



## Recent Mortality and Morbidity Rates of Japanese Atrial Fibrillation Patients – Racial Differences and Risk Stratification –

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Atrial fibrillation (AF) is becoming an epidemiologically important syndrome among the developed countries. Although racial differences exist with regard to AF prevalence, it remains unclear whether the AF mortality and morbidity rates exhibit racial differences. Medical treatment and management of AF is aimed at improving the clinical course of AF patients who reside in a particular region; therefore, the AF mortality and morbidity rates should be assessed from both global and local viewpoints. AF is a progressive disease that might be first detected as paroxysmal, persistent, or permanent. The associations between AF progression and AF-related cardiovascular morbidities and those between the cardiovascular morbidity and mortality rates of AF are important matters of discussion, as they reflect the rationale of AF therapy. At present, AF patients have a wide variety of backgrounds, and these analyses would require stratification by risks, which would not be free from racial differences. In this review, the mortality and morbidity rates of Japanese AF patients are reviewed and discussed. (*Circ J* 2013; **77**: 864–868)

**Key Words:** Atrial fibrillation; Heart failure; Mortality; Stroke

Atrial fibrillation (AF) is the most common arrhythmia among the developed countries, and its prevalence nearly doubles with each decade of life, increasing by as much as 25% on a lifetime basis.<sup>1</sup> As the population ages, the number of AF patients is predicted to increase. This dependence of AF prevalence on age also indicates another important issue. Aged people frequently have common diseases such as hypertension, diabetes mellitus, and other cardiovascular diseases. AF generally does not stand alone, but frequently co-exists with other cardiovascular diseases. Thus, AF is becoming an epidemiologically important individual syndrome rather than simply one of the arrhythmias.

In principle, when we treat or manage diseases, we should understand their natural course and the associated mortality and morbidity rates, as the aim of therapy is to improve the natural prognosis. Without this information, the effects of any new AF therapy cannot be compared with the present standard management and thus cannot be supported. The knowledge of the recent natural course is, therefore, the appropriate standpoint from which to determine any medical and surgical interventions.

This simple point of view raises 2 important issues regarding the treatment of AF syndrome in Japan. The first is racial differences. The mortality and morbidity rates do not significantly differ between countries for most stand-alone diseases. However, these rates could be affected by several intrinsic and environmental conditions in the case of syndromes, as the prevalence or treatment of comorbidities could be affected by

regional situations. Therefore, the natural course should be determined in each region and compared. The second issue arises from the variety of AF comorbidities. Because AF is not a stand-alone disease, its prognosis should be affected by the prognosis of the AF comorbidities in each patient. Therefore, questions regarding the mortality and morbidity rates of AF are not simple to answer, but should be discussed with stratification by clinical manifestations or/and comorbidities.

Unfortunately, we do not yet fully understand the natural course or the mortality and morbidity rates of Japanese AF patients, and stratified data are scarce. In this review, these important issues are discussed with reference to currently available data. The discussion is based on the assumed clinical courses of AF (Figure).

### Mortality Rates of Japanese AF Patients

When my colleagues and I planned the multicenter clinical trial regarding AF therapy (J-RHYTHM study) in 2003,<sup>2</sup> our largest challenge was, surprisingly, to estimate the basic mortality rate of Japanese AF patients, as previous Japanese studies had focused primarily on ECG findings and not on mortality. This observation was in contrast to the situation in foreign countries, where many reports, such as the Framingham study,<sup>3</sup> have provided data regarding the mortality rates of AF patients. However, since 2005, several reports have started to address this important issue in Japan.<sup>4–6</sup>

The first of these studies was NIPPON DATA 80,<sup>4</sup> in which

Received January 7, 2013; revised manuscript received February 7, 2013; accepted February 18, 2013; released online March 1, 2013  
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ISSN-1346-9843 doi:10.1253/circj.CJ-13-0002

