The guidelines for pharmacotherapy of arrhythmia in Japan are based on the concepts of the Sicilian Gambit. The Sicilian Gambit is a project that was established to consider optimal antiarrhythmic drug treatment during the period of time when the results of the Cardiac Arrhythmia Suppression Trial (CAST) published in 1989 caused concerns regarding the safety of antiarrhythmic drugs throughout the world. The members of the project hold four meetings during the period from 1990 to 2000. The new concepts developed at the meetings of the Sicilian Gambit have significantly affected the preparation of guidelines in Japan. In April 1996, the Japanese Section of the Sicilian Gambit was established through the support of the Japan Heart Foundation, and initiated its dissemination of the concepts of the Sicilian Gambit. Immediately after the third meeting of the Sicilian Gambit in October 1996, the Japanese Society of Electrocardiology established “the Committee for Guidelines for Antiarrhythmic Drugs”. In April 1997, “the Task Force for Preparation of Guidelines for Selection of Antiarrhythmic Drugs according to the Sicilian Gambit” was established and began its activities. The Task Force published a guidelines CD-ROM in 2000, on the basis of which the Guidelines for Pharmacotherapy of Atrial Fibrillation in 2001 were created.

In Europe and the United States, the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) jointly published the Guidelines for the Management of Patients with Atrial Fibrillation in 2001, and revised them in 2006. These guidelines, however, include little related to the concepts of the Sicilian Gambit. The ACC/AHA/ESC Guidelines highlight evidence-based recommendations, though the logical rationales supplied for selection of antiarrhythmic drugs are
rather poor. It is important to select antiarrhythmic drugs based on logical rationales for the treatment of arrhythmia disorders, especially atrial fibrillation (AF), the mechanisms of onset and pathophysiology of which have recently become clearer.

Figure 1 shows an example of how drugs are selected for the treatment of AF according to the concepts of the Sicilian Gambit. First, the mechanism of AF is considered random reentry. Then refractory period of atrial myocardium is identified as the most likely vulnerable parameter from among the electrophysiological properties required to maintain random reentry. Since the targets for prolonging refractory period are sodium channels and potassium channels, sodium and potassium channel blockers should be selected for this case of AF. Then appropriate drugs are selected from a list of drugs (Figure 2) based on cardiac, renal, and hepatic function and concomitant drug use by individual patients to ensure the safety of treatment. Recent findings have indicated that abnormal automaticity in the pulmonary vein may trigger the development of AF, and treatments targeting this may become available.

Recent basic studies have demonstrated that continuation of AF induces progression of electrical remodeling of the atrial myocardium and modification of ion channels targeted by antiarrhythmic drugs, which may decrease the efficacy of such drugs over time. Effective treatment of AF requires the clinical application of these findings of basic studies in humans. Sodium channels are the best target of treatment during the early stages after the development of AF. However, since sodium channels are down-regulated as remodeling progresses, the efficacy of sodium channel blockers decreases over time, and conduction disorder may worsen further, inducing arrhythmia. At this stage, sodium channel blockers should be replaced by drugs which predominantly block the potassium channels. It is known that potassium channels are not significantly down-regulated during remodeling processes. Physicians should utilize the guidelines most efficiently by understanding the pathophysiological characteristics of AF in individual patients and their degree of progression of remodeling of ion channels.

As noted above, the selection of drugs in the Guidelines for Pharmacotherapy of Arrhythmia in Japan is not evidence-based and instead based on the concepts of the Sicilian Gambit and the efficacy and safety of treatment according to the Sicilian Gambit have yet to be demonstrated. This is the most important weakness of the guidelines in Japan, although specialists in arrhythmia treatment who participated as members of the Guideline Committee verified the concepts of the Sicilian Gambit sufficiently during preparation of the guidelines and confirmed that treatment according to to does not differ significantly from pharmacological treatment provided by specialists based on their own experience. In March 2007, the results of the J-RHYTHM study, a nation-wide clinical study in patients with AF in Japan begun in 2003, demonstrated the validity of the guidelines in Japan. The J-RHYTHM study also represented current treatment of AF with antiarrhythmic drugs as well as anticoagulation in Japan.

In preparing the completely revised “Guidelines for Pharmacotherapy of Atrial Fibrillation”, we attempted to include the current basic and clinical findings and the findings of the J-RHYTHM study. The chapter on specific methods of treatment begins with antithrombotic therapy, which is positioned as the most important strategy during treatment of AF. Following the 71st Annual Meeting of the Japanese Circulation Society in March 2007, Nikkei Medical Online conducted an Internet-based survey on the penetration of guidelines for the diagnosis and treatment of cardiovascular diseases, which revealed that “the Guidelines for Pharmacotherapy of Atrial Fibrillation” were the most widely used, by 56% of respondents (73% of cardiologists). This high degree of interest in the pharmacotherapy of AF reflects the fact that AF treatment is often difficult in the clinical setting. We hope that the present guidelines will satisfy the needs of practitioners.

Treatment must be individualized by making the most of knowledge and skills accumulated through clinical experience. However, physicians may differ in their experience and knowledge, and each patient has his or her own unique pathophysiological characteristics. It is impossible to prepare treatment guidelines applicable for all patients, and evidence obtained in large-scale clinical studies cannot be used efficiently in individualized treatment. The guidelines in Japan, which have prepared been on the basis of the advanced concepts described in the Sicilian Gambit, yield an optimal approach to highly individualized treatment of AF. In the present guidelines, however, we assigned classifications of recommendations and evidence levels based on the guidelines of the Science Committee of the Japanese Circulation Society. Although evidence in Japan on the efficacy of the treatment for patients with AF has yet to accumulate to a sufficient extent, this is our first attempt to combine the concepts of the Sicilian Gambit and evidence-based medicine. Recommendations for selection of drugs were partially modified in the present guidelines. Some recommendations are not consistent with the Sicilian Gambit, and the reasons for modifications are described individually. We hope that accumulation of further findings will demonstrate the validity of selection of drugs according to the concept of the Sicilian Gambit, and that the guidelines will be revised according to the results of validation.
The present guidelines include as options of drugs that are currently not covered for the use for AF by the National Health Insurance (NHI) in Japan but are expected to be effective based on evidence obtained in Europe and the United States or clinical experience in Japan (e.g., amiodarone for patients with AF associated with heart failure and bepridil for patients with long-lasting AF), and exclude drugs that are covered by the NHI but have rarely been used in clinical practice.

Lastly, as with any guidelines, the present ones provide “guidance” for selection of treatment options by practitioners, who must understand the pathophysiological characteristics of AF in each patient and determine the optimal treatment strategy for him or her accordingly. It should be noted that determination of treatment by attending physicians based on the specific conditions and circumstances of their patients should take precedence over the guidelines, and that the present guidelines provide no grounds for argument in cases of legal prosecution.

---

**Table:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ion channels</th>
<th>Receptors</th>
<th>Pumps</th>
<th>Clinical efficacy</th>
<th>ECG finding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>Med</td>
<td>Slow</td>
<td>Ca</td>
<td>K</td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procainamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprindine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cibenzoline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirmenol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecaainide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilsicainide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bepridil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifekalant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Framework for classification of drugs proposed in the Sicilian Gambit (Japanese version). Relative blocking potency: ○ low; ● moderate; ● high; A, activated state channel blocker; I, inactivated state channel blocker; $\alpha$, agonist; ATP, adenosine triphosphate; LV, left ventricular; ECG, electrocardiogram. Modified from Members of the Sicilian Gambit, Antiarrhythmic therapy: a pathophysiologic approach. New York: Futura Publishing Company, Inc; 1994.
I Epidemiology of AF

The prevalence of AF increases with age. Epidemiological surveys in North America and Western Europe have indicated that the prevalence of AF increases very slowly with age in people under 60 years of age, and that it is less than 2% in people in their early 60s. The prevalence then increases significantly in more elderly people to 9 to 14% in the general population over 80 years of age. Although some surveys have reported no difference between sexes, many studies have reported that the prevalence of AF is higher in men than in women. In Japan, the results of a national survey of randomly sampled populations in different areas in Japan and an epidemiological survey conducted by the Japanese Circulation Society indicated that the prevalence of AF increases slowly up to 60 years of age to approximately 1% of the general population, and that the increase beyond 70 years of age is slower than in Western countries. The prevalence of AF is only around 3% in the general population over 80 years of age in Japan. Male patients are strongly predominant in Japan. The types and prevalences of diseases underlying AF differ between Japan and Western countries, as well. Recent studies in North America and Western Europe have reported that hypertension is observed in about half of patients and ischemic heart diseases in one out of three or four patients with AF, while valvular heart disease is uncommon. In Japan, the prevalences of hypertension, ischemic heart disease, and valvular heart diseases in patients with AF are about 30%, 10%, and 20%, respectively, and substantially different from those in Western countries. Lone AF accounts for one out of three or four patients with AF in Japan and about 30% in one study and 10 to 19% in another study in Western countries. Risk factors for the development of AF that have been identified in studies in Western countries include aging, diabetes mellitus, hypertension, cardiac diseases (ischemic and valvular heart diseases), heart failure, excessive alcohol consumption, and obesity, while those specified in the Hisayama Study, an epidemiological survey in Hisayama town, Kyushu, Japan include aging, heart diseases (ischemic and valvular diseases), and alcohol consumption.

