Pharmacological Treatment for Atrial Fibrillation

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Pharmacological treatment for atrial fibrillation has a variety of purposes, such as pharmacological defibrillation, maintenance of sinus rhythm, heart rate control to prevent congestive heart failure and prevention of both cerebral infarction and atrial remodeling. Sodium channel blockers are superior to potassium channel blockers for atrial defibrillation, while both sodium and potassium channel blockers are effective in the maintenance of sinus rhythm. In general, digitalis or Ca antagonists are used to control heart rate during atrial fibrillation to prevent congestive heart failure, while amiodarone or bepridil also reduce heart rates during atrial fibrillation. Anticoagulant therapy with warfarin is recommended to prevent cerebral infarction and angiotensin converting enzyme antagonists or angiotensin II receptor blockers are also used to prevent atrial remodeling. One should select appropriate drugs for treatment of atrial fibrillation according to the patient’s condition.

(Key words: Atrial fibrillation, Pharmacological treatment, Antiarrhythmic agent, Anticoagulant therapy)

Introduction

Pharmacological treatment for atrial fibrillation encompasses various topics including defibrillation by antiarrhythmic agents, maintenance of sinus rhythm with antiarrhythmic agents, rate control during atrial fibrillation by suppression of atrioventricular nodal conduction for prevention of heart failure, and anticoagulant therapy to prevent thromboembolism. Furthermore, patients with decreased cardiac functions and certain patients suffering from recurrent atrial fibrillation have been extensively treated with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) to prevent congestive heart failure and occurrence of atrial remodeling attributable to atrial fibrillation, indicating significant multiplicity of drugs to be used for different types of atrial fibrillation. Accordingly, there has been a controversial issue regarding whether any guidelines for treatment of atrial fibrillation developed in Europe and America, or the results obtained in comparative studies on rate controls and rhythm controls, could be incorporated into the existing Japanese guidelines for atrial fibrillation. The present article is a review of drug therapies for atrial fibrillation in Japan.

Indication of drug therapies for treatment of atrial fibrillation

For deciding the therapeutic strategy for atrial fibrillation, classification of atrial fibrillation according to its pathophysiology plays a useful role. For the benefits of effective classification leading to practical therapeutic strategy, atrial fibrillation can be classified as follows: transient atrial fibrillation induced by ingestion of alcoholic beverages, inadequate sleep and overwork; paroxysmal atrial fibrillation with recurrence and spontaneous termination; persistent atrial fibrillation characteristic of no spontaneous
termination but being responsive to defibrillation; and permanent atrial fibrillation characterized by the absence of spontaneous termination and failure to defibrillate and the planning of further attempts to restore sinus rhythm. Customarily, chronic atrial fibrillation has been defined as permanent atrial fibrillation combined with a part of persistent atrial fibrillation which is left untreated with defibrillation. This classification is directly correlated with the intervention for atrial fibrillation, suggesting that transient atrial fibrillation can be prevented by elimination of the inducing factors. In principle, it is advocated to try defibrillation at first for treatment of either paroxysmal or persistent atrial fibrillation, while in patients presenting with recurrence within a short period of time despite reaching sinus rhythm antiarrhythmic drug therapy is required to maintain sinus rhythm. For the treatment of patients with persistent atrial fibrillation and with long-lasting permanent atrial fibrillation, rate control for prevention of heart failure, and anticoagulant therapies for prevention of thromboembolism occupy a major position.

Once atrial fibrillation occurs, the atrium is irregularly excited at the frequency of 450–600 per minute and its excitation wave is conducted in a disorder by manner through the atrioventricular node, certainly resulting in irregular ventricular excitation. This is the reason why atrial fibrillation is termed as absolute arrhythmia. With the atrioventricular node possessing good conductivity, the ventricular response increases in number, evolving to irregular tachycardia. Due to these features, the patients perceive significant palpitation and abnormal sensation around their chests when atrial fibrillation initiates. These symptoms derive from pulse irregularity and tachycardia. Despite the presence of pulse irregularity, suppression of tachycardia successfully leads to disappearance of subjective symptoms. These experiences imply that inhibition of atrioventricular nodal conduction is effective. On the other hand, among the patients with atrial fibrillation admitted to the intensive care unit (ICU), improvement of cardiac functions by treatment of underlying heart diseases is associated with disappearance of atrial fibrillation; on the other hand, aggravation of underlying heart diseases is sometimes accompanied with onset of atrial fibrillation. As a natural consequence, pharmacological treatments should be decided by not only focusing one’s attention on atrial fibrillation itself but also considering alleviation of systemic conditions. To realize these objectives, ACE inhibitors and ARB have been used clinically.