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a random sample of 10,897 subjects throughout Japan was studied in a national survey. Although the number of AF patients in the study group was small ( $n=60$ ), the observation period and the follow-up rate were satisfactory (19 years and 91.4%, respectively). The study reported (1) that the age-adjusted relative risk of death attributable to AF was 1.87, and (2) that the overall mortality rate was approximately 1%/year in the total AF patient cohort. The second study was the J-TRACE study,<sup>5</sup> which was a nationwide prospective cohort study of stable outpatients with myocardial infarction, stroke, and/or AF. The AF patient cohort ( $n=2,056$ ) showed a total mortality rate of approximately 1.8%/year. The last study was the Shinken Database study,<sup>6</sup> which prospectively evaluated a single hospital-based cohort in Tokyo. The study reported that the relative risk of AF-related mortality was 1.7 and that the total mortality rate of AF patients ( $n=1,942$ ) was approximately 1%/year. It was striking that all 3 studies consistently reported that the total mortality rates of AF patients were quite low relative to those reported in foreign countries. For example, the recent Euro Heart Survey on AF<sup>7</sup> reported a total mortality rate of 5.3%/year, which was similar to that reported in the Framingham study<sup>3</sup> and in the large AFFIRM clinical trial.<sup>8</sup>

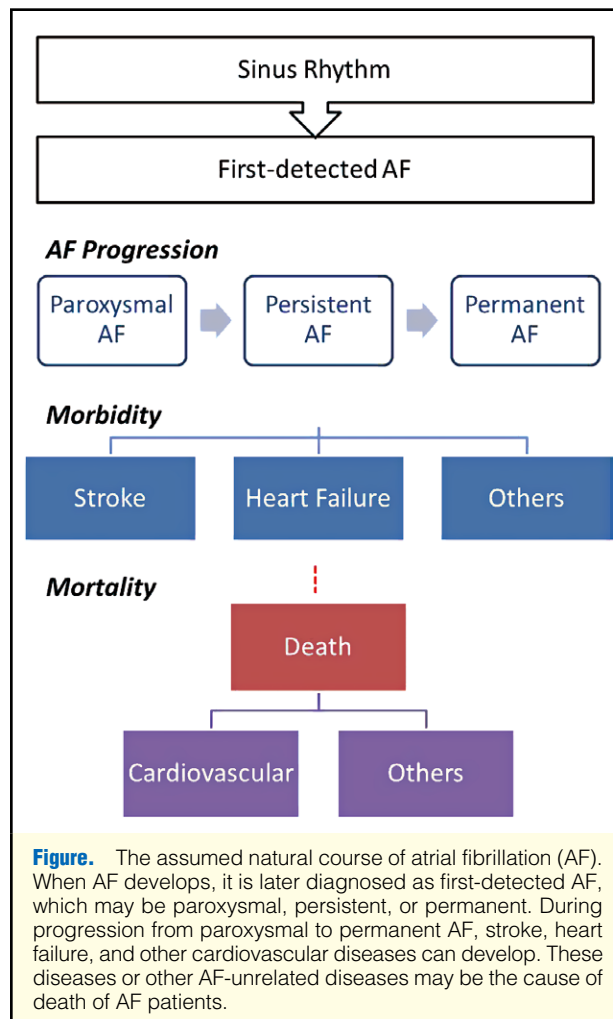
Although it remains unknown why such a remarkable difference in AF mortality rates exists between Japan and Western countries, the finding suggests that AF therapy in Japan should be based on our own database, regardless of whether the strategy differs from those used abroad. At the same time, it should be noted that Japanese data are still lacking in terms of quantity and quality, and 2 important problems should be solved before optimizing AF therapy from the viewpoint of the mortality of Japanese AF patients.