II Pathophysiology of AF

1. Pathophysiology of AF

AF is characterized by uncoordinated and rapid irregular atrial activation with loss of the contribution of atrial contraction to ventricular filling, resulting in decrease in cardiac output. This causes hemodynamic impairment and exacerbation of heart failure. A persistently rapid ventricular rate may cause tachycardia-induced cardiomyopathy. In addition, AF decreases atrial blood flow velocity, which may cause intra-atrial thrombogenesis.

2. Initiation and Maintenance of AF

Recent studies have demonstrated that paroxysmal AF is often triggered by abnormal excitability emanating from sleeves of the atrial myocardium extending into the pulmonary veins. Abnormal excitability in the superior vena cava and the vein of Marshall may also trigger paroxysmal AF. It is supposed that rapid ectopic activity originating from the pulmonary veins is conducted into the atrium, and contributes to the initiation and maintenance of AF. Electrical isolation techniques using catheter ablation have been developed to eliminate the electrical connections between the affected pulmonary veins and the atrium, and have proven effective in the treatment of paroxysmal AF.

3. Substrates of AF

The longer the duration of AF, the more the refractory period of atrial myocardium shortens. This is referred to as electrical remodeling of the atria, and is caused by a decrease in calcium influx current and an increase in potassium efflux current in the early stages and by modification of expression of ion channel-related genes and other atrial myocardium-related genes in later stages. In patients with AF, the refractory period of atrial myocardium is short immediately after recovery to sinus rhythm and gradually returns to normal over 24 hours. Electrical remodeling both induces and maintains AF. Persistence of AF may eventually result in structural remodeling of the atria as a result of effects of the renin-angiotensin system (RAS) and oxidative stress. Gap junctions in atrial myocardium are also altered in patients with AF. This electrical and structural remodeling results in atrial stunning, i.e., atrial systolic dysfunction. Atrial stunning resolves within several days or months, during which time patients exhibit increased susceptibility to thrombus formation in the atria.

4. Underlying Diseases

Some diseases are frequently associated with AF. AF without underlying cardiac diseases is referred to as lone AF. The pathophysiology of familial AF is now being established. At the onset of AF, (1) mechanical load on the left atrium, (2) autonomic nervous system activity, and (3) changes in ion channels in the atrial myocardium are involved simultaneously or in sequence as substrates for the development of AF. Hypertension is a major risk factor for new-onset AF, and it has been demonstrated that appropriate antihypertensive treatment, especially with RAS inhibitors, decreases the incidence of new-onset AF.

In patients with hyperthyroidism and those with familial AF, altered or abnormal expression of potassium channel-related genes promotes the development of AF.

5. Types and Clinical Significance of AF

AF is classified by its duration of continuation, into paroxysmal, persistent, and permanent AF. May progress from paroxysmal to chronic AF, and then eventually to permanent AF.
AF. During AF, a decrease in cardiac output may occur due to loss of atrial contraction. Patients with AF thus experience easy fatigability during effort including exercise. In patients with poor cardiac function or those with hypertrophic cardiomyopathy, AF may significantly exacerbate heart failure and induce pulmonary congestion.

In patients with AF, ventricular rate may increase abruptly during exercise, resulting in easy fatigability and poor exercise performance. AF may cause left heart failure in elderly patients and those with poor cardiac function. A persistently elevated ventricular rate during AF can produce cardiomyopathy. In patients with Wolff-Parkinson-White (WPW) syndrome, AF may in rare cases lead to ventricular fibrillation. AF may cause low blood flow velocity in the atrium and changes in expression of the genes for thrombomodulin and plasminogen activator inhibitor-1 (PAI-1) and other mediators in the atrial endothelium, resulting in the formation of left atrial thrombi which may induce cerebral embolism. Patients with AF are treated according to the type and pathophysiology of AF.

### III Electrophysiological Mechanism of AF

#### 1. Mechanism of Onset of AF

When atrial action potentials are recorded during AF, irregular, very fast, and uncoordinated activation is observed in many segments. This abnormal activation is believed to be due to a focal mechanism, ie, abnormal focal excitability (automaticity), and random reentry of multiple wavelets.

**1 Focal Mechanism**

The focal mechanism is characterized by rapidly abnormal firing atrial foci and fibrillatory conduction in the atria. Electrophysiologically, it is similar to atrial tachycardia. On clinical grounds, focal AF originating from the atrium or vena cava is believed to be due to a focal mechanism. On the other hand, about 90% of cases of frequent atrial premature contractions observed in patients with paroxysmal AF originate in the pulmonary veins. Short runs of atrial premature contractions may lead to a rapidly firing driver, which can cause fibrillatory conduction and eventually AF. In addition, premature contractions originating in the pulmonary veins may trigger reentry in the atrium, causing AF. It has been suggested that the development of premature atrial contractions originating in the pulmonary veins and a rapidly firing driver result from triggered activity in the pulmonary veins or reentry in the region of the junction of the left atrium and pulmonary vein.

**2 Reentry of Multiple Wavelets**

In an experiment using Langendorff-perfused hearts in which AF was induced under infusion of acetylcholine, focal activations were observed simultaneously at least 3 to 6 foci in the atrium. Some of these simultaneously circulating wavelets may disappear and the others split into branches, causing random reentry which continues to maintain AF. Reentry of multiple wavelets has also been observed during AF induced in a model of sterile epicarditis. The role of reentry in the development of AF is still unclear anatomically, and reentry may result from functional barriers such as refractory period and anisotropic conduction. Various types of reentry such as leading circle reentry, anisotropic reentry, and spiral reentry have been experimentally identified.

#### 2. Electrical and Structural Remodeling

Reentry of multiple wavelets will occur only when the excitation wavelength is short enough or the atria are large enough. The latter case, of atrial enlargement, is mainly observed in patients with severe valvular disease and functions as an anatomic substrate of AF. In patients without atrial enlargement, short excitation wavelength is a substrate for the development of AF. Since excitation wavelength is determined by the product of conduction velocity and refractory period, the conduction velocity must be slow or the refractory period must be short enough to maintain AF. Allessie et al have proposed the concept of “AF begets AF@”, according to which AF (tachycardia) shortens the atrial refractory period (this change is referred to as electrical remodeling), making possible the reentry of multiple wavelets. This is an important factor in the induction of chronic AF. It has been proposed that electrical remodeling develops through the accumulation of intracellular calcium ions, a decrease in calcium-membrane current, and decreased duration of the action potential. When tachycardia persists, the excitation wavelength decreases further due to down-regulation of ion channels and a decrease in conduction velocity due to a decrease in sodium current.

When AF persists for a long period of time, structural changes such as hypertrophy and fibrosis of the atrial myocardium and altered gap junctions may occur (these changes are referred to as structural remodeling). Fibrosis will decrease conduction velocity and increase the heterogeneity of conduction, making the atria susceptible to reentry. In patients with AF complicated by organic heart disease, atrial structural remodeling tends to progress further, and AF tends to develop more frequently and to persist for long periods of time. Renin-angiotensin-aldosterone (RAA) system inhibitors can inhibit AF by inhibiting atrial fibrosis.

### IV Clinical Picture

#### 1. Classification of AF

Since AF is a chronic progressive disease with a variety of clinical pictures and there is uncertainty regarding diagnosis of AF due to methodological and time-dependent factors, accurate classification of AF may not be clinically useful. Given the long-term natural history of AF, in which episodes terminate spontaneously in the early stages, increase in duration and incidence over time, as they repeat and even-
Paroxysmal AF returns to sinus rhythm within 7 days (within 48 hours in many cases) with or without pharmacological or non-pharmacological treatment, and is observed during the early phases of chronic AF. Although in many cases patients with AF respond well to pharmacotherapy early after onset, they tend to become unresponsive to pharmacotherapy later. In a long-term observational study, in which patients with AF were followed for 15 years on average, paroxysmal AF progressed to persistent AF average of 5.5%/year in patients receiving Class I drugs. Independent risk factors for progression to persistent AF appeared to be age, left atrial diameter, history of myocardial infarction, and valvular disease in a study using multivariate analysis, and age, left atrial diameter, heart failure, diabetes mellitus, cardiothoracic ratio, f wave amplitude in lead V1, and left ventricular ejection fraction in a study using univariate analysis.

Patients with poor QOL due to paroxysmal AF should be treated with antiarrhythmic drugs to prevent episodes of AF. However, the duration of pharmacotherapy needed to maintain sinus rhythm should be determined for individual patients based on comprehensive evaluation of the duration of treatment, background characteristics, and feasibility of non-pharmacological treatment with catheter ablation. Patients should continue anticoagulation based on their risk of cerebral infarction regardless of whether the treatment selected is designed to maintain sinus rhythm or to control heart rate.

### 4. Persistent AF

Persistent AF is defined as an episode of AF lasting longer than 7 days. It is difficult to distinguish persistent AF from permanent AF when neither pharmacological nor electrical cardioversion is performed. Although persistent AF cannot be treated with pharmacological cardioversion except when certain types of antiarrhythmic drugs are used, patients respond well to electrical cardioversion, and 94% of them return to sinus rhythm. However, AF frequently recurs after cardioversion; the percentages of patients who remain in sinus rhythm with common pharmacotherapy are about 50% at year 1, 40% at year 2, and 30% at year 3. The rate of recurrence differs depending on patient characteristics, and known risk factors for recurrent AF include age, hypertension, heart failure, and duration of AF episode. Cardioversion followed by maintenance of sinus rhythm is considered appropriate treatment for patients with poor QOL without known risk factors. For other patients, heart rate control and anticoagulation based on the risk of cerebral infarction are also acceptable options of AF treatment.

### 5. Permanent AF

Permanent AF is defined as AF not responding to pharmacological or electrical cardioversion. Common policies of treatment for permanent AF aim at preventing possible sequelae of it rather than controlling AF itself, and perform heart rate control and anticoagulation based on the risk of cerebral infarction.
V Treatment

1. Treatment Strategies Specific to Underlying Diseases

In the treatment of AF, it is important to target improvement of controllable underlying diseases other than arrhythmia. Patients with cardiac dysfunction and ischemia should thus be treated for such diseases before considering whether antiarrhythmic treatment is necessary. During treatment, control of thromboembolism should be appropriately performed.

1 Valvular Heart Disease

With the prevalences of rheumatic fever and syphilis, which are major causes of valvular heart disease, have decreased, patients with valvular heart disease now often have regurgitation or stenosis due to mitral valve prolapse and bicuspid aortic valve, among other diseases. In addition to deterioration of cardiac hemodynamics, degeneration of the atrial myocardium due to underlying diseases is also believed to be involved in the development of AF. AF develops especially frequently in patients with mitral valve stenosis, and is often associated with aortic valve insufficiency and mitral valve insufficiency.

When AF develops in patients with valvular heart disease, there is further deterioration of cardiac hemodynamics and thromboembolism occurs more frequently. It is thus important to prevent the development of AF in such patients. Physicians should consider surgical treatment of valvular heart diseases such as valve replacement/valvuloplasty before atrial remodeling progresses. In patients with valvular heart diseases and AF, use of the Maze procedure or Radial incision approach to reestablish and maintain sinus rhythm is recommended. Long-term treatment with Class I antiarrhythmic drugs is not recommended. Patients should aggressively undergo upstream treatment to prevent atrial remodeling through improvement of cardiac function.

2 Hypertension

It has long been pointed out that there is a strong association between hypertension and AF. In clinical studies in patients with AF, hypertension was found to be a major cause of AF in about 60% of participants. In the J-RHYTHM study, hypertension was observed in 42.8% of patients with paroxysmal AF and 44.2% in patients with persistent AF. Development of AF may possibly be prevented by early treatment of hypertension to ensure appropriate blood pressure control. Prevention of remodeling of the atria and pulmonary veins due to hypertension is an important upstream treatment in controlling the substrates of AF. Indeed, it has been reported that treatment with angiotensin II receptor blockers (ARBs) may prevent the onset of AF in hypertensive patients.

Blood pressure control is important in patients with any type of AF, and high blood pressure should not be ignored during treatment of AF. Hypertension may facilitate the development and maintenance of AF and increase the risk of thromboembolism. It is recommended that hypertensive patients with AF should be treated mainly with ARBs or angiotensin converting enzyme (ACE) inhibitors, and combinations of different types of antihypertensive drugs may be needed to ensure sufficient antihypertensive efficacy. Prevention of recurrent AF with Class I antiarrhythmic drugs may be effective in patient without cardiac dysfunction.

3 Coronary Artery Disease

AF induces deterioration of clinical condition in patients with angina pectoris and myocardial infarction by increasing heart rate and decreasing cardiac output. The prevalence of coronary artery disease in AF patients is about 30% in Western countries but less than 10% in Japan. Treatment targeting AF alone is potentially dangerous in such patients. Basically, improvement of myocardial ischemia should be prioritized. AF complicated by acute coronary syndrome should be treated with cardioversion whenever necessary, though Class I antiarrhythmic drugs are not recommended for this purpose. Although Class III drugs such as sotalol and amiodarone are preferable, use of them in patients with acute coronary syndrome is not covered by the NHI in Japan. Particularly in patients with left heart dysfunction, ACE inhibitors and ARBs should be used aggressively from the early stage to prevent not only left ventricular remodeling but also left atrial remodeling.

4 Heart Failure (Left Heart Dysfunction)

AF often develops in patients with poor cardiac function due to cardiomyopathy and coronary artery disease. It has been demonstrated that the prevalence of AF is higher in patients with poorer heart function as measured by the New York Heart Association (NYHA) Functional Classification. Although AF may promote further deterioration of cardiac function and is thus an unfavorable condition in patients with cardiac dysfunction, prevention of AF with antiarrhythmic drugs that block sodium channels is not recommend, since they may worsen the prognosis of such patients. Since the incidence of thromboembolism is high in patients with AF complicated by heart failure, if not contraindicated, anticoagulation should be promptly initiated and treatment should focus on improving cardiac function. It has been reported in clinical studies of patients with left heart dysfunction that ACE inhibitors and ARBs are effective in preventing the development of AF, and these drugs are expected to be effective for this purpose.

5 Dilated Cardiomyopathy

Dilated cardiomyopathy is characterized by dilatation and impaired systolic function of the left ventricle due to degeneration of cardiomyocytes and interstitial fibrosis. Since dilated cardiomyopathy causes increases in left atrial pressure and left atrial dimension due to chronic left ventricular dysfunction, the incidence of AF in patients with dilated cardiomyopathy is reported to be 20 to 30%. AF promotes heart failure, increases the risk of thromboembolism, and worsens the prognosis of dilated cardiomyopathy. In patients with AF and dilated cardiomyopathy, heart rate control should be prioritized to maintain cardiac function and prevent the progression of heart failure. Patients with chronic heart failure require stabilization of hemodynamics and prevention of thromboembolism.

6 Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is characterized by development of left ventricular hypertrophy. In patients complicated by left ventricular outflow tract obstruction, AF may cause an abrupt decrease in cardiac output, which may progress to ventricular fibrillation. The incidence of AF is as high as more than 10 to 20%, and although electrical cardioversion is
7 Chronic Respiratory Disease
It is important to treat hypoxemia and acidosis in AF in patients with chronic respiratory disease. Bronchodilators may induce AF. Heart rate control should be initiated using verapamil and diltiazem. Electrical cardioversion is indicated for AF in patients with hemodynamic instability. Beta-blockers that may worsen underlying respiratory disease, and theophylline, which may increase the likelihood of development of AF, should be avoided.

8 Hyperthyroidism
It has long been known that hyperthyroidism can induce AF. Normalization of thyroid function should thus be prioritized, and AF should be treated with β-blockers to control heart rate. When β-blockers cannot be used, verapamil and diltiazem should be administered. AF often terminates spontaneously (in about 70% of patients) after normalization of thyroid function. Cardioversion is indicated for patients with a long history of AF and patients who have not returned to sinus rhythm for at least 3 months after normalization of thyroid function. In these cases, electrical cardioversion following antiarrhythmic and preventative treatment with antiarrhythmic drugs are necessary.

9 WPW Syndrome
In patients with WPW syndrome and short anterograde refractory period of the accessory pathway, ventricular fibrillation may develop shortly after the development of paroxysmal AF. Careful monitoring for this is essential. It should also be noted that AF may result in sudden death in patients with WPW syndrome. The incidence of AF in patients with WPW syndrome is believed to be 15 to 30%. Patients with a shortest RR interval during AF of ≤250 msec are at high risk of sudden death. Catheter ablation of accessory pathways is the first-line treatment for patients with WPW syndrome and AF. When pharmacotherapy is administered, use of digitalis and calcium channel blockers other than dihydropyridines that impair conduction through the atrioventricular (AV) node should be avoided, since these drugs may speed conduction into the accessory pathway. Class I antiarrhythmic drugs with low anticholinergic activity may be used.

10 Sick Sinus Syndrome
In patients with bradycardia-tachycardia syndrome, a variant of sick sinus syndrome, paroxysmal AF may be followed by sinus arrest. Treatment of bradycardia should in principle be prioritized in such patients, and pacemaker implantation should be performed if required. Treatment of AF as a manifestation of tachycardia may be performed using antiarrhythmic drugs after pacemaker implantation. Appropriate atrial pacing is expected to decrease the incidence of AF. The risk of thromboembolism is high and anticoagulation is required.

11 AF in Elderly Patients
Many epidemiological surveys have indicated that the prevalence of AF increases with age. The prevalence of asymptomatic AF is also high, and it has been recommended that upstream treatment using ARBs, ACE inhibitors, and statins rather than antiarrhythmic treatment be aggressively performed. Heart rate control should be performed as required to maintain cardiac function. Hepatic and renal dysfunction should be considered in optimizing pharmacotherapy. It is important to note that aging is an independent major risk factor for thromboembolism and that anticoagulation is in principle required for elderly patients.

12 AF in Children
Although AF is rare in children, it may occur following surgery for congenital heart disease. Since excessive atrial overload is a major factor in inducing AF, management and treatment of primary diseases and cardiac function are necessary.

13 AF During Pregnancy
No drugs for the treatment of AF have been demonstrated to be safe during pregnancy. Pregnant women with AF complicated by heart failure should be treated to decrease heart failure and control heart rate for AF. Pregnant women should not receive ACE inhibitors and ARBs for the treatment of heart failure. Although appropriate measures differ by the type of underlying diseases, delivery by pregnant women with paroxysmal AF is generally possible without treatment to prevent recurrence of AF.

14 Lone AF
Lone AF was previously defined as AF without evidence of underlying diseases, but is now defined as AF without clinical or echocardiographic evidence of underlying diseases such as cardiopulmonary disease and thyroid disease and without hypertension. Although the prognosis of lone AF is generally considered favorable, the risk of cerebrovascular disorder in patients with it is high and the incidence of cerebrovascular disorder increases in patients over 60 years of age. It has been suggested that being up to 60 years of age should be added to the criteria for diagnosing lone AF. The percentage of patients with lone AF among those with AF has ranged between 2.1 to 32% in various studies. The size of this range may be explained by differences in the diagnostic criteria used in these studies and the advancement of diagnostic techniques. Since lone AF is a collective term for AFs for which definitive factors contributing to the development of arrhythmia could not be detected at the time of diagnosis of AF and it may subsequently be possible to clarify the reasons for its development, it is sometimes suggested that the term lone AF not be used.

2. Guidance of Pharmacotherapy According to the Results of the J-RHYTHM Study
Treatment strategies for AF have been based on the concept that maintenance of sinus rhythm will improve symptoms and exercise tolerance, decrease the risk of development of cerebral infarction, enable discontinuation of anticoagulation, and improve prognosis. However, the results of large-scale clinical studies in Europe and the United States (such as the Pharmacological Intervention in Atrial Fibrillation [PIAF], Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM], Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation [RACE], Strategies of Treatment of Atrial Fibrillation [STAF]) published in 2000 or later have not supported it, and have emphasized that...
anticoagulation should be continued for life in high risk patients with AF even when sinus rhythm can be maintained, and that heart rate control can provide sufficient improvement of QOL and is a safer method of treatment than antiarrhythmic treatment, considering the adverse drug reactions (ADRs) to antiarrhythmic drugs. In fact, serious ADRs may develop during treatment with antiarrhythmic drugs to maintain sinus rhythm, and antiarrhythmic treatment cannot maintain sinus rhythm for a long period of time and may lead to continuous and chronic AF in many patients. There are many patients with chronic AF in whom sufficient clinical efficacy is obtained only with heart rate control and anticoagulation. However, many clinicians realize that heart rate control is ineffective in patients who experience severe discomfort subjective symptoms during paroxysmal episodes of AF. The numbers of patients with paroxysmal AF included in the PIAF, AFFIRM, RACE, and STAF were very small. Although 30% of patients evaluated in the AFFIRM had paroxysmal AF, these patients were analyzed together with those with persistent AF. There are marked differences in the types of drugs and guidelines for use of antiarrhythmic treatment to maintain sinus rhythm between Western countries and Japan. In the AFFIRM, amiodarone, which may feature serious ADRs, was used in nearly 70% of patients evaluated. This drug could negatively impact the efficacy of treatment to maintain sinus rhythm. In the guidelines in Europe and the United States, which place great emphasis on clinical evidence, drugs that have not been proven effective in large-scale clinical studies are ranked low, and these guidelines do not consider selection of drugs on the basis of recently obtained findings regarding the mechanism of onset and pathophysiology of AF. In Japan, the J-RHYTHM study was conducted to compare the effects of sinus rhythm maintenance and heart rate control in patients with paroxysmal AF and persistent AF who received antiarrhythmic drugs according to guidelines specifically designed in Japan.

The J-RHYTHM study was the first large-scale prospective multicenter randomized controlled clinical study in patients with arrhythmia initiated by the Japanese Society of Electrophysiology. The study was initiated in January 2003, and the results of it presented at the Annual Meeting of the Japanese Circulation Society in March 2007 demonstrated the appropriateness of the Japanese treatment guidelines for patients with AF, and especially those with paroxysmal AF. The report of the J-RHYTHM study will be published elsewhere. Its contents are briefly described below. Following registration of the first patient in January 2003, a total of 1,065 patients (885 patients with paroxysmal AF and 180 patients with persistent AF) in 182 institutions were registered during the 2.5-year period up to June 2005. This study is the first in the world to compare sinus rhythm maintenance and heart rate control in more than 800 patients with paroxysmal AF. Following informed consent in writing, patients were randomly allocated to a sinus rhythm maintenance group or a heart rate control group. Eligible patients included those with paroxysmal AF who had sinus rhythm at baseline and those with persistent AF who exhibited AF at baseline. In patients with persistent AF in the sinus rhythm maintenance group, cardioversion was performed for return of sinus rhythm prior to initiation of the study.

Use of antiarrhythmic drugs according to the guidelines in Japan was recommended for patients in the sinus rhythm maintenance group, and the target heart rate at rest was set at 60 to 80 bpm in the heart rate control group. Patients were...
evaluated for 3 years for the occurrence of endpoints and ADRs. Primary endpoints were death, symptomatic cerebral infarction, systemic embolism, massive bleeding, and hospitalization due to heart failure, as well as “intolerance of allocated basic treatment method”. The latter measure included the occurrence of intolerable subjective symptoms, aversion to repeated electrical cardioversion, and anxiety regarding ADRs. Intolerance of treatment is a “soft endpoint” that may reflect subjective evaluation by the attending physician, and may or may not be appropriate as an endpoint. However, QOL assessment was also performed in the study to objectively evaluate tolerability of treatment, and analysis of these factors was considered important. The results of the study revealed that “tolerability” of treatment is the most important measure in the treatment of AF, especially paroxysmal AF.

Patients with paroxysmal AF were a mean age of 64.7 years in the J-RHYTHM study, and younger than those in the AFFIRM study (mean age of 70 years). The percentage of patients with underlying heart disease was ≤30% in the J-RHYTHM study while it was as high as ≥70% in the AFFIRM study. Hypertension and diabetes mellitus were observed in about 40% and 12%, respectively, of subjects in the J-RHYTHM study. These percentages were similar in patients with persistent AF. Cardiac function was normal in all participants.

The antiarrhythmic drugs prescribed at the time of registration were mainly sodium channel blockers; ≥80% of patients received pilsicainide, cibenzoline, propafenone, disopyramide, aprindine, or flecainide. Bepridil, which has attracted attention for its efficacy in patients not responding to sodium channel blockers, was prescribed to 6.7% and 15.2% of patients with paroxysmal and persistent AF, respectively, at the time of registration. Notably, amiodarone was prescribed to only 0.5% and 1.3% of patients with paroxysmal and persistent AF, respectively, and thus at rates substantially lower than those in the AFFIRM. Heart rate control was performed with β-blockers, calcium channel blockers, and digitalis.

Patients were followed up for 585.8 days on average. The results of the J-RHYTHM study provided both an answer to the question whether patients with AF should be treated with sinus rhythm maintenance or heart rate control and findings useful in the diagnosis of AF. This study also yielded clear treatment guidelines for patients with AF, and especially paroxysmal AF. Although pharmacotherapy based on the pathophysiology of AF according to the Sicilian Gambit has been criticized for the absence of evidence on its behalf, the results of the J-RHYTHM study demonstrated that treatment with antiarrhythmic drugs selected using this method could maintain sinus rhythm for a longer period of time than expected (periodic ECG monitoring demonstrated sinus rhythm in ≥80% of patients with paroxysmal AF at year 2.5 and in ≥50% in patients with persistent AF at year 2) (Figure 4). It is also important that this study demonstrated that the incidence of serious ADRs to antiarrhythmic drugs was very low. Although the participants were mainly patients with a relatively low risk of thromboembolism (patients with CHADS2 score 0/1 accounted for 90% of participants), many patients were treated with warfarin and the incidence of cerebral infarction was
only 2.3% during the mean follow-up period. These findings suggest that the level of treatment of AF is quite high in Japan. In patients with paroxysmal AF, the actual event-free survival rate was significantly higher in the sinus rhythm maintenance group than in the heart rate control group. Moreover, the incidence of adverse events including death was very low in both groups, with no significant difference in it between the two groups, and the occurrence of “discontinuation of study participation due to patient intolerance of treatment”, a measure considering patient QOL, was significantly prevented with treatment with antiarrhythmic drugs (Figure 5).

