

[ ORIGINAL ARTICLE ]

## Relationship between Impairment of the Vascular Endothelial Function and the CHA<sub>2</sub>DS<sub>2</sub>-VASc Score in Patients with Sinus Rhythm and Non-valvular Atrial Fibrillation

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### Abstract:

**Objective and methods** There is little information concerning the influence of the heart rhythm on the vascular endothelial function in patients with non-valvular atrial fibrillation (AF) compared with studies concerning sinus rhythm (SR). The present study included paroxysmal (n=184) or chronic (n=53) AF patients without heart failure and control subjects with SR (n=79) matched for age, gender and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Paroxysmal AF was defined as episodes that terminated spontaneously within 7 days, while chronic AF was defined as longstanding AF that was refractory to cardioversion for 12 months or longer. There were no significant differences in the numbers of patients receiving renin-angiotension-aldosterone system inhibitors or statins among the three groups.

**Results** Among the 237 AF patients (155 men, mean age 64±9 years, mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score 1.8±1.4), the flow-mediated dilatation (FMD) was 5.4%±2.6% in the paroxysmal AF group, 4.3%±2.1% in the chronic AF group and 6.5%±3.5% in the SR group. There were significant differences among the 3 groups (all, p<0.05). Nitroglycerin-induced dilatation (NMD) was noted in 14.6%±6.5% of the paroxysmal AF group, 16.5%±9.1% of the chronic AF group and 12.7%±5.9% of the SR group, with no significant differences among the 3 groups. There was a significant negative correlation between the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and the FMDs value in all 3 groups (paroxysmal AF group:r=-0.322, p<0.01; chronic AF group:r=-0.291, p<0.05; SR group:r=-0.326, p<0.01).

**Conclusion** In comparison with SR, the frequency and duration of AF episodes appear to cause deterioration of the vascular endothelial function.

**Key words:** atrial fibrillation, vascular endothelial function, flow mediated dilatation, CHA<sub>2</sub>DS<sub>2</sub>-VASc score

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### Introduction

Epidemiological studies in Western countries indicate that the incidence of atrial fibrillation (AF) increases significantly with population aging, occurring in approximately 4% of those in their 70s and approximately 10% of those

over 80 years of age (1). The proportion of elderly individuals in the Japanese population is rapidly increasing, and the incidence of AF in people in their 60s and 70s was recently reported to be about 1% and 2-3%, respectively (2). These numbers are comparable to those observed in Western countries. The number of patients with AF in 2020 is expected to reach 1,000 per 100,000 population (2). The increasing inci-

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dence of AF is therefore a major medical and social problem.

AF causes cardiovascular complications, such as thromboembolism or heart failure (3). In addition, it has been reported that the annual incidence of ischemic stroke is 4-5 times higher in non-valvular AF cases than in sinus rhythm (SR) cases (4). It has been suggested that AF not only impairs the atrial hemodynamics and coagulation activity but also induces endothelial damage and thrombogenesis in patients with non-valvular AF (5). It has recently been suggested that antithrombotic therapies for non-valvular AF may be effective in preventing ischemic stroke and systemic embolism.

The guidelines published in 2010 by the European Society of Cardiology (ESC) recommend that risk stratification for stroke, a serious complication in patients with non-valvular AF, be performed based on CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and that antithrombotic treatment be administered accordingly (6).

Several studies have suggested that an irregular heart rhythm and low pulsation flow are factors that impair the vascular endothelial function. In addition, an impaired vascular endothelial function has been reported in patients with congestive heart failure and hypertension, diabetes mellitus and stroke (7). Aging is also a critical factor that reduces the vascular endothelial function. Given the above, we hypothesized that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score might be a useful index for evaluating vascular endothelial dysfunction in patients with non-valvular AF.