The first is the cause of death, because death is not necessarily linked to AF itself or AF-related cardiovascular diseases, particularly in aged patients. NIPPON DATA 80<sup>4</sup> reported that approximately 40% of the deaths were not of cardiovascular origin. In the J-TRACE study,<sup>5</sup> approximately 80% of the deaths were classified as “other” (not due to stroke, myocardial infarction, or major bleeding). Additionally, in the Shinken Database,<sup>6</sup> approximately 30% of the deaths were not cardiovascular in origin. The available information remains confusing. The second important issue is stratification. Age is a major determinant of AF mortality. Interestingly, patient mortality was remarkably dependent on age in both the NIPPON DATA 80<sup>4</sup> and Shinken Database<sup>6</sup> studies. These data, however, are limited in view of other comorbidities. A cohort study of heart failure (HF) patients in Japan (JCARE-CARD)<sup>9</sup> reported that the mortality rates of patients with AF and HF increased up to approximately 10%, a remarkably high figure compared with that of the total AF patients. The information regarding the mortality of Japanese AF patients remains insufficient.

### HF in Japanese AF Patients

It is well known that AF frequently coexists with HF and acts as a major cause of HF.<sup>10</sup> Therefore, HF is an important morbidity of AF, as well as stroke. The Framingham study reported that HF events occur at a rate of approximately 3%/year in AF patients.<sup>11</sup> The randomized clinical trial of the ACTIVE-I study also reported a similar rate of HF admission among the enrolled AF patients with particular risks.<sup>12</sup> Both studies indicated that prevention of HF is a necessary task to be accomplished in AF therapy.

Unfortunately, limited data are currently available from



Japanese AF patients. To my knowledge, 2 reports from a single institution have tried to address this issue.<sup>13,14</sup> In the first report,<sup>13</sup> the investigators followed AF patients without structural heart diseases and found that HF admission occurred at a rate of approximately 2%/year. In the second report from the Shinken Database,<sup>14</sup> they followed AF patients with and without structural heart diseases and observed that HF admission occurred concentrically within 1 year after AF diagnosis ( $\approx 4\%$ ) and steadily thereafter at a rate of approximately 1%/year. These rates were quite low compared with those in Western countries.

In this respect, however, stratification would play an important role in the rate of occurrence of HF admission. Koitabashi et al reported that HF admission was  $>8\%$ /year in patients with AF and a history of HF.<sup>15</sup> Additionally, the JCARE-CARD<sup>9</sup> study demonstrated that this rate was  $>10\%$ /year in patients with AF and hospitalized HF. Although universal risk stratification criteria based on the HF risks of AF remain unknown, the report from the Shinken Database developed a new risk scoring scale for HF events, the H2ARDD score (heart diseases=2, anemia=1, renal dysfunction=1, diabetes=1, and diuretics=1; total: 0–6 points).<sup>14</sup> In this scoring system, the rate of occurrence of HF in AF patients varied widely from 0.2% to 40% according to the patient's background. This risk stratification scheme might explain the high rate of HF events in the reports of Koitabashi et al<sup>15</sup> and the JCARE-CARD study.<sup>9</sup>

However, the data remain limited and this scoring system should be validated with other AF patient data sets. When this validation is completed, this stratification scheme might explain the difference in HF events between Japan and Western countries and provide a useful tool for developing strategies for preventing HF.

### Stroke in Japanese AF Patients

It is also well known that AF carries an increased risk of thromboembolism.<sup>16</sup> The risk ratio for stroke in AF patients ranges from 4 to 8 in Western countries, and can be stratified by the CHADS<sub>2</sub> score and the recent CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>17–20</sup> However, these data and stratification scores are based on accumulated data obtained in Western countries.