Irrespective of paroxysmal atrial fibrillation or permanent atrial fibrillation (chronic atrial fibrillation), there is no significant difference in incidence of cerebral infarction. Accordingly, prophylaxis of thromboembolism is a useful therapeutic remedy to be applied to any type of atrial fibrillation.

**Pharmacological defibrillation**

For the purpose of selecting the effective antiarrhythmic agents for the treatment of defibrillation, comparison was made between sodium (Na) channel blockers and potassium (K) channel blockers (Figure 1, 2), indicating that Na channel blockers exhibited definitely superior defibrillation effects. Accordingly, we can conclude that Na channel blockers...
channel blockers are the first-line therapy for defibrillation of atrial fibrillation, with K channel blockers being recognized as the second-line therapy. In Japan, currently available are 9 different kinds of Na channel blockers which can be used for defibrillation of atrial fibrillation (Table 1). On defibrillation, we have to make proper selection of either intravenous or oral administration of antiarrhythmic agents according to the situation and condition of the patient. Intravenous administration is mainly used for defibrillation because of the rapid appearance of the drug’s effect; in contrast, however,
oral medication of antiarrhythmic agents is preferred when defibrillation is not urgently required.

1) Intravenous administration of antiarrhythmic agents
As for intravenous injection, antiarrhythmic agents currently available for defibrillation in Japan include procainamide, disopyramide, cibenzoline, aprindine, flecainide and pilsicainide. Most of these antiarrhythmic agents exert defibrillation effect at the levels of 50–70%, except for aprindine which demonstrates weaker defibrillation effect following its injection at the usual dose of 100 mg. Selection of the drugs shall be made by referring to the cardiac functions, as well as the hepatic and renal functions of the patients.

If patients with significant subjective symptoms but without any lowered cardiac function must be promptly defibrillated with antiarrhythmic agents, either of the following Na channel blockers is intravenously injected: pilsicainide 50–100 mg/more than 5 min., flecainide 50–100 mg/more than 5 min., disopyramide 100 mg/more than 5 min., cibenzoline 70–140 mg/more than 5 min., procainamide 600–1000 mg/more than 5 min., or aprindin 100 mg/10 min. When intravenous injection of antiarrhythmic agents is selected for defibrillation, care should be exercised to administer one intravenous injection of one drug at least within one hour even though the cardiac functions are normal.

Even in lone paroxysmal atrial fibrillation, persistence of atrial fibrillation with rapid heart rate occasionally evolves into a condition characteristic of heart failure, known as tachycardia-induced cardiomyopathy. It is well documented that administration of antiarrhythmic agents under the condition with heart failure not only aggravates hemodynamics but also provokes arrhythmogenic effects. As a natural consequence, unless decrease of heart rates could improve heart failure, direct current electrical cardioversion should be performed. If electrical cardioversion fails to restore sinus rhythm, aprindin at a dose of 100 mg is intravenously infused over 10 minutes, followed by re-defibrillation. According to the past experiences, this method offers a significantly greater precision of defibrillation. However, prior to electrical cardioversion intravenous anesthesia is indispensable; therefore, when this pretreatment is rejected by the patient, all we have to do is to select antiarrhythmic agents with less suppression of cardiac functions (Table 1). In particular, nifekalant, a novel K channel blocker, possesses little suppressive effect for cardiac functions, thereby being only intravenously administered as a K channel blocker. The National Health Insurance System does not cover the payment for defibrillation of atrial fibrillation; however, it was reported that nifekalant was effective in defibrillation of atrial flutter and fibrillation accompanied with lowered cardiac functions. For defibrillation of atrial fibrillation, nifekalant at a dose of 0.3 mg/kg/5 min. should be intravenously injected. Electro-Pilsicainide Placebo

Figure 3 Time course of conversion to sinus rhythm with pilsicainide and placebo. The ordinate indicates the cumulative conversion rate and the abscissa represents time after a single oral administration of the drug. P < 0.05, +P < 0.01 (Represented with permission from reference 19)
cardiographic monitoring is indispensable throughout intravenous administration, besides precautions being taken to prevent QT prolongation during injection. In the meantime, we have experience with defibrillation over time by lowering the ventricular response rate in the patients with decreased cardiac functions due to atrial fibrillation with rapid heart rate. For this purpose, digoxin 0.25 mg was intravenously infused over 10–20 minutes, resulting in reduction of heart rates, thereby eventually restoring sinus rhythm. To the patients with renal dysfunction, the antiarrhythmic agents highly metabolized in the liver should be selected. Aprindin and procainamide represent such agents. If the patients suffer from hepatic dysfunction, antiarrhythmic agents excreted through kidneys should be selected. Such agents are represented by disopyramide, cibenzoline, flecainide and pilsicainide.

2) Oral administration of antiarrhythmic agents

As noted above, oral administration of antiarrhythmic agents is usually applied when adequate time is available. When short-acting agents like pilsicainide are administered as a single dose medication at higher doses like 1.5–2-fold doses of the usual single dose, they exert stronger defibrillation effects but there is a concern about occurrence of severe adverse reactions in the aged patient. A cooperative multicenter randomized placebo control study (Figure 3) revealed that the defibrillation ratio by pilsicainide accounted for 45% until 90 minutes after administration. In some cases, administration of class Ic antiarrhythmic agents evolved atrial fibrillation into atrial flutter without restoring to sinus rhythm.

In the patients with lowered cardiac functions, electrical cardioversion should be selected as the first-line method to defibrillate. However, if medi-
cation with antiarrhythmic agents is indispensable, we have to avoid using class Ic antiarrhythmic drugs (flecainide, propafenone, pilsicainide and cibenzoline) possessing stronger Na channel blocking effects, as well as disopyramide characteristic of exerting suppression of cardiac functions (Figure 4). In these patients, amiodarone 200 mg/day or bepridil 200 mg/day which show K channel blocking effects will be selected. In this connection, it should be noted that amiodarone and bepridil exhibit their antiarrhythmic effects 1–2 weeks after beginning of administration. Particularly in patients treated with bepridil, defibrillation usually occurs within 1–2 months (Figure 5). Nakazato reported that bepridil showed favorable conversion effects in patients with persistent atrial fibrillation. Furthermore, when amiodarone or bepridil are given during atrial fibrillation with rapid heart rate, it should be recognized that heart rates are decreased about 2 weeks later, resulting in alleviation of both subjective symptoms and heart failure.

Adverse reactions to be noted are aggravation of hemodynamics and arrhythmogenic effects in the patients with lower cardiac functions. So as to prevent onset of arrhythmogenic effects, all we have to do is to record the electrocardiogram repeatedly and to pay attention to QT prolongation following administration of antiarrhythmic agents with K channel blocking effects, besides giving attention to prolongation of QRS width after medication with antiarrhythmic agents with stronger Na channel blocking effects (Table 1).

Maintenance of sinus rhythm by antiarrhythmic agents

It is well known that irregular heart rates are increased immediately after occurrence of atrial fibrillation. Persistence of this situation is associated with suppression of cardiac functions, leading to persistent atrial fibrillation with heart rates of more than 130/minute and finally evolving to heart failure. Nevertheless, this heart failure-like condition is reversible; conversion of atrial fibrillation to sinus rhythm permits tapering of this undesirable condition to attain improvement of cardiac function.
Therefore, as heart failure precedes atrial fibrillation we reach the conclusion that atrial fibrillation should be prevented to the greatest possible extent.