The results of the J-RHYTHM study demonstrated the efficacy of sinus rhythm maintenance in younger patients suffering from severe symptoms associated with paroxysmal AF, who are prevalent in the clinical setting, by appropriately administering antiarrhythmic drugs available in Japan. The purpose of sinus rhythm maintenance was to improve QOL rather than to decrease mortality or prevent cerebral infarction. The study thus supported clinical findings clinically familiar with. However, it should be noted that participants in the J-RHYTHM study had a mean age of 64 years and normal cardiac function without underlying heart disease. Further studies are needed to determine appropriate treatment for patients with AF who have poor cardiac function and cannot be treated with sodium channel blockers.

### 3. Antithrombotic Therapy

#### 1 Antithrombotic Therapy in Patients With AF

Practical recommendations regarding antithrombotic therapy in patients with AF are described in Table 1 and Figure 6. Since patients with mitral valve stenosis and those with mechanical valves are at high risk of embolism, warfarin therapy with a target international normalized ratio (INR) of 2.0 to 3.0 is recommended.

It is recommended that appropriate antithrombotic therapy be performed on the basis of assessment of risk of cerebral infarction in patients with non-valvular AF, defined as AF in patients with a history of neither rheumatic mitral valve disease, prosthetic valve replacement, nor mitral valve repair.86 Lone AF, on the other hand, is defined as AF in patients under 60 years of age without clinical or echocardiographic evidence of cardiopulmonary disease including hypertension.87,88 In patients with non-valvular AF, history of cerebral infarction or transient ischemic attack (TIA),89,90 and cardiomyopathy, are high risk factors for non-valvular AF.

Based on the finding that the incidence of cerebral infarc-

<table>
<thead>
<tr>
<th>Table 1. Antithrombotic Therapy for Patients With Atrial Fibrillation (AF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
</tr>
<tr>
<td>1. Anticoagulation therapy based on evaluation of risk for cerebral infarction and bleeding:</td>
</tr>
<tr>
<td>High risk factors are a history of cerebral infarction, transient ischemic attack (TIA), or systemic embolism, mitral valve stenosis, and use of prosthetic (mechanical) valve. Moderate risk factors are age ≥75 years of age, hypertension, heart failure, left ventricular systolic dysfunction (ejection fraction ≤35% or fractional shortening ≤25%), and diabetes mellitus. (Level of Evidence: A)</td>
</tr>
<tr>
<td>1-1. Administer warfarin to high risk patients with a target international normalized ratio (INR) of 2.0 to 3.0 (Level of Evidence: A)</td>
</tr>
<tr>
<td>1-2. Administer warfarin to patients with ≥2 moderate risk factors with a target INR of 2.0 to 3.0 (Level of Evidence: A)</td>
</tr>
<tr>
<td>2. Monitor INR at least weekly during the period of induction of warfarin therapy and at least monthly after achieving a stable INR (Level of Evidence: C)</td>
</tr>
<tr>
<td><strong>Class IIa</strong></td>
</tr>
<tr>
<td>1. Administer warfarin to patients with one moderate risk factor with a target INR of 2.0 to 3.0 (Level of Evidence: A)</td>
</tr>
<tr>
<td>2. Administer warfarin to patients with cardiomyopathy with a target INR of 2.0 to 3.0 (Level of Evidence: B)</td>
</tr>
<tr>
<td>3. Administer warfarin to patients with unilateral risk factors, ie, 65 to 74 years of age, female, or coronary artery disease, with a target INR of 2.0 to 3.0 (Level of Evidence: C)</td>
</tr>
<tr>
<td>4. Administer warfarin regardless of the type of AF (paroxysmal AF, persistent AF, or permanent AF) (Level of Evidence: A)</td>
</tr>
<tr>
<td>5. Control patients with non-valvular AF ≥70 years of age who are indicated for warfarin therapy with a target INR of 1.6 to 2.6 (Level of Evidence: C)</td>
</tr>
<tr>
<td>6. Periodically reevaluate patients for indications for anticoagulation (Level of Evidence: C)</td>
</tr>
<tr>
<td>7. Anticoagulation therapy for patients with atrial flutter in the same fashion as patients with AF (Level of Evidence: C)</td>
</tr>
<tr>
<td><strong>Class IIb</strong></td>
</tr>
<tr>
<td>1. Add aspirin ≤100 mg or clopidogrel 75 mg in patients with coronary artery disease to prepare for percutaneous transluminal coronary angioplasty (PTCA) or surgical revascularization (Level of Evidence: C):</td>
</tr>
<tr>
<td>However, the efficacy of these methods has not been sufficiently evaluated, and the risk of bleeding may be increased.</td>
</tr>
<tr>
<td>2. Discontinue warfarin therapy to avoid access site bleeding during PTCA (Level of Evidence: C):</td>
</tr>
<tr>
<td>Following angioplasty, resume warfarin therapy promptly to maintain the INR within the appropriate therapeutic range. Although aspirin may be administered temporarily during discontinuation of warfarin therapy, maintenance therapy should be performed with clopidogrel 75 mg and warfarin with a target INR of 2.0 to 3.0. Duration of treatment with clopidogrel differs by type of stent used. When antplatelet therapy is combined with warfarin therapy, care should be taken to maintain INR values within the appropriate therapeutic range.</td>
</tr>
<tr>
<td>3. Antithrombotic therapy for patients with lone AF under 60 years of age (Level of Evidence: C):</td>
</tr>
<tr>
<td>In this patient population, the incidence of thromboembolism is low even in those not receiving antithrombotic therapy, and it is unclear whether the benefits of preventing thromboembolism outweigh the risk of bleeding complications due to antithrombotic therapy with warfarin and/or aspirin. When antithrombotic therapy is performed, monitoring is needed for the development of bleeding complications.</td>
</tr>
<tr>
<td>4. Add antplatelet drugs and control with a target INR of 2.5 to 3.5 when ischemic cerebrovascular disease or systemic embolism develops during anticoagulation to achieve an INR of 2.0 to 3.0 (Level of Evidence: C)</td>
</tr>
<tr>
<td>5. Administer antplatelet drugs to patients who cannot receive warfarin (Level of Evidence: C)</td>
</tr>
<tr>
<td><strong>Class III</strong></td>
</tr>
<tr>
<td>1. Administer warfarin to patients who are contraindicated for warfarin (Level of Evidence: C)</td>
</tr>
<tr>
<td>2. Administer antplatelet drugs to patients who are indicated for or not contraindicated for warfarin (Level of Evidence: A)</td>
</tr>
</tbody>
</table>
tion is high in patients with multiple risk factors. Use of the CHADS: score has been proposed. CHADS is an acronym for Congestive heart failure, Hypertension, Age ≥75 years of age, Diabetes mellitus, Stroke/TIA. The CHADS: score is calculated as the sum of points for each risk factor (1 point for each of the former 4 factors and 2 points for the latter [history of stroke/TIA]), with a higher score representing higher risk of the occurrence of cerebral infarction. In the present guidelines, the CHADS: score is used to evaluate whether patients with non-valvar AF have moderate risk of cerebral infarcion (Figure 6), and warfarin therapy is recommended for patients with at least 2 risk factors and may be considered for patients with one risk factor. In the case of the remaining 5 factors, whose effects on the occurrence of cerebral infarction have not been sufficiently evaluated, warfarin therapy may be considered if at least one of them is present.

It is recommended that a target INR of 2.0 to 3.0 be set when warfarin is administered. Patients 70 years of age or older should be maintained with an INR 1.6 to 2.6, since an INR less than 1.6 increases the incidence of serious cerebral infarction and an INR above 2.6 increases serious bleeding complications.

2 Antithrombotic Therapy During Cardioversion (Table 2)
Warfarin therapy (Prothrombin Time [PT]-INR of 2.0 to 3.0) for 3 weeks before and 4 weeks after cardioversion is indicated for patients with AF lasting ≥48 hours or of unknown duration. Patients with unstable hemodynamics associated with episodes of AF should immediately undergo cardioversion with intravenous heparin therapy. The risks of recurrent AF and thromboembolism should be considered in determining whether antithrombotic therapy should be continued for ≥4 weeks after cardioversion.

In the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) study, there were no significant differences in the rate of success of cardioversion or the incidence of embolism or massive bleeding between patients with AF lasting ≥48 weeks who, after confirmation of the absence of thrombi with transesophageal echocardiography (TEE), received heparin prior to cardioversion and warfarin for 4 weeks after cardioversion and patients receiving conventional warfarin therapy before and after elective cardioversion. Since it has also been reported that cerebral infarction and systemic embolism occurred after cardioversion in patients with atrial flutter, such patients should receive warfarin therapy in a fashion similar to those with AF.