In Japan, numerous investigators have been working on the theme of stroke in Japanese AF patients. In the literature, the first large epidemiological study of AF patients (n=2,457) was reported in 2000 from Hokkaido in a 13-hospital collaborative study.<sup>21</sup> The study found that stroke occurred at a rate of approximately 3%/year in nonvalvular AF patients and that this rate was remarkably decreased by warfarin therapy but not antiplatelet therapy. In that era without the CHADS<sub>2</sub> scoring system, the investigators also observed that age, history of stroke, and structural heart diseases were risk factors for stroke in their patients. Thereafter, more reports were published regarding the stroke rate in Japanese AF patients.<sup>22–25</sup> Their primary limitation, however, was the small number of patients, which prohibited analysis of the stroke rates. According to the increased use of the risk scoring system and anticoagulation therapy, a large number of patients had to be analyzed under classification with many affecting factors. With a small number of patients, many studies reported a wide confidence interval of stroke rates, with limited reliability. If all the data from these studies were pooled and analyzed, a more reliable stroke rate in Japanese AF patients might be obtained. My impression, however, is that the previously published stroke rate was similar to or slightly lower than that of Western countries. The slight difference might be explained by the differences between the studies in the patients' comorbidities.

Recently, the J-TRACE study<sup>5</sup> reported the stroke rate in Japanese AF patients (n=2,056). Under the conditions of 70% of the patients being treated with warfarin, this rate was reported to be approximately 1.5%/year, similar to that reported under warfarin therapy in the first report from Hokkaido<sup>21</sup> and those based on real-world clinical data in Western countries. In addition, the J-TRACE study<sup>5</sup> demonstrated a clear and linear relationship between the CHADS<sub>2</sub> score and the event rate (stroke, myocardial infarction, and death). Based on these reports, it would be plausible to estimate that the stroke rate of Japanese AF patients would not be so different from that of Western countries, although the intensity of anticoagulation for stroke prevention merits discussion about potential racial differences. The similarity of stroke rates in Japan and Western countries is quite different from the situations of mortality and HF.

However, data regarding risk stratification in Japanese AF patients are limited. Although the J-TRACE study approached this issue, the number of patients would have to be greater when stratified by several risk scoring systems such as the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Moreover, at present, it would be difficult to obtain data from AF patients not on anticoagulation regimens. Further, no reliable data have been published on the HAS-BLED scoring system under anticoagulation in Japan. Recently, the J-RHYTHM registry<sup>26,27</sup> has been completed,

which includes more than 7,000 patients with and without anticoagulation. The registry data will help clarify the relation between risk stratification and stroke/bleeding rates, as well as between anticoagulation intensity and stroke/bleeding rates.

### Progression From Paroxysmal to Persistent AF in Japanese AF Patients

Clinically, apart from mortality and morbidity, progression from paroxysmal to persistent AF is an important issue for patients and physicians. This process might cause severe symptoms just before AF perpetuation because of frequent paroxysmal attacks. It might also result in a drastic change in treatment strategy from rhythm control to rate control, which might trouble physicians. Therefore, the AF progression rate is an important issue for clinical practice from the viewpoint of quality of life. However, the rate of progression from paroxysmal to persistent AF had not been clarified until recently.

In Japan, several studies have been published regarding this issue. A JALT-2 cohort study of 244 patients with paroxysmal AF demonstrated that it progressed to the persistent form at a rate of 8.4%/year.<sup>28</sup> A single hospital-based study also demonstrated that paroxysmal AF was converted to persistent AF at a rate of approximately 5.5%/year in their total patient cohort and at a rate >10% in patients with structural heart diseases; the transition rate was affected by age, the existence of structural heart diseases, and left atrial dimensions.<sup>29</sup> The recent J-RHYTHM II study of 318 patients reported that the progression rate was approximately 10%/year in patients with hypertension and paroxysmal AF.<sup>30</sup> The findings from these studies are nearly consistent in both the progression rate and its dependence on the patient's background. Reports from Western countries also show similar or slightly higher progression rates. The Euro Heart Survey on AF found that 15% of patients with paroxysmal AF progressed to persistent AF within 1 year.<sup>7</sup> The RecordAF study also demonstrated the same AF progression rate of 15%/year.<sup>31</sup> In a study from the United Kingdom, paroxysmal AF progressed to persistent AF at a rate of 6.2%/year.<sup>32</sup> A Canadian study reported a progression rate of 8.6% within 1 year.<sup>33</sup> Taken together, these data demonstrate that the rate of progression from paroxysmal to persistent AF seems to exhibit no apparent racial differences.