It has also been pointed out that atrial fibrillation persisting over 48 hours facilitates formation of thrombus in the left atrium and left atrial appendage. Reduction of atrial contractility compared with that under sinus rhythm is responsible for thrombus formation. Transesophageal echocardiography disclosed higher incidences of spontaneous echo contrast during atrial fibrillation compared with those during sinus rhythm. Spontaneous echo contrast implies blood flow reduction in the left atrium which is considered to be a facilitating factor to induce thrombus formation. The patients with atrial fibrillation are vulnerable to develop cerebral embolism because of transfer of the isolated thrombus in left atrium. Moreover, defibrillation of persistent atrial fibrillation is associated with subsequent left atrium stunning, leading to thrombus formation in the left atrium following defibrillation. Cardioembolic cerebral embolism induces extensive cerebral infarction characteristic of hemorrhagic features, thereby being intractable to treatment. In any event, the prevalence of cerebral embolism is 5-fold higher in patients with atrial fibrillation compared with those with sinus rhythm. Therefore, maintenance of sinus rhythm plays an essential role in prevention of these events. Indeed, Komatsu reported that long-term prognosis of patients with paroxysmal atrial fibrillation varies with the response to antiarrhythmic drug therapy. When sinus rhythm is maintained, the prognosis is good even without anticoagulation therapy.

When the atrium is experimentally excited by frequent stimulation, the incidence of subsequent atrial fibrillation is increased, leading to prolongation of the persistent period of atrial fibrillation. Furthermore, incidence of atrial excitation during atrial fibrillation is incrementally increased. Allesie et al. called this phenomenon of susceptibility to occurrence of atrial fibrillation as electrical remodeling. Electrical remodeling bears its fundamental features such as shortening of effective refractory period of atrium and change of adaptation of the atrial refractory period in heart rate, all of which are assumed to be due to overload of Ca$^{2+}$ ions induced by frequent atrial excitation. In parallel with progress of electrical remodeling, structural remodeling is also present, whereby together they are called atrial remodeling due to atrial fibrillation. Given the structural remodeling formation, it is conceivable that prompt restoration to sinus rhythm and prevention of recurrence are really important. Since maintenance of sinus rhythm even in the ICU is important after defibrillation, oral antiarrhythmic agents are used for this purpose. For patients under tracheal intubation, powdered antiarrhythmic drugs are frequently administered by oral tube.

According to the meta analysis of 8 reports so far documented on prevention of atrial fibrillation after defibrillation, it was revealed that the maintenance ratio of sinus rhythm 3 months and 12 months after defibrillation with quinidine (70% and 50%) was significantly lower ($P < 0.0001$) than those of amiodarone (72.6% and 59.8%) while following administration of flecainide, the corresponding ratio (48.5% and 34%) was significantly much more lower than those of quinidine. Similar comparison of the recurrence ratio of atrial fibrillation over an average of 16 months among amiodarone, sotalol or propafenone disclosed that the recurrent ratio of amiodarone accounted for 35%, with the counterparts of sotalol and propafenone being 63% ($P < 0.001$), indicating a higher maintenance effect of sinus rhythm with administration of amiodarone. In the patients with chronic heart failure characteristic of presenting higher complication ratio with atrial fibrillation, the reduction ratio of heart rate during atrial fibrillation following administration of amiodarone accounted for 20% 2 weeks later and 14% even 12 months later, indicating a higher ratio relative to that with placebo ($P = 0.006$) while the recovery ratio from atrial fibrillation to sinus rhythm was 31% and 8% ($P = 0.002$), with the transition ratio from sinus rhythm to atrial fibrillation being 4.1% and 8.3%, respectively ($P = 0.005$), suggesting the effectiveness of amiodarone. These findings clearly indicate that the efficacy of K channel blockers is high in maintenance of sinus rhythm during lowered cardiac functions. As a natural consequence, the first-line therapy is Na channel blockers for defibrillation of atrial fibrillation and K channel blockers exert higher efficacy for maintenance of sinus rhythm. However, it is evident that the shorter the observation period the higher the prophylactic efficacy, and with higher dosage the preventive effect is also higher. In clinical situations, it is difficult to achieve complete suppression of atrial fibrillation over a longer period, whereby selection of antiarrhythmic agents and titration of doses should be independently decided according to the patient’s condition.