### Table 2. Antithrombotic Therapy During Cardioversion

<table>
<thead>
<tr>
<th>Class I</th>
<th>1. Anticoagulation therapy for patients with atrial fibrillation (AF) lasting ≥48 hours or of unknown duration using warfarin for 3 weeks before and 4 weeks after cardioversion (international normalized ratio [INR] 2.0 to 3.0 for patients under 70 years, 1.6 to 2.6 for patients ≥70 years) (Level of Evidence: B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IIb</td>
<td>2. In patients in whom thrombus is detected by TEE: Administer warfarin for at least 3 weeks before cardioversion and at least 4 weeks after recovery to sinus rhythm (INR 2.0 to 3.0 for patients under 70 years, 1.6 to 2.6 for patients ≥70 years of age) (Level of Evidence: C)</td>
</tr>
<tr>
<td>Class III</td>
<td>3. Anticoagulate patients with atrial flutter to prepare for cardioversion in the same fashion as patients with AF (Level of Evidence: C)</td>
</tr>
</tbody>
</table>

- None

Class Ib
- None

Class III
- None
In the hospital setting, and avoidance of dehydration, fluid therapy, and heparin therapy should be considered based on the risk of thromboembolism during the perioperative period. The appropriate duration of preoperative discontinuation of antithrombotic drugs differs by type of drugs. When antithrombotic therapy must be discontinued to prepare for invasive procedures such as endoscopic biopsy and endoscopy-guided treatment, patients should be treated similarly to those undergoing major surgery.

4 Treatment of Bleeding
Class I recommendations for treatment of anticoagulant-related bleeding include conventional emergency treatment decrease in dose or discontinuation of warfarin in patients receiving warfarin, administration of vitamin K, and decrease in dose or discontinuation of heparin and neutralization of heparin with protamine sulfate in patients receiving heparin (Table 4). Class IIa recommendations for prompt normalization of INR in patients receiving warfarin include infusion of fresh frozen plasma or freeze-dried human blood coagulation factor IX complex (500 to 1,000 units).

5 Pregnancy and Childbirth (Table 5)
It is most important that women of childbearing age who are undergoing antithrombotic therapy receive an explanation in detail, preferably before pregnancy and childbirth, of the facts that mothers are at risk of thromboembolism even when their cardiac function and general body function are good under appropriate antithrombotic therapy, that oral warfarin may be teratogenic and may cause intracranial hemorrhage in fetuses, and that optimal management of antithrombotic therapy during pregnancy and childbirth has not been established. For patients who wish to become pregnant or give birth after this explanation, warfarin should be replaced by therapy, and heparin therapy should be considered based on the risk of thromboembolism during the perioperative period. The appropriate duration of preoperative discontinuation of antithrombotic drugs differs by type of drugs. When antithrombotic therapy must be discontinued to prepare for invasive procedures such as endoscopic biopsy and endoscopy-guided treatment, patients should be treated similarly to those undergoing major surgery.

### Table 3. Indications for Antithrombotic Therapy During Tooth Extraction and Surgery

<table>
<thead>
<tr>
<th>Class</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
</tr>
<tr>
<td>IIa</td>
<td>Administer warfarin to maintain international normalized ratio (INR) within the optimal therapeutic range and continue treatment with oral warfarin during tooth extraction (Level of Evidence: B)</td>
</tr>
<tr>
<td>IIa'</td>
<td>Continue treatment with oral antplatelet drugs during tooth extraction (Level of Evidence: B)</td>
</tr>
<tr>
<td>IIb</td>
<td>None</td>
</tr>
<tr>
<td>III</td>
<td>Discontinuation of antithrombotic therapy (Level of Evidence: C): When antithrombotic therapy must be discontinued, consider alternative treatments such as heparin therapy, avoidance of dehydration, and fluid therapy.</td>
</tr>
</tbody>
</table>

### Table 4. Treatment of Bleeding Complications

<table>
<thead>
<tr>
<th>Class</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1. Conventional emergency treatment established for each type of bleeding complication (Level of Evidence: C)</td>
</tr>
<tr>
<td></td>
<td>2. Decrease the dose or discontinue warfarin depending on the severity of the bleeding complication (moderate or severe) occurring during warfarin therapy and administer vitamin K whenever necessary (Level of Evidence: C)</td>
</tr>
<tr>
<td></td>
<td>3. Decrease the dose or discontinue heparin and neutralize heparin with protamine sulfate, depending on the severity of bleeding complications occurring during heparin therapy (Level of Evidence: C)</td>
</tr>
<tr>
<td>IIa</td>
<td>1. Administer fresh frozen plasma or freeze-dried human blood coagulation factor IX complex to patients who require prompt control of the effects of warfarin (Level of Evidence: C): Although the control effect of freeze-dried human blood coagulation factor IX complex is much stronger, the use of it in this case is not covered by the National Health Insurance (NHI) in Japan.</td>
</tr>
<tr>
<td></td>
<td>2. Administer freeze-dried human blood coagulation factor IX complex (not covered by the NHI) and vitamin K to avoid increase again in international normalized ratio (INR) controlled by freeze-dried human blood coagulation factor IX complex (Level of Evidence: C)</td>
</tr>
<tr>
<td>IIb</td>
<td>1. Administer recombinant coagulation factor VII drug (not covered by the NHI) to patients who require prompt inhibition of the effects of warfarin (Level of Evidence: C)</td>
</tr>
<tr>
<td>III</td>
<td>None</td>
</tr>
</tbody>
</table>


---

3 Treatment During Tooth Extraction and Surgery (Table 3)
Class IIa recommendation for treatment with warfarin or antplatelet drugs should be continued during tooth extraction. Serious thromboembolism occurs in about 1% of patients with AF following discontinuation of warfarin. Randomized controlled studies and observational studies have reported that tooth extraction can be safely performed in patients receiving antithrombotic drugs. Similar types of antithrombotic therapy are recommended for patients undergoing minor body surface surgery for whom postoperative bleeding can readily be treated. Many ophthalmologists perform cataract surgery in patients with AF while continuing antithrombotic therapy since the cornea and lens have no blood vessels and the risk of bleeding is thus low during surgery. For patients with AF undergoing major surgery, warfarin and antplatelet drugs should be discontinued in the hospital setting, and avoidance of dehydration, fluid
heparin or low molecular weight heparin, since warfarin, a low molecular weight compound that readily crosses the placenta, may cause malformation of the fetus during the first trimester of pregnancy.

6 Development of Novel Oral Anticoagulants

Ximelagatran, an oral antithrombin drug investigated in international clinical studies including the Stroke Prevention using an Oral Thrombin Inhibitor in Patients with Atrial Fibrillation (SPORTIF III) study, in which institutions in Japan participated, caused hepatic dysfunction at a significantly high rate. In Europe, it was initially approved for use in patients with deep venous thrombosis, but has been withdrawn from the market.

Recently, similar oral antithrombin drugs and anti-Xa inhibitors have been developed, and some drugs are currently being investigated in clinical studies. These drugs, when approved, will significantly improve antithrombotic therapy throughout the world.

Table 5. Treatment During Pregnancy and Childbirth

<table>
<thead>
<tr>
<th>Class</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Avoid warfarin therapy and replace it with subcutaneous heparin during the first 13 weeks of pregnancy, based on reports of placental transfer and teratogenicity of warfarin (Level of Evidence: C)</td>
</tr>
<tr>
<td>Class IIa</td>
<td>1. Avoid warfarin therapy and replace it with subcutaneous heparin during the first 13 weeks of pregnancy, based on reports of placental transfer and teratogenicity of warfarin (Level of Evidence: C)</td>
</tr>
<tr>
<td>Class IIa</td>
<td>2. Administer warfarin during weeks 14 to 33 of pregnancy (Level of Evidence: C)</td>
</tr>
<tr>
<td>Class III</td>
<td>3. Decrease warfarin dose and intravenous infusion of heparin in hospital to prevent the development of intra-cranial bleeding in the fetus during weeks 34 to 36 of pregnancy or later (Level of Evidence: C)</td>
</tr>
<tr>
<td>Class III</td>
<td>4. Perform early delivery after discontinuation of heparin therapy and early restart intravenous infusion of heparin to prevent the development of thrombosis in the mother due to acceleration of coagulation in weeks 34 to 36 of pregnancy or later (Level of Evidence: C)</td>
</tr>
<tr>
<td>Class III</td>
<td>1. Pregnancy and childbirth during anticoagulation (Level of Evidence: C)</td>
</tr>
</tbody>
</table>

4. Indications for Heart Rate Control

When heart rate is maintained at ≥130 bpm during AF, left ventricular diastolic failure may develop and induce congestive heart failure. Even if organic heart disease is absent, persistent high-rate AF may cause heart failure. In order to prevent the development of heart failure, heart rate during AF must be decreased to 60 to 80 bpm at rest and 90 to 115 bpm during moderate exercise. Heart rate control can be ensured with use of drugs that block AV nodal conduction. According to the results of the J-RHYTHM study and the AHA/ACC/ESC guidelines in 2006, β-blockers, non-dihydropyridine calcium channel blockers (verapamil or diltiazem), and digitalis may be used for this purpose.

In patients with poor cardiac function, digitalis is the drug of first choice. Antiarrhythmic drugs such as amiodarone, bepridil, and sotalol may decrease heart rate in patients during AF by blocking AV nodal conduction, even when they are administered for pharmacological cardioversion. The same holds for atrial flutter, though care is needed when sodium channel blockers are used:

When such drugs are administered, atrial activation frequency is decreased slightly, which may permit 1:1 AV conduction and increase ventricular activation frequency.