In this study, we compared the degree of vascular endothelial dysfunction in patients with non-valvular AF with that in patients with SR and examined the relationship between the vascular endothelial function and CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

## Materials and Methods

### Study patients

We enrolled a total of 729 consecutive patients with paroxysmal or chronic AF confirmed on the basis of symptoms, standard 12-lead electrocardiogram (ECG) and/or ambulatory 24-h monitoring findings at our institute between August 2010 and July 2014. Database registration started in August 2010, with continual registration thereafter. The principal aim for establishing this hospital-based database was to monitor the prognosis of cardiovascular disease in a local area of Japan. The study protocol was approved by the local institutional review board. Patients were excluded if they had a history of significant valvular heart disease or intracardiac operation as determined by transthoracic echocardiography. Demographic data, cardiovascular risk factors and medications were recorded at baseline. The index date was defined as the date of the first occurrence of AF.

The study included 184 paroxysmal and 53 chronic non-valvular AF patients without present heart failure (155 men,

mean age 64±9 years, mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score 1.8±1.4). We also recruited control SR counterparts matched for age, gender and CHA<sub>2</sub>DS<sub>2</sub>-VASc score (n=79, 53 men, mean age 64±11 years, mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score 1.8±1.3).

All subjects were treated on an outpatient basis every two to four weeks and were followed for one year or more. Fasting blood glucose and hemoglobin A<sub>1c</sub>, fasting serum cholesterol and triglycerides were measured to screen for diabetes and dyslipidemia. flow-mediated dilatation (FMD) and nitroglycerin-induced dilatation (NMD) were also measured to evaluate the vascular endothelial function in subjects with SR and non-valvular AF. To detect underlying cardiopulmonary disease, noninvasive tests were conducted, including history-taking, chest X-ray, exercise testing and transthoracic echocardiography. Attending physicians ordered pulmonary function tests, chest computed tomography (CT) and cardiac catheterization if necessary.

The study excluded patients with the following conditions: hepatorenal dysfunction; women in whom pregnancy was likely; or patients with drug allergy or severe hemorrhagic tendency. Risk factors for thromboembolism in terms of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score [C: congestive heart failure (1 point), H: hypertension (1 point), A<sub>2</sub>: age 65 to 74 years (1 point) and age ≥75 years (2 points), D: diabetes mellitus (1 point), S: prior stroke or transient ischemic attack (2 points), VA: vascular disease (1 point) and Sc; sex category (female, 1 point)] were determined by the 2012 ESC guidelines (6).

We examined the background factors, FMD and NMD based on the patients' CHA<sub>2</sub>DS<sub>2</sub>-VASc scores among SR and paroxysmal and chronic AF subjects.

### Definitions

Paroxysmal AF was defined as AF terminating spontaneously within seven days of onset (8). Chronic AF was defined as AF refractory to antiarrhythmic drug therapy or electrical cardioversion in which an SR could not be maintained for more than 12 months, as assessed by ECG (9). Valvular AF was defined as AF with mitral stenosis and/or a history of valvular surgery (both biological and mechanical valve). Cerebral thromboembolism was confirmed based on clinical symptoms and the presence of a ≥3-mm infarct area, as obtained by brain CT or magnetic resonance imaging (MRI). The diagnosis of hypertension followed the 2009 Japanese Society of Hypertension (JSH) guidelines (10). Dyslipidemia was defined as fasting serum cholesterol of ≥220 mg/dL and triglycerides of ≥150 mg/dL (11). Diabetes mellitus was diagnosed if fasting venous blood glucose was ≥126 mg/dL or hemoglobin A<sub>1c</sub> was ≥6.5% (12). AF was divided into three types, depending on the time of onset: diurnal type (from 7:00 to 17:00), nocturnal type (from 17:00 to 7:00) and mixed type (any time) (13). Chronic obstructive pulmonary disease was defined as a forced expiratory volume in 1 second of <70%, as measured by a lung function test.

### Protocols and antiarrhythmic drug therapy

Paroxysmal and chronic AF patients were treated with rhythm or rate control therapy. Antiarrhythmic drugs were prescribed to maintain a normal SR in patients with paroxysmal AF as reported in our previous study (14). To confirm the clinical course of AF, symptoms were assessed by interview, and a standard 12-lead ECG was recorