmal AF, and reported that the AF-free rate was 93% in the CA group whereas it was only 35% in pharmacological therapy group. Therefore, it is reasonable that the recent therapeutic guidelines for AF list CA as a therapeutic option in patients with drug-refractory paroxysmal AF. In the JCS guideline, CA is described as a class IIa indication, and the recent ESC guideline shows that CA can be used prior to antiarrhythmic drugs in some patients with paroxysmal lone AF.

However, the results and outcomes of CA in patients with structural heart diseases are not as extensive as for paroxysmal lone AF, and the role of CA of AF in patients with CHF has not yet been established, because persistent/long-lasting AF is frequently observed in patients with structural heart diseases. In these patients, enlarged atria and damaged atrial myocardium, as well as the PVs, can be acting as the arrhythmogenic substrate of AF. Therefore, in addition to electrical isolation of the PVs, complex linear ablation and/or complex fractionated atrial electrogram (CFAE) ablation are usually required in most of this group of patients. If such ablation procedures can be successfully applied without any major complications within a reasonably short procedural time, CA may be a therapeutic option even in patients with AF associated with CHF. Indeed, Hsu et al reported excellent results for AF ablation in both patients with (n=58, NYHA class 2.3±0.5, LVEF 35±7%) and without CHF (n=58, NYHA class 1.3±0.5, LVEF 66±7%). In their series, there was no difference between the 2 groups in the success rate free of antiarrhythmic drugs (69% with CHF vs. 71% without CHF). They concluded that restoration and maintenance of sinus rhythm by CA without the use of drugs in patients with CHF and AF significantly improved cardiac function, symptoms, exercise capacity and quality of life. However, in that study, the mean left atrial parasternal dimension in patients with CHF was relatively small at 50±7 mm, and additional linear ablation was attempted in most of the patients (91%).

More recently, Cappato et al reported the updated worldwide survey of the methods, efficacy, and safety of CA for human AF. Their study included 16,309 patients from 24 countries and showed that CA of AF was effective in about 80% of patients after 1.3 procedures per patient, with about 70% of them not requiring further antiarrhythmic drugs during intermediate follow-up. The success rate free of antiarrhythmic drug was greater in patients with paroxysmal AF (74.9%) than in patients with persistent AF (64.8%) and with long-lasting AF (63.1%). Major complications, including death, were reported in 4.5%.

CA may be superior as compared to other non-pharmacological treatments. In the Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure (PABA-CHF) study, Khan et al studied 81
patients with symptomatic drug-resistant AF associated with CHF (NYHA class II–III, LVEF <40%). They attempted either CA or atrioventricular node ablation with biventricular pacing in these subjects and the effects of each therapy were compared. From the analysis, they concluded that PV isolation was superior to atrioventricular node ablation with biventricular pacing at all endpoints.

**Limitations and Problems in CA Ablation for AF Associated With CHF**

CA is one of the most powerful therapeutic options for AF associated with CHF, but for the following reasons, we do not believe that it is the best initial treatment of AF associated with CHF. First, complex ablation (additional line, CFAE, and/or ganglion plexus etc) is required to restore and maintain sinus rhythm, and such techniques can be safely performed only by the more experienced arrhythmic treatment centers. Second, complex CA takes longer and requires greater numbers of medical staff. Third, as we described before, the number of patients who are suffering from AF associated with CHF is too large (estimated at least 0.2 million people) for this therapy to be generally applied as an initial treatment. Lastly, one of the beneficial points of non-pharmacological treatments is the ability to cease the antiarrhythmic drugs and/or anticoagulation treatment. The success rate of CA without the use of antiarrhythmic drugs is limited to 63–75%. Besides the antiarrhythmic drugs, warfarin is recommended for all patients for at least 2 months following an AF ablation procedure, according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) expert consensus statement. Decisions regarding the use of warfarin for more than 2 months following ablation should be based on the patient’s risk factors for stroke and not on the presence or type of AF. Discontinuation of warfarin therapy post ablation is generally not recommended in patients who have a CHADS score ≥2. In patients with AF associated with CHF, the CHADS score is ≥1 (CHF). Therefore, we think that discontinuation of warfarin is not recommended in most patients even after successful CA. Although anticoagulation therapy with the new drugs (direct thrombin inhibitor or factor Xa inhibitor, etc) will soon be available in Japan, the recommended anticoagulation therapy after CA will likely be unchanged by the introduction of new anticoagulation agents.

**Proposed Therapeutic Strategies of AF Associated With CHF**

As we have described, pharmacological ventricular rate control is usually effective and should be considered first in most patients with AF associated with CHF. However, in some patients cardiac symptoms associated with AF may continue after achieving reasonable ventricular rate control using β-blockers and digitalis. Pharmacological and non-pharmacological rhythm control needs to be considered at that time. Amiodarone has been used as a rhythm control drug for AF, but it also has a ventricular rate control effect, as reported in a sub-analysis of The Survival Trial Of Antiarrhythmic Therapy In Congestive Heart Failure (CHF-STAT) study. Therefore, amiodarone can be used both for rhythm and rate control of AF, especially in patients for whom β-blockers are inappropriate and/or insufficient to control the ventricular rate of AF.

Some cardiologists argue that each patient’s success rate following CA may decrease during their follow-up in association with the progression of structural and electrical remodeling of the atrial myocardium. Of course, the severity of cardiac symptoms, the magnitude of cardiac dysfunction and/or progression of atrial remodeling is different in each patient with AF. Therefore, there is no question that some patients require early non-pharmacological rhythm control instead of long-lasting rate control. The indication and appropriate timing of CA may need to be decided according to the clinical and electrophysiological characteristics of each patient, as well as on the experience with this procedure in each institution.

**Conclusions**

Pharmacological rate control (the use of β-blockers, digitalis and/or amiodarone) should be considered initially in patients with AF associated with CHF. Amiodarone is the only recommended antiarrhythmic drug in the recent therapeutic guidelines, but its efficacy in maintaining sinus rhythm is limited. CA can be applicable, even in AF associated with CHF, but the indication and appropriate timing of the procedure needs to be carefully examined in each individual.

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Authors’ Comments on the Rhythm-Side Authors

As Dr Kurita et al emphasize in their article in this issue of the Journal, it is reasonable to think that rhythm control therapy for AF provides favorable hemodynamic effects in patients with CHF in the case where either pharmacological or non-pharmacological intervention is simple and has been successfully used without any major adverse effects. However, for rhythm control treatment of AF associated with CHF, amiodarone is recommended but has only a limited efficacy, and a complex procedure is usually required during catheter ablation. It, of course, does not mean that rhythm control treatment is useless for the treatment of AF associated with CHF. If we can initially identify those patients in whom amiodarone or simple pulmonary vein isolation is effective to restore and maintain sinus rhythm, physicians may consider rhythm control as an initial therapeutic choice in such patients. However, until now, we have not had any reliable methods for identifying those patients who respond well to therapeutic rhythm control intervention. In addition, thromboembolic events commonly develop within a few days after AF is restored to sinus rhythm. Therefore, anticoagulation treatment using warfarin is recommended in most patients with AF and CHF. Since the primary aim of the prescription of class III/IV antiarrhythmic drugs is to restore and maintain sinus rhythm, these antiarrhythmic drugs can be used for patients who are being appropriately treated by warfarin. However, we may need to start AF management without warfarin pretreatment, especially in some patients on their first visit or who have been referred for further treatment. Therefore, in real clinical situations, it is not unusual that we have to start from rate control and anticoagulation therapies in order to avoid possible complications of thromboembolic events in patients of AF associated with CHF.