The optimal treatment for patients with permanent AF consists of heart rate control to avoid increases in heart rate and thus prevent heart failure and anticoagulation to prevent embolism. However, there have been no randomized clinical studies performed to determine the optimal drugs and methods for control of heart rate and the target heart rate in this patient population. Currently, digoxin, verapamil, diltiazem, and β-blockers are used for heart rate control. Lundstrom et al conducted a placebo-controlled study to evaluate the efficacy of diltiazem and verapamil in heart rate control in patients with chronic AF. Mean heart rate measured by Holter monitor was 88 ± 14 bpm in patients receiving placebo, 76 ± 13 bpm in patients receiving diltiazem 270 mg/day (p < 0.001), and 80 ± 11 bpm in patients receiving verapamil 240 mg/day (p < 0.01). The two calcium channel blockers provided similar degrees of inhibition of AV nodal conduction and improvement of exercise tolerance. It should be noted, however, that the doses of these calcium channel blockers were about twice the mean doses used in Japan.

In the Digitalis in Acute Atrial Fibrillation (DAAF) trial, in which the effects of cardioversion with digoxin, which is commonly used in the treatment of AF, were investigated, rapid intravenous infusion of digoxin in 239 patients with AF without underlying disease did not significantly increase the percentage of patients achieving cardioversion during a 16-hour observation period compared with placebo, but did decrease heart rate.

5. Indications for Cardioversion

Cardioversion of AF is indicated for patients with paroxysmal or persistent AF. Both electrical cardioversion and pharmacological cardioversion are available for this purpose.

Electrical cardioversion is indicated for patients in near shock due to hypotension, with heart failure due to poor cardiac function or angina pectoris, patients who have not responded to or cannot undergo pharmacological cardioversion with antiarrhythmic drugs, patients who require prompt cardioversion, patients with severe subjective symptoms, patients in whom AF has persisted within one year, patients without substantial left atrial enlargement, patients who still have AF after improvement of hyperthyroidism, and patients in whom AF developed and has persisted after heart surgery, among others. Patients in whom electrical cardioversion should not be aggressively performed include those in whom direct current cardioversion appears to be ineffective, those at high risk of recurrent AF, and those who have AF persisting for ≥2 days and are not undergoing anticoagulation. Direct current cardioversion should be avoided in patients receiving digitalis for a long period of time, patients with hypokalemia, and patients known to have bradycardia-
cardia syndrome, since electrical cardioversion may cause sinus arrest, sinoatrial block, or ventricular fibrillation.

Even in patients not responding to a first electrical cardioversion, pretreatment with amiodarone, flecainide, propafenone, aprindine, or sotalol may improve the rate of success of direct current cardioversion. Pharmacological cardioversion is indicated for patients who do not require prompt cardioversion, patients in whom AF repeatedly recurs after electrical cardioversion, patients who or whose family declines electrical cardioversion, and patients with severe subjective symptoms associated with AF. In patients with sick sinus syndrome, pharmacological cardioversion is contraindicated since antiarrhythmic drugs may exacerbate sinus arrest or sinoatrial block.

When pharmacological cardioversion by intravenous administration of antiarrhythmic drugs is attempted, sodium channel blockers such as procainamide, disopyramide, cibenzoline, flecainide, and pilsicainide are used. Cardioversion is generally achieved during or immediately after intravenous administration of these drugs. Treatment should be considered ineffective when cardioversion is not achieved within one hour after intravenous treatment. Patients must be monitored for blood pressure and heart rate during the intravenous infusion of antiarrhythmic drugs, and this requires considerable manpower and time.

Cardioversion using oral antiarrhythmic drugs requires a considerable length of time for achievement of efficacy, and does rarely cause abrupt changes in hemodynamics. However, since antiarrhythmic drugs may promptly induce decrease in cardiac function, proarrhythmic effect, and extracardiac ADRs even when they are administered orally, it is desirable that patients, especially those who have never received antiarrhythmic drugs, be hospitalized briefly during pharmacological cardioversion. Since proarrhythmic effects of and ADRs to antiarrhythmic drugs may develop in the first week of treatment, ambulatory patients should be monitored at least weekly or biweekly. According to the results of the J-RHYTHM study, the antiarrhythmic drugs commonly used in the treatment of AF in Japan include pilsicainide, cibenzoline, propafenone, disopyramide, and flecainide. These sodium channel blockers are also used for pharmacological cardioversion. For the treatment of AF in patients with WPW syndrome and stable hemodynamic, these sodium channel blockers are administered orally or intravenously. Amiodarone, which is frequently used in Europe and the United States, is rarely used in patients with AF in Japan. Another unique feature of treatment in Japan is that bepridil, a calcium channel blocker with potent potassium channel blocking activity, is used in a fashion similar to sodium channel blockers. It has been reported that cardioversion of AF persisting for more than 1 year can be performed with bepridil. In patients with paroxysmal or persistent AF in whom prompt recovery to sinus rhythm is not required, outpatient treatment with amiodarone may be beneficial.

6. Specific Use of Antiarrhythmic Drugs

1 Drugs for Heart Rate Control

Heart rate control in patients with AF targets the AV node, and calcium channel blockers, β-blockers and digitalis are effective for this purpose. Digitalis exerts its effects via parasympathetic activity, and its heart rate slowing effect is weak during activity. In patients with normal cardiac function, β-blockers and calcium channel blockers should be tried first instead of digitalis to ensure heart rate control (Class I), and digitalis should be added when patients do not respond well to these drugs (Class IIa) (Figure 7). Intravenous drugs are used when prompt rate control is required. When calcium channel blockers are used, verapamil 5 to 10 mg should be administered intravenously over 2 minutes or diltiazem 0.25 mg/kg over 2 minutes. The most frequently used intravenous β-blocker for heart rate control is propranolol, which should be administered intermittently at single intravenous doses of 2 mg with a total dose of 0.15 mg/kg. Intravenous administration of digoxin is often used in patients with heart failure or those with poor cardiac function; it should be performed at doses of 0.25 mg every two hours to a total dose of up to 1 mg.

In patients with WPW syndrome, heart rate control can be performed by blocking conduction over the accessory pathway with sodium channel blockers and potassium channel blockers (Figure 7). Intravenous drugs such as pilsicainide, cibenzoline, disopyramide, flecainide, and procainamide used for heart rate control may not only slow heart rate but also yield cardioversion. Needless to say, radiofrequency catheter ablation of the accessory pathway is whenever possible the preferred method of treatment for patients with WPW syndrome.
2 Drugs Maintaining Sinus Rhythm

(1) Maintenance of Sinus Rhythm in Patients With Lone AF

a. Paroxysmal AF

In the treatment of lone paroxysmal AF, sodium channel blockers that exert antiarrhythmic effects on both the triggers and substrates of AF, and in particular drugs that dissociate from receptors of sodium channels slowly (slow kinetic drugs), are effective (Class I). In patients with AF at night or after meals that results from increased vagal tone, drugs that block muscarinic M2 receptors may be effective. In the present guidelines, procainamide, cibenzoline, propafenone, disopyramide, and flecainide are listed as drugs of first choice for lone paroxysmal AF (Figure 8). These drugs should be administered intravenously when prompt termination of AF is required, though oral administration of them is needed to maintain sinus rhythm for a long period of time. Table 6 shows standard doses of these drugs for the treatment of lone AF. The type and dose of drugs to be used should be adjusted individually according to age, renal and hepatic function, and other characteristics of individual patients. Care is needed in the use of sodium channel blockers, since these drugs may induce transition from AF to atrial flutter, facilitate sinus arrest due to sinus nodal dysfunction, and increase ST elevation in patients with Brugada’s syndrome, possibly resulting in fatal arrhythmia.140

b. Persistent AF

Cardioversion with antiarrhythmic drugs is difficult in patients with AF lasting at least 1 week and whose atrial myocardium exhibits advanced remodeling.132,141 In such patients, QOL may be improved with heart rate control rather than cardioversion (Class I). Although direct current cardioversion is often needed for successful cardioversion, it has been reported that pharmacological cardioversion using bepridil (with or without aprindine),138,139 sotalol,42 amiodarone (oral),82,142-144 and other drugs is also effective (Figure 8). Treatment with bepridil is usually started at 100 mg/day, and is then increased up to 200 mg/day when possible, with careful monitoring for prolongation of the QT interval. When bepridil is ineffective, addition of aprindine may prove effective. Sotalol is usually started at 80 mg/day, and may be increased to 160 to 320 mg/day. The daily doses listed above are typically administered in two divided doses. Amiodarone is usually started at 400 mg/day and is then decreased to 200 mg/day after the first 2 weeks of treatment: in patients responding well to 200 mg/day, the dose may further be decreased to 100 mg/day.