The patients' comorbidities in these studies, including those in Japan, were somewhat different, thus explaining the slight differences in the AF progression rates. To explain this diversity, a scoring system has been developed to predict the progression rate.<sup>34</sup> Using data from the Euro Heart Survey on AF, the investigators found that HF, age, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, and hypertension were risk factors for AF progression, and developed a new predictive scoring system (HATCH score).<sup>34</sup> Although risk stratification using the HATCH score should be validated in other cohorts of paroxysmal AF patients, it may aid in understanding individual diversity.

The progression from paroxysmal to persistent AF is important in terms of quality of life, and it might be related to the morbidity of AF patients. The Euro Heart Survey on AF observed that patients with AF progression had more frequent hospital admissions and more major adverse cardiovascular events.<sup>7</sup> Another report noted that mortality rates tended to be worse in patients with AF progression.<sup>32</sup> Therefore, the progression from paroxysmal to persistent AF might be related to the mortality and morbidity of paroxysmal AF patients, and thus could be an important clinical marker for predicting prognosis. However, the temporal relationships between AF pro-



gression and the mortality/morbidity rates remain unclear. In addition, the independent effect of other comorbidities of AF patients and the progression of each should be determined in the future.

### Future Perspectives

In this review, several important AF-related issues have been discussed: mortality, HF, stroke, and AF progression in Japan. The prevalence of AF is known to exhibit significant racial differences.<sup>35</sup> Similarly, the mortality rates and the risk of HF development in AF patients might have racial differences as discussed, although it appears that there are no significant racial differences in stroke and AF progression. Racial differences, if any, would be a risk factor affecting the management of AF therapy. Therefore, physicians in Japan have to continue the compilation of a large database of Japanese AF patients and to cooperate in assembling the database for each region and each registry study. This is the key to pursuing more effective AF therapy in Japan.

The treatment and management of AF has continuously progressed. Catheter ablation has been established as an effective therapy since the 2000s,<sup>36</sup> and several novel anticoagulants have been recently developed and used in clinical practice.<sup>37</sup> These new interventions will definitely affect the AF-related issues discussed here. However, we cannot be confident about this assertion, as sufficient data from Japanese AF patients have not been accumulated with regard to the relations between new therapeutic tools and AF mortality and morbidity rates. Once we know where we are, we can determine where we are going.

AF is a wide-spectrum syndrome in terms of age, lifestyle factors, and various comorbidities. Therefore, the simple phrase “mortality and morbidity rates of AF” will not make sense in the future. The necessary question to answer before discussing these rates will be, “What is the clinical background of the AF you mention?” Race will be a part of the clinical background. Risk stratification according to clinical background and/or clinical biomarkers will provide a mandatory basis for discussing the mortality and morbidity rates of AF patients in the future. To determine the effectiveness of a particular AF treatment in a particular region, we should understand the racial differences in the important AF factors and discuss them while aligning the risks for the intended purpose of AF therapy.

