41.8%, and an area under the ROC curve of 0.659; the optimal cutoff DBP level was ≥81 mm Hg with a sensitivity of 53.6%, specificity of 74.2%, and an area under the ROC curve of 0.676. Both SBP3 ≥130 mm Hg (OR, 6.23; 95% CI, 2.16 to 26.35; $P<0.001$) and DBP3 ≥81 mm Hg (OR, 3.49; 95% CI, 1.64 to 7.52; $P=0.001$) were independently associated with ICH after adjustment for the 8 established ICH predictors.

Discussion

A major new finding of the present observational study was that BP levels during the follow-up, but not the level at entry, were independently associated with the development of ICH. In particular, ICH risk increased linearly as BP levels at the last clinic visit increased. The estimated cutoff BP level to predict impending risk of ICH was ≥130/81 mm Hg. BP levels did not appear to be associated with major systemic (excluding intracranial) bleeding events.

Hypertension is an established modifiable risk factor for ICH during warfarin therapy along with intensity of anticoagulation, concomitant use of antiplatelets, and smoking and heavy drinking habits.[4] However, major trials involving anticoagulant users failed to show entry BP level as a predictor for major bleeding events.[9–11] To resolve the contradiction, we designed the present study, which assessed BP levels during follow-up. The present antithrombotic users developing ICH had approximately 2 to 4 mm Hg higher entry SBP than those without bleeding events, which was not statistically significant. However, their SBP and DBP increased by an average of approximately 4 mm Hg at the follow-up as compared with at entry, and this increase may trigger ICH. Such an increase might result from careless BP management or resistance to antihypertensive therapy. Regardless of the cause, avoidance of a BP increase would lessen the risk for ICH.

Based on differences in average BP levels at the last visit between the ICH group and the other 2 groups, we hypothesized that the cutoff SBP level to predict impending development of ICH was roughly between 132 and 142 mm Hg, and the cutoff DBP level was roughly between 75 and 81 mm Hg. After ROC curve analyses, 130/81 mm Hg appears to be the cutoff level. Although the statistical power judged from the area under the ROC curve is not strong, this cutoff level seems to be reasonable, because recent guidelines from the European Society of Hypertension and the European Society of Cardiology and those from the Japanese Society of Hypertension advocated <130/80 mm Hg as the target BP level in diabetics and in high- or very-high-risk patients.[12,13] Real target BP levels during antithrombotic therapy should be determined by systematic comparative trials.

Combination therapy with antithrombotics and antihypertensives appears to be preventive for ICH. In the interim report of the Secondary Prevention of Small Subcortical Strokes (www.sps3.org/), in which SBP was lowered to <149 mm Hg or <130 mm Hg, risk of ICH was less than expected in patients with stroke taking aspirin alone or aspirin plus clopidogrel (personal communication). Success in reducing ICH in PROGRESS, in which 82% of enrolled patients were receiving antithrombotics, was reviewed.[6] On the other hand, an angiotensin receptor blocker, telmisartan, did not reduce the risk of ICH for antiplatelet users who recently had ischemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study (HR, 0.81; 95% CI, 0.63 to 1.05)[14]; the relatively small number of patients developing ICH may be a reason for this failure to show an effect.

Major systemic (not intracranial) bleeding events developed under identical BP levels as those in our patients without major bleeding events. This indicates that hypertensive damage to gastrointestinal, dermal, and other systemic circulations is milder than the damage to cerebral circulation. Preventive strategies other than antihypertensives, including proton pump inhibitors and H2 receptor antagonists, appear to be promising for reducing gastrointestinal bleeding.[15,16]

The limitations of the present study include the relatively short duration of the observation period and the small numbers of bleeding events as a result, which may affect the statistical results and made it difficult to perform subanalyses for patients with different clinical backgrounds and different antithrombotic regimens. Second, information on patients' antihypertensive therapy was not given. Third, clopidogrel, a universal antiplatelet agent, was not used in our patients because the agent was approved for use in Japan in 2006, after the study was finished. Finally, data of many patients were not included in the analysis of the follow-up BP measurements during 7 and 12 months and after 13 months partly because of early discontinuance of the observation due to bleeding events. To overcome this limitation and to introduce a message that BP levels at the last clinic visit are important for ICH risk, we used the BP levels at the last visit for some analyses, including the ROC. However, it is not originally appropriate to use the last available measurement as a predictor of a bleeding event in a prospective study.

Because ischemic events are much more common than bleeding events, the use of antithrombotic agents has been increasing. The present study suggests that one should be careful to avoid BP elevations in antithrombotic users, and it is important to lower their BP adequately to avoid ICH.