In these clinical studies on prevention of atrial fibrillation, comparison was made on the number of recurrent cases of atrial fibrillation to investigate the efficacy of antiarrhythmic agents. However, even if atrial fibrillation recurs, treatment with the antiar-
rhythmic agent was judged somewhat effective provided that the persistent period was obviously shortened or subjective symptoms were alleviated due to remarkable decrease in the incidences; therefore, treatment with the antiarrhythmic agent was usually continued. Considering these points, we compared efficacy of several antiarrhythmic agents which are currently used in Japan. In 60 patients of 63 years of average age presenting with paroxysmal atrial fibrillation, the efficacy ratios of pilsicainide, cibenzoline, pirmenol, and bepridil were assessed during the average observation period of $788 \pm 898$ days. In Figure 6, the results obtained disclosed that the efficacy ratios accounted for $57\%$ with pilsicainide, $31\%$ with cibenzoline, $33\%$ with pirmenol and $73\%$ with bepridil.31) In Japan, K channel blockers are less frequently used for prevention of atrial fibrillation because the coverage of the National Health Insurance System price for amiodarone is limited to use in patients with atrial fibrillation accompanied by hypertrophic cardiomyopathy. However, based on clinical results in Europe and America,12–15,21,29,30) application of K channel blockers is gradually increasing to include patients suffering from intractable atrial fibrillation. Considering this background, the enrolled patients were still
limited but we compared preventive effects of some antiarrhythmic agents possessing strong K channel blocking effects in intractable patients. If intractable patients are defined as those unresponsive to more than 3 kinds of antiarrhythmic agents, the ratios of intractable patients accounted for 50% with amiodarone, 40% with sotalol and 51% with bepridil.12 (Figure 7), deserving administration of K channel blockers to the nonresponders to Na channel blockers.

On selection of antiarrhythmic agents with the objective for defibrillation and maintenance of sinus rhythm, further consideration on the patient’s condition is required. In principle, antiarrhythmic drugs which were proved to be effective in defibrillation should be attempted for maintenance of sinus rhythm, whereby we have sometimes experienced that antiarrhythmic agents like aprindine and amiodarone indicative of lower defibrillation efficiency are effective in prevention of relapse. The factors for selection of antiarrhythmic drugs to prevent atrial fibrillation are as follows.

1) Non-elderly patients without underlying diseases: They can be treated with any antiarrhythmic agents including Ic class antiarrhythmic drugs characteristic of exerting effective defibrillation and maintenance of sinus rhythm. Any antiarrhythmic agents to which attending physicians are accustomed are acceptable. Mainly selected for this purpose are pilsicainide, flecainide, cibenzoline, disopyramide, pirmenol, quinidine, bepridil, propafenone, and aprindine.

2) Patients with lowered left ventricular functions (patients with heart failure): Aprindine and amiodarone which exhibit less suppression of cardiac function are selected. The Japanese guidelines indicate the selection of antiarrhythmic agents depends on cardiac function (Figure 8).

3) Patients with renal dysfunction: As first-choice drugs, quinidine, aprindine and amiodarone are to be selected because these antiarrhythmic agents are chiefly metabolized in the liver.

4) Patients with hepatic dysfunction: As first-line drugs, pilsicainide, pirmenol and disopyramide are selected as these antiarrhythmic agents which are excreted through the kidneys.

5) Patients whose atrial fibrillation occurs due to physical work or psychological tension: Usually β blockers are selected while propafenone possessing weak β blocking effects is also selected.

6) Patients whose atrial fibrillation occurs at night or while resting: Disopyramide, pirmenol and cibenzoline are selected because of their anti-cholinergic effects.

7) Patients resistant to multiple drugs: Bepridil or amiodarone and sotalol are considered for use.