### References

- Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: The Framingham Heart Study. *Circulation* 2004; **110**: 1042–1046.
- Yamashita T, Ogawa S, Aizawa Y, Atarashi H, Inoue H, Ohe T, et al; J-RHYTHM Investigators. Investigation of the optimal treatment strategy for atrial fibrillation in Japan. *Circ J* 2003; **67**: 738–741.
- Benjamin EJ, Levy D, Vaziri SM, D’Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: The Framingham Heart Study. *JAMA* 1994; **271**: 840–844.
- Ohsawa M, Okayama A, Okamura T, Itai K, Nakamura M, Tanno K, et al. Mortality risk attributable to atrial fibrillation in middle-aged and elderly people in the Japanese general population: Nineteen-year follow-up in NIPPON DATA80. *Circ J* 2007; **71**: 814–819.
- Goto S, Ikeda Y, Shimada K, Uchiyama S, Origasa H, Kobayashi H; J-TRACE Investigators. One-year cardiovascular event rates in Japanese outpatients with myocardial infarction, stroke, and atrial fibrillation: Results from the Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events (J-TRACE). *Circ J* 2011; **75**: 2598–2604.
- Suzuki S, Yamashita T, Otsuka T, Sagara K, Uejima T, Oikawa Y, et al. Recent mortality of Japanese patients with atrial fibrillation in an urban city of Tokyo. *J Cardiol* 2011; **58**: 116–123.
- Nieuwlaar R, Prins MH, Le Heuzey JY, Vardas PE, Aliot E, Santini M, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: Follow-up of the Euro Heart Survey on atrial fibrillation. *Eur Heart J* 2008; **29**: 1181–1189.
- Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; **347**: 1825–1833.
- Hamaguchi S, Yokoshiki H, Kinugawa S, Tsuchihashi-Makaya M, Yokota T, Takeshita A, et al; Japanese Cardiac Registry of Heart Failure in Cardiology Investigators. Effects of atrial fibrillation on long-term outcomes in patients hospitalized for heart failure in Japan: A report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; **73**: 2084–2090.
- Ben Morrison T, Jared Bunch T, Gersh BJ. Pathophysiology of concomitant atrial fibrillation and heart failure: Implications for management. *Nat Clin Pract Cardiovasc Med* 2009; **6**: 46–56.
- Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham Heart Study. *Circulation* 2003; **107**: 2920–2925.
- ACTIVE I Investigators, Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG, et al. Irbesartan in patients with atrial fibrillation. *N Engl J Med* 2011; **364**: 928–938.
- Fukuda T, Yamashita T, Sagara K, Kato T, Sawada H, Aizawa T. Development of congestive heart failure in Japanese patients with atrial fibrillation. *Circ J* 2007; **71**: 308–312.
- Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Uejima T, et al. A new scoring system for evaluating the risk of heart failure events in Japanese patients with atrial fibrillation. *Am J Cardiol* 2012; **11**: 678–682.
- Koitabashi T, Inomata T, Niwano S, Nishii M, Takeuchi I, Nakano H, et al. Paroxysmal atrial fibrillation coincident with cardiac decompensation is a predictor of poor prognosis in chronic heart failure. *Circ J* 2005; **69**: 823–830.
- Cairns JA, Connolly SJ. Nonrheumatic atrial fibrillation: Risk of stroke and role of antithrombotic therapy. *Circulation* 1991; **84**: 469–481.
- Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE; ATRIA Study Group. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2008; **51**: 810–815.
- Boriani G, Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, et al; Italian AT-500 Registry Investigators. Improving stroke risk stratification using the CHADS2 and CHA2DS2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. *Stroke* 2011; **42**: 1768–1770.
- Medi C, Hankey GJ, Freedman SB. Stroke risk and antithrombotic strategies in atrial fibrillation. *Stroke* 2010; **41**: 2705–2713.
- Lip GY, Halperin JL. Improving stroke risk stratification in atrial fibrillation. *Am J Med* 2010; **123**: 484–488.
- Tomita F, Kohya T, Sakurai M, Kaji T, Yokoshiki H, Sato M, et al; Hokkaido Atrial Fibrillation Study Group. Prevalence and clinical characteristics of patients with atrial fibrillation: Analysis of 20,000 cases in Japan. *Jpn Circ J* 2000; **64**: 653–658.
- Inoue H, Nozawa T, Hirai T, Iwasa A, Okumura K, Lee JD, et al. Accumulation of risk factors increases risk of thromboembolic events in patients with nonvalvular atrial fibrillation. *Circ J* 2006; **70**: 651–656.
- Komatsu T, Tachibana H, Sato Y, Ozawa M, Kunugida F, Orii M, et al. Relationship between CHADS2 score and ischemic stroke during rhythm control therapy for paroxysmal atrial fibrillation. *Int Heart J* 2010; **51**: 24–29.
- Iwahana H, Ishikawa S, Ishikawa J, Kabutoya T, Kayaba K, Gotoh T, et al. Atrial fibrillation is a major risk factor for stroke, especially in women: The Jichi Medical School cohort study. *J Epidemiol* 2011; **21**: 95–101.
- Nakayama T, Yokoyama T, Yoshiike N, Zaman MM, Date C, Tanaka H, et al. Population attributable fraction of stroke incidence in middle-aged and elderly people: Contributions of hypertension, smoking and atrial fibrillation. *Neuroepidemiology* 2000; **19**: 217–226.
- J-RHYTHM Registry Investigators. Determinants of warfarin use and international normalized ratio levels in atrial fibrillation patients in Japan: Subanalysis of the J-RHYTHM Registry. *Circ J* 2011; **75**: 2357–2362.
- Atarashi H, Inoue H, Okumura K, Yamashita T, Kumagai N, Origasa H; J-RHYTHM Registry Investigators. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation: A report from the J-RHYTHM Registry. *Circ J* 2011; **75**: 1328–1333.
- Kato T, Inuma H, Inoue H, Ohe T, Ogawa S, Kasanuki H, et al.