(2) Maintenance of Sinus Rhythm in Patients With AF Associated With Underlying Heart Diseases

Since development of AF induces rapid deterioration of condition in patients with underlying heart diseases such as cardiac hypertrophy, heart failure, and ischemic heart disease, direct current cardioversion is used when prompt termination of AF is required (Class I). However, it is difficult to prevent recurrence of AF, and antiarrhythmic drugs may often induce severe ventricular proarrhythmic effect and exert negative inotropic effects in patients with such underlying heart diseases. Patients with underlying heart diseases should receive treatment for their underlying diseases (upstream treatment). Improvement of ischemia should be prioritized in patients with ischemic heart disease, and treatment with ACE inhibitors, ARBs,43,145-147 or β-blockers148 should be considered first in patients with cardiac hypertrophy or heart failure. Treatment should then be followed by heart rate control using drugs with low incidences of ADRs, though maintenance of sinus rhythm using antiarrhythmic drugs such as aprindine, bepridil, sotalol, and amiodarone may be necessary, especially in patients with severe symptoms associated with paroxysmal AF.

7. Single-Dose Treatment With Antiarrhythmic Drugs (Pill-in-the-Pocket Approach)149

In the “pill-in-the-pocket” approach,150 patients bring their drugs with them and take them at their own discretion whenever necessary. Since episodes of paroxysmal arrhythmia do not occur at regular intervals, the absence of arrhythmia episodes after intake of drugs is not necessarily indicative of drug efficacy. In patients who experience arrhythmic episodes at most once per month, daily administration of drugs to prevent infrequent episodes of arrhythmia may be excessive even if it is effective in preventing arrhythmia. Instead, when physicians prescribe drugs proven to be safe and effec-

Table 6. Dose Regimens of Drugs for Lone Atrial Fibrillation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral daily dose</th>
<th>Schedule</th>
<th>Intravenous administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone (po)*</td>
<td>150 mg</td>
<td>Divided into 3 doses</td>
<td>1 mg/kg over 10 min</td>
</tr>
<tr>
<td>Cibenzoline</td>
<td>300 mg</td>
<td>Divided into 3 doses</td>
<td>1.4 mg/kg over 2 to 5 min</td>
</tr>
<tr>
<td>Propafenone</td>
<td>450 mg</td>
<td>Divided into 3 doses</td>
<td>–</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>300 mg</td>
<td>Divided into 2 doses</td>
<td>1 to 2 mg/kg over 5 min</td>
</tr>
<tr>
<td>Flecainide</td>
<td>200 mg</td>
<td>Divided into 2 doses</td>
<td>1 to 2 mg/kg over 10 min</td>
</tr>
</tbody>
</table>

tive in individual patients in the treatment of episodes of arrhythmia when taken as a single dose as required, patients may take their drugs in the early stages of episodes of AF to ensure efficacy and may thus control AF by themselves at night or outside the home without seeking emergency care.

For the pill-in-the-pocket approach, drugs should be rapidly absorbable from the gastrointestinal tract after oral intake to achieve peak blood concentrations promptly and reach sufficient effective blood concentrations after a single administration. It should be noted that the first administration of antiarrhythmic drugs should be performed under ECG monitoring to confirm that the treatment is effective and safe, i.e., that the drugs do not induce sinus arrest or conduction disorder, induce excessive prolongation of the QT interval, and lead to Brugada-type ECG findings. Patients should be able to understand the pharmacological characteristics of drugs and refrain from inappropriate additional intake of their drugs even when expected effects are not obtained.

**8. Upstream Treatment**

Treatment of episodes of arrhythmia is referred to as “downstream treatment”, while treatment to prevent progression of underlying diseases that cause arrhythmia is referred to as “upstream treatment”. When AF lasts several hours, the proteins comprising ion channels begin to change. The changes in such proteins may shorten refractory periods of the atrial myocardium, which may result in continuation of AF. It is believed that, when AF persists for 1 to 2 weeks, the electrophysiological changes (electrical remodeling) of atrial myocardium that occur may be associated with structural changes (structural remodeling) such as atrial dilation and fibrosis, which will eventually result in permanent AF. Although AF is usually treated using antiarrhythmic drugs, the progression of underlying diseases causing AF cannot be prevented with antiarrhythmic drugs alone. Upstream treatment has thus attracted attention.

Atrial extrasystole, one of the triggers of AF, often originates within the pulmonary veins. It is believed that even in patients with lone AF left ventricular end-diastolic pressure is increased, which causes stretching and enlargement of the left atrium and thereby stretching of the pulmonary veins. At the level of the cardiomyocyte, extracellular stretch causes the gates of stretch-activated channel to open, inducing calcium overload in the cardiomyocytes. Angiotensin II (AT1) binds to AT1 receptors, and also causes calcium overload. Protein kinase C (PKC) and mitogen activated protein kinase (MAPK) are produced in the phospholipase C (PLC) pathway, and activate signals that induce cardiac hypertrophy. It thus appears that stretching activates AT1 and opens the gates of stretch-activated channel and thereby causes calcium overload and abnormal automaticity especially in the left atrium and pulmonary veins.

It is believed that shortening of the refractory period plays a role in the development of AF in short-term remodeling, while conduction disorder due to interstitial fibrosis plays an important role in the continuation of AF in long-term remodeling. Experiments have demonstrated that inhibition of the RAS is effective in preventing electrical as well as structural remodeling. Increase in AT1 activates the Erk cascade and thereby promotes fibrosis. When myocardial fibrosis induces conduction disorder and provides an environment facilitating development of reentry, multiple wavelets develop and AF continues. ACE inhibitors and ARBs, which are known to prevent atrial remodeling, are expected to be important components of upstream treatment to prevent chronic AF.

ACE inhibitors and ARBs have been demonstrated to significantly decrease the incidence of development of AF in patients with heart failure. Among hypertensive patients with left ventricular hypertrophy, the incidence of development of new AF was lower in those receiving ARBs than in those receiving β-blockers. The percentage of patients who maintained sinus rhythm after cardioversion was significantly higher in those receiving ARBs than in those receiving amiodarone monotherapy. It has been reported that, among hypertensive patients with paroxysmal AF, the incidence of chronic AF is significantly lower in those receiving than in those not receiving ACE inhibitors. In a meta-analysis of large-scale clinical studies, no difference was found between ACE inhibitors and ARBs in efficacy of AF prevention. Both ACE inhibitors and ARBs significantly prevented the development of new AF by 44% on average in patients with heart failure, but no significant prevention of AF by these drugs was observed in patients with hypertension. In Japan, the J-RHYTHM II study, a large-scale clinical study to investigate whether ARBs are more effective in the treatment of AF in patients with hypertension, is currently ongoing. In that study, hypertensive patients with paroxysmal AF were randomized to a group receiving candesartan, an ARB, or a group receiving anmlodipine, a calcium blocker, and days of AF, incidence of chronic AF, incidence of cardiovascular events, and QOL will be compared after one year of treatment. It is expected that the results of the study will demonstrate which antihypertensive drug is preferable for hypertensive patients with AF.

Inflammation is a factor involved in the pathogenesis of AF, and upstream treatment targeting inflammation of the myocardium is thus required. It has been reported that the level of C-reactive protein (CRP) is higher in patients with AF than in control patients. In experiments in a canine model of sterile pericarditis performed to investigate the effects of inflammation on atrial electrophysiological changes and the efficacy of statins in preventing electrophysiological changes of the atrium, animals in the statin group exhibited significantly lower CRP, longer refractory period, shorter conduction times, and shorter durations of AF than those in the control group on the second postoperative day. Infiltration of inflammatory cells and fibrosis were also significantly inhibited in the statin group.

The above findings suggest that inflammation plays an important role in the establishment of an electrophysiological substrate required for reentry, and that statins may prevent the establishment of a substrate for AF by exerting anti-inflammatory effects.

ACE inhibitors, ARBs and statins may prevent atrial remodeling, and are expected to be effective as components of upstream treatment to prevent chronic AF.

**9. Non-Pharmacological Treatment of AF**

1 Catheter Ablation in the Atrium

Catheter ablation for AF has evolved rapidly following a report that AF is triggered by focal firing originating at the ostium of the pulmonary veins and that catheter ablation targeting the focal source may induce termination of AF. Currently, anatomical isolation techniques to eliminate the electric connection between the superior and inferior pulmonary veins and the left atrium (such as circumferential pulmonary
Since the long-term prognosis following ablation has not yet been established, no conclusion has been reached regarding how long patients should continue anticoagulant following ablation.

References


139. Pedersen OD, Bagger H, Kaber L, Trop-Pedersen C; on behalf of the TRACE Study Group. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with...


Appendix

Chair:
Satoshi Ogawa, International University of Health and Welfare Mitaka Hospital

Members:
Yoshifusa Aizawa, Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences
Hirotsubo Atarashi, Nippon Medical School Tama Nagayama Hospital
Hirotsugu Atarashi, Nippon Medical School Tama Nagayama Hospital
Yoshifusa Aizawa, Division of Cardiology, Niigata University

Independent Assessment Committee:
Kazumasa Hiejima, Kudanazaka Hospital
Isao Kodama, Department of Cardiovascular Research, Research Institute of Environmental Medicine, Nagoya University
Tohru Ohe, The Sakakibara Heart Institute of Okayama
Katsusuke Yano, Faculty of Health Management, Nagasaki International University

(The affiliations of the members are as of March 2010)