Appendix

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Disclosures

None.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Sex-Related Differences in the Risk Factor Profile and Medications of Patients With Atrial Fibrillation Recruited in J-TRACE

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Background: Clinical characteristics, including risk factors for thromboembolism, and medications differ between men and women with atrial fibrillation (AF) in Western countries. Whether such a difference exists for Japanese patients with AF is unclear, so data from J-TRACE were used to investigate this issue.

Methods and Results: A total of 2,892 patients (2,028 men, 864 women; 70.3 years old) with AF were analyzed for the respective prevalences of risk factors and medications. CHADS2 score was calculated to determine thromboembolic risk level. Women were older (P<0.001), and more frequently had heart failure (P<0.001), and hypertension (P=0.051) than men. The proportion of subjects aged 75 years or older was higher among women than among men (P<0.001). CHADS2 score was therefore significantly higher in women than in men (2.05±1.29 vs 1.88±1.33, P<0.001). Sex-related differences were not observed for the prevalence of diabetes mellitus, myocardial infarction or ischemic stroke, nor did warfarin usage differ between men and women.

Conclusions: Sex-related differences were observed in the risk factor profile and medications of Japanese patients with AF. CHADS2 score was higher in women than in men. (*Circ J* 2010; **74:** 650–654)

Key Words: Atrial fibrillation; CHADS2 score; Clinical characteristics; Medications; Sex differences

Atrial fibrillation (AF) is a common cardiac arrhythmia seen in general practice as well as in the cardiology clinic. The prevalence of AF differs between men and women in Western countries,[1–3] and also in Japan.[4,5] Several studies have reported that there are sex-related differences in the clinical characteristics and medications of patients with AF.[6–10] A prospective, cohort study indicated that the effects of AF on the risk of stroke were greater in women than in men after adjustment for age and comorbidity.[9] Other studies also showed that AF is associated with an increase in cardiovascular events, including mortality and stroke, especially in women.[7,11,12] Some risk stratification schemes consider women to be at high risk for ischemic stroke,[13,14] while others do not.[15,16] However, because the sex-related differences in risk factors for cardiovascular diseases and medications of Japanese patients with AF have yet to be clarified, registry data for a large, nation-wide, multicenter, cooperative study, J-TRACE (The Japan Thrombosis Registry for Atrial Fibrillation, Coronary or Cerebrovascular Events),[17,18] were analyzed to address this issue in the present study.

Methods

The details of J-TRACE have been reported elsewhere.[17,18] Briefly, J-TRACE has a steering committee of 5 members and 41 regional coordinators selected from 10 regions of Japan (Appendix 1). Recruitment of patients to investigate risk factor profiles and current status of medications for risk factors and for prevention of cardiovascular events in patients with

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Table 1. Clinical Characteristics of Japanese Patients With AF

	Men (n=2,028)	Women (n=864)	P value
Age (years)	69.4±9.4	72.6±8.5	<0.001
≥75 years (%)	32.0	44.5	<0.001
Chronic AF* (%)	68.8 (1,062/1,543)	66.1 (462/699)	0.199
BMI (kg/m²)	23.8±3.2	23.4±4.1	<0.001
CHF (%)	17.0	27.1	<0.001
Hypertension (%)	57.2	61.1	0.051
DM (%)	19.1	16.7	0.125
Ischemic stroke (%)	29.4	26.3	0.089
VHD (%)	10.1	21.1	<0.001
MI (%)	7.6	5.9	0.096
HC (%)	25.1	35.5	<0.001
Drinker (%)	46.3	5.2	<0.001
Smoker (%)	21.2	4.3	<0.001
CHADS2 score	1.88±1.33	2.05±1.29	<0.001

Data are mean±SD or % of patients.
*In the myocardial infarction and stroke categories; subtypes of AF were not specifically determined.
AF, atrial fibrillation; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus; MI, myocardial infarction; VHD, valvular heart diseases including valve replacement; HC, hypercholesterolemia.

prior stroke, myocardial infarction (MI) or AF began in January 2005 and ceased in December 2006.

Study Population

Patients aged 20–90 years were eligible for enrollment if they had at least 1 of the 3 cardiovascular diseases (stroke, MI or AF). The study protocol was approved by an Institutional Review Board at each participating site and all patients gave informed consent. Those in the AF category, and those in the stroke and MI categories who also had AF, comprised the study subjects for this subanalysis of J-TRACE. Those in the recovery phase of acute MI or acute stroke were not eligible for enrollment in J-TRACE.

Baseline Characteristics

All subtypes of AF were included. AF was diagnosed electrocardiographically using standard diagnostic criteria. Risk factors and comorbidities were collected from the medical record as baseline data. Among them were hypertension, diabetes mellitus, hypercholesterolemia, valvular diseases, MI, ischemic stroke, congestive heart failure, smoking, and drinking. Regular use of medications, including anticoagulants, antiplatelet agents, and drugs for hypercholesterolemia, hypertension, and diabetes mellitus, was also determined from the medical record. Each patient's CHADS2 score[15] was calculated to determine the level of cardioembolic risk: 1 point was given for advanced age (≥75 years), hypertension, congestive heart failure, or diabetes mellitus, and 2 points for prior stroke or transient ischemic attack.