- Multicenter prospective nonrandomized study of long-term antiarrhythmic drug therapy in patients with tachyarrhythmias: Japanese Antiarrhythmics Long-Term Study-2 (JALT-2 Study). *Jpn Circ J* 2001; **65**: 275–278.
29. Kato T, Yamashita T, Sagara K, Iinuma H, Fu LT. Progressive nature of paroxysmal atrial fibrillation: Observations from a 14-year follow-up study. *Circ J* 2004; **68**: 568–572.
  30. Yamashita T, Inoue H, Okumura K, Kodama I, Aizawa Y, Atarashi H, et al; J-RHYTHM II Investigators. Randomized trial of angiotensin II-receptor blocker vs. dihydropyridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II study). *Europace* 2011; **13**: 473–479.
  31. De Vos CB, Breithardt G, Camm AJ, Dorian P, Kowey PR, Le Heuzey JY, et al. Progression of atrial fibrillation in the REGistry on Cardiac rhythm disORDers assessing the control of Atrial Fibrillation cohort: Clinical correlates and the effect of rhythm-control therapy. *Am Heart J* 2012; **163**: 887–893.
  32. Ruigómez A, Johansson S, Wallander MA, García Rodríguez LA. Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. *BMC Cardiovasc Disord* 2005; **5**: 20.
  33. Kerr CR, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M, et al. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: Results from the Canadian Registry of Atrial Fibrillation. *Am Heart J* 2005; **149**: 489–496.
  34. de Vos CB, Pisters R, Nieuwlaet R, Prins MH, Tieleman RG, Coelen RJ, et al. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010; **55**: 725–731.
  35. Borzecki AM, Bridgers DK, Liebschutz JM, Kader B, Kazis LE, Berlowitz DR. Racial differences in the prevalence of atrial fibrillation among males. *J Natl Med Assoc* 2008; **100**: 237–245.
  36. Lee G, Sanders P, Kalman JM. Catheter ablation of atrial arrhythmias: State of the art. *Lancet* 2012; **380**: 1509–1519.
  37. Suzuki S, Otsuka T, Sagara K, Matsuno S, Funada R, Uejima T, et al. Dabigatran in clinical practice for atrial fibrillation with special reference to activated partial thromboplastin time. *Circ J* 2012; **76**: 755–757.