Control of heart rates

Repeated paroxysmal atrial fibrillation is associated with increase of incidence as well as longer duration. Subsequently, it evolves into persistent atrial fibrillation which cannot be spontaneously terminated, leading to atrial fibrillation resistant to defibrillation. This progression represents the natural course of atrial fibrillation frequently encountered in clinical situations. During such a course, atrial fibrillation of more than 130/minute frequently occurs at onset and long-lasting persistence of atrial fibrillation with rapid heart rate associated with elevation of the left ventricular end-diastolic pressure results in presentation of congestive heart failure.16 In order to prevent this progression, rate control to reduce the heart rate down to 80–100/minute is required. Given the fact that both prevention of atrial fibrillation and maintenance of sinus rhythm play an important role in averting occurrence of complications, however, long-term administration of antiarrhythmic agents is needed to maintain sinus rhythm. Antiarrhythmic agents possess suppressive effects of cardiac function, arrhythmogenic effects and non-cardiac adverse reactions despite their variation in potency (Table 1). The CAST study found that arrhythmogenic effects of antiarrhythmic agents contributed to occurrence of lethal arrhythmia, whereby the prognosis in the medicated patients was worse than those in the non medicated patients with antiarrhythmic agents.33,34 Coupled with these findings, it is of interest to note that maintenance of 100% sinus rhythm is rather difficult to achieve by administration of antiarrhythmic agents;35 therefore, it is advocated that rate controls without medication clinically outweighs the pharmacological treatment in terms of prevention of heart failure. Indeed, three studies, PIAF,6 AFFIRM,7 and RACE,8 found that rate control is not worse than rhythm control in regard to mortality.

Either digoxin, Ca channel blockers or β blockers should be administered for control of heart rates because these drugs can suppress atrioventricular
nodal conduction. The DAAF study revealed that digoxin possessed weak effect for defibrillation but significantly reduced heart rate\(^3\) (Figure 9). The result of a comparison of the heart rate reducing effects in the patients with heart failure between diltiazem and verapamil as the Ca channel blockers, and placebo with use of Holter electrocardiogram,\(^3\) the respective heart rates were 88 ± 14 beat/min. with placebo, 76 ± 13 beats/min. with diltiazem 270 mg/day (\(P < 0.001\)) and 80 ± 11 beats/min. with verapamil 240 mg/day (\(P < 0.01\)), suggesting that both Ca channel blockers exhibited equipotent

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**Figure 8** Prevention of atrial fibrillation according to the Japanese guidelines for atrial fibrillation. (Reproduced with permission from reference 20).

**Figure 9** Digitalis in acute atrial fibrillation (DAAF) trial. Left panel shows time course of restoration to sinus rhythm, and right panel shows efficacy for heart rate during atrial fibrillation. (Represented with permission from reference 36)
suppression of conduction through atrioventricular node and improvement in exercise tolerance. \( \beta \) blockers also inhibit atrioventricular nodal conduc-
tion. Particularly, \( \beta \) blockers are recommended to be used in the patients who show elevation of heart rates during the daytime. In the ICU, intravenous administration of these drugs is usually used to improve subjective symptoms at early stages. Intra-
venous injection of digoxin provides the simplest application in the clinical situation because proce-
dures consist of dissolving digoxin 0.25 mg in one syringe either in 20 ml of saline or 5% glucose solution, followed by intravenous bolus injection for several minutes. Alternatively, there is another method comprising addition of one syringe of digoxin to 100 ml of intravenous solution and subsequent administration of the solution within 15–30 minutes. Given the fact that amiodarone and bepridil for defibrillation in the patients with lower cardiac functions lead to time-course decrease in heart rates during atrial fibrillation, it is conceivable that these drugs should be used with due care paid to adverse reactions. However, anticoagulant therapy should be attempted even in the patients who are classified to be treated with heart rate controls.

### Thromboembolism and cerebral infarction

Although atrial fibrillation is not a lethal arrhyth-
tmia, it cannot be clinically neglected from the major cause of cardiogenic cerebral infarction. The patients with atrial fibrillation are characterized with lowered blood flow both in the left atrium and the left atrial appendage, resulting in retention of blood flow in the left atrium and appendage, thereby causing fibrin thrombus. Medication with anticoagulants is effective in prevention of such thrombus formation. According to the large-scale clinical studies in Europe and America which compared efficacies on prevention of cerebral infarction in the patients with atrial fibrillation between warfarin as anticoagulant and aspirin as antiplatelet agent, warfarin was superior to aspirin.\(^{30}\) Although aspirin is effective, warfarin as an anticoagulant exerts higher efficacy in prevention of thromboembolism. The effect of warfarin appears approximately 4 to 5 days after initiation of oral administration. When prompt efficacy is expected, administration of heparin as anticoagulant is required.