Statistical Analysis

Continuous variables are shown as the mean±SD, and categorical variables as percentages. Continuous variables were compared by analysis of variance or Student's t-test, and categorical variables with the chi-square test, with $P<0.05$ considered significant.

Table 2. Distribution of CHADS2 Scores

CHADS2 score	Men	Women
0	15.9	11.1
1	28.4	25.0
2	23.5	29.6
3	19.2	20.6
4	10.5	10.0
5	2.2	3.4
6	0.3	0.3

Figures are % of patients.
P<0.001 between men and women.

Table 3. Age and CHADS2 Score

	Age			P value
	<65 years	65–74 years	≥75 years	
Men	1.24±1.12 (n=572)	1.63±1.22 (n=808)	2.74±1.17 (n=648)	<0.001
Women	1.38±1.16 (n=153)	1.57±1.14 (n=326)	2.72±1.12 (n=385)	<0.001

Data are mean±SD.

Results

Risk Factor Profile

A total of 2,892 patients (2,028 men, 864 women; mean age, 70.3 years) with AF comprised the study group. Numbers of patients and their mean age in the 3 categories were as follows: AF category, 1,543 men (68.9±9.6 years old) and 699 women (72.4±8.5); stroke category, 399 men (70.6±8.4) and 141 women (73.0±8.3); MI category, 86 men (71.7±8.1) and 24 women (75.3±8.0). Their clinical characteristics are summarized in **Table 1**. Some of the characteristics exhibited differences by sex. Women were older (P<0.001), and more frequently had congestive heart failure (P<0.001), hypertension (P=0.051), valvular diseases or valve replacement (P<0.001), and hypercholesterolemia (P<0.001) than the men, but drank (P<0.001) and smoked (P<0.001) less frequently than men. The proportion of subjects aged 75 years or older was higher and body mass index was slightly but significantly lower in women than in men (P<0.001, each case). The prevalences of chronic AF, diabetes mellitus, MI, and ischemic stroke did not differ between men and women.

The CHADS2 score was slightly but significantly higher in women than in men (**Table 1**, P<0.001) because of their higher prevalence of older age (≥75 years), hypertension, and congestive heart failure. The distribution of CHADS2 scores differed significantly between men and women (**Table 2**, P<0.001). It increased with age for both men and women, but did not differ between men and women in any age group (**Table 3**).

Medications

Medications are summarized in **Table 4**. Use of warfarin and antiplatelet agents did not differ between men and women. Reflecting the differences in prevalence of hypertension and hypercholesterolemia between men and women, drugs for the treatment of these diseases were used more frequently in women than in men (P<0.001, each case). In contrast, use of antidiabetic drugs was similar in men and women.

There were no apparent sex-related differences in the rate of use of warfarin or aspirin at any CHADS2 score (**Table 5**).

Table 4. Medications at Baseline

	Men	Women	P value
Warfarin	73.1	72.7	0.807
Antiplatelet agents	37.9	36.0	0.328
Aspirin	32.1	30.8	0.504
Ticlopidine	5.0	5.0	0.316
Cilostazol	2.0	1.3	0.191
Antihypertensives	71.8	78.8	<0.001
ACEI	17.4	14.8	0.087
ARB	28.4	32.2	0.039
β-blockers	21.4	21.3	0.927
Calcium antagonists	36.4	42.5	0.002
Diuretics	18.6	33.4	<0.001
Lipid-lowering drugs	16.7	26.4	<0.001
Statins	14.9	23.7	<0.001
Antidiabetic drugs	10.6	10.9	0.825
Oral	8.7	8.6	0.921
Insulin	1.4	2.2	0.111

Data are % of patients.
Only major drugs for treatment of comorbidities and prevention of thromboembolism are listed (see Uchiyama et al[18] for more detailed information on medications in J-TRACE).
ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers.

Table 5. Use of Warfarin and Aspirin at Each CHADS2 Score

CHADS2 score	Warfarin use (%)		Aspirin use (%)	
	Men	Women	Men	Women
0	57.9	61.4	32.3	28.1
1	68.9	66.2	33.9	31.4
2	74.8	73.8	30.6	32.0
3	84.9	77.0	26.9	30.3
4	81.1	87.2	34.4	29.1
5	77.3	79.3	31.3	27.6
6	83.3	66.7	83.3	66.7
P value	<0.001	0.001	0.008	0.852

Warfarin usage differed significantly among CHADS2 scores in both men (P<0.001) and women (P=0.001). It increased gradually from approximately 60% to 80% as the score increased from 0 to 3 for both men and women; thereafter it reached a plateau, except in the case of women with a score of 6. Aspirin usage also differed significantly among CHADS2 scores in men (P=0.008), but not in women (P=0.852). It did not show any apparent score-dependent increase as observed in the case of warfarin usage.

Discussion

The major findings of the present study are as follows. First, there were sex-related differences in the risk factor profile and medications of patients with AF recruited in J-TRACE. Women were older and more frequently had hypertension, valvular diseases, congestive heart failure, and hypercholesterolemia than men. The prevalence of diabetes mellitus, ischemic stroke, and MI did not differ between men and women. Second, CHADS2 score was consequently slightly but significantly higher in women than in men with AF. This sex-related difference could be largely related to the higher proportion of women aged 75 years or older. Third, no sex-related differences in the use of warfarin or aspirin were observed at any CHADS2 score.

Risk Factor Profile of Patients With AF

Reports from Western countries[6–10] suggest that sex-related differences could exist in the risk factors for cardiovascular diseases of patients with AF. In the present study, mean age was higher and the prevalence of hypertension also tended to be higher in women than in men, consistent with the previous reports;[6–9] however, the prevalence of congestive heart failure was also higher in women than in men in the present study, a finding that is inconsistent with those reports from Western countries.[6–9] Notably, the prevalence of diabetes mellitus and of a prior history of ischemic stroke were not consistent.[6–9]

Cohort studies of the general population in Japan have indicated that the prevalences of hypertension and diabetes mellitus are higher in men than in women.[19–21] The prevalence of cardiac diseases was not higher in women than in men with AF,[4,5] so the higher prevalences of hypertension and congestive heart failure in women with AF found in the present study do not simply reflect the prevalence of these diseases in the general population of Japan. Valvular disease is a well-known risk factor for AF,[22] especially for Japanese women.[23] Drinking and smoking could promote the development of AF,[22–25] and were present more frequently in men than in women in the present study, as in the general population of Japan.[4,5,19–21] The electrophysiological properties of the atria differ between men and women,[26] so greater comorbidity and age might be required for AF to develop in women than in men.

Thromboembolic Risk

A sex difference in CHADS2 score was found in the present study, a finding consistent with the ATRIA study.[7] In the Euro Heart Survey the score might have been higher in women than in men, because mean age and the prevalences of hypertension, diabetes mellitus, and prior ischemic stroke were significantly higher in women than in men.[9] In some studies the levels of biomarkers of a prothrombotic state were higher in women with AF than in men with AF.[27,28] These findings could explain the inclusion of female sex as a risk factor in some schemes for predicting thromboembolic events in patients with AF.[13,14] In fact, among patients with acute stroke, embolic infarction is observed more frequently in women than in men.[29] It is difficult to determine the reasons for the sex-related difference in thromboembolic risk; however, some components of the CHADS2 score were observed more frequently in women in the ATRIA study,[7] Euro Heart Survey,[9] and in the present study.

Medications

Registry studies in Western countries have indicated that warfarin usage does not differ between men and women.[6,9] In the present study, the rate of warfarin usage did not differ between men and women as a whole nor did it differ between them at any CAHDS2 score (**Table 5**). Warfarin usage is at present not necessarily less frequent in women than in men, as reported in earlier registry[6] and community-based cohort[30] studies.

Use of aspirin and antidiabetic drugs was similar in men and women; however, drugs for hypertension and hypercholesterolemia were used more frequently by women than by men. The latter finding might reflect the sex-related differ-

ences in the prevalence of these diseases in the present study.

Study Limitations

First, enrollment of consecutive patients with stroke, MI, and AF was recommended, but may not necessarily have occurred at each participating site and this possible selection bias could have affected the present results. Second, data for subjects with AF were collected from 3 categories of J-TRACE,[17,18] possibly resulting in increased prevalences of ischemic stroke and MI. However, this might not necessarily have affected sex-related differences in the frequency of these diseases in the present study. Actually, when only patients of AF category were analyzed, the results did not differ in terms of sex-related differences in mean age, CHADS2 score, and prevalences of heart failure, hypertension, smoking, drinking habit and warfarin usage (data not shown). Third, the study design of the J-TRACE did not define the diagnostic criteria of comorbidities, including hypertension, hypercholesterolemia and others; however, data of comorbidities were collected from the medical record. If strict diagnostic criteria of comorbidities were used, the present results would not have changed greatly. Finally, the intensity of anticoagulation was not determined systematically, and follow-up data are not yet available.

Clinical Implications

Our findings indicate sex-related differences in the clinical risk factor profile of patients with AF, with the CHADS2 score slightly but significantly higher in women with AF than in men with AF in the clinical setting in Japan. Further follow-up studies are required to elucidate the effects of these sex-related differences on subsequent thromboembolic events.

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Disclosure

There is no conflict of interest to declare.

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Appendix 1

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