The dosages of warfarin should be independently titrated according to individual patients; accordingly, its dosage is adjusted based on either thrombotest or prothrombin time. The efficacy of warfarin is represented as international normalized ratio (INR). In SPAF III a large-scale clinical study in Europe and America,\(^{30}\) comparison was made between the warfarin group whose INR was adjusted to the levels of 2.0 to 3.0 and the combination therapy group in which warfarin at the fixed initial dose (1.2 to 1.5 as the INR) and aspirin at the dose of 325 mg were concomitantly administered. The results obtained in this study revealed lower prevalence of embolism in the group with higher INR levels, leading to firm contention that warfarin is not effective unless INR was more than 2.0. On the other hand, taking into account the findings that most of patients with hemorrhagic complications due to warfarin administration in EAFT\(^{40}\) were found to show INR at levels of more than 5.0, care should be exercised to avoid raising the INR level to more than 5.0. Therefore, it has been perceived in Europe and America that warfarin administration at doses of INR 2.0 to 3.0 is effective in prevention of cerebral embolism.

**Appropriate patients indicated for anticoagulant therapy**

There are several issues as to whether anticoagu-
lants should be administered to all the patients with atrial fibrillation. According to the results obtained by large-scale clinical studies, in principle, warfarin administration is recommended to all patients of more than 65 years of age to prevent embolism secondary to non valvular atrial fibrillation whereas even in the patients of less than 65 years of age, warfarin medication is advocated if they have a past history of hypertension, diabetes mellitus, embolism or temporary cerebral ischemia attacks, as well as underlying heart diseases. It is recommended to administer aspirin 325 mg to the patients who are inappropriate to be medicated with or contraindicated to warfarin. However, these findings were obtained in European and American subjects, indicating that we must separately investigate to which levels warfarin dosage should be titrated for treatment of a Japanese population characterized by a trend toward a greater susceptibility to hemorrhage. We have a concern about long-term administration of aspirin to Japanese people suffering from gastro-
intestinal disorders. Clinical study by Yamaguchi\(^{41}\) on prevention of secondary cerebral infarction evidenced that warfarin at the INR levels of 1.5 to 2.1 was found effective in prevention of cerebral infarction, whereby we think that INR should be adjusted to 1.5 to 2.1 for Japanese patients.

In addition, it is also recommended that upon
defibrillation of paroxysmal atrial fibrillation lasting for more than 3 days and persistent atrial fibrillation responsive to defibrillation, warfarin is administered 3 weeks prior to defibrillation, followed by additional warfarin medication for 4 weeks after restoration to sinus rhythm. However, there is a concern about the possibility that atrial remodeling (i.e. atrium becoming vulnerable to onset of atrial fibrillation) might progress in parallel with administration of warfarin for as long as 3 weeks before defibrillation, thereby lending some support to the suggestion that prompt defibrillation should be performed. Under these situations, it is conceivable that defibrillation with heparin as an anticoagulant for intravenous use and simultaneous medication with warfarin are really warranted.

In this connection, transesophageal echocardiography is also recommended to achieve early defibrillation. Even in the patients with long-lasting atrial fibrillation, early defibrillation is feasible unless transesophageal echocardiography reveals spontaneous echo contrast or thrombus clot either in left atrium or left atrial appendage. In reality, there is a possibility that atrial stunning after defibrillation contributes to occurrence of thrombus clot after defibrillation; therefore, for prevention of these secondary complications, anticoagulant therapy should be strictly conducted after defibrillation. Naturally, if transesophageal echocardiography detects thrombus, defibrillation should be discontinued and we must wait until thrombus clot is dissolved by warfarin treatment. As is obvious from the above, the advantage of performing transesophageal echocardiography exists only on confirmation of absence of thrombus clot either in left atrium or left atrial appendage just before defibrillation. One must keep in mind that absence of thrombus clot does not necessarily guarantee successful prevention of embolism after defibrillation.

**Conclusions**

This article deals with pharmacological treatment for atrial fibrillation according to pharmacological defibrillation, maintenance of sinus rhythm, heart rate control and antiembolism therapy. In addition, ACE inhibitors to prevent atrial remodeling or ARB are currently used in clinical situations. One should select appropriate drugs for pharmacological treatment of atrial fibrillation based on definite objectives.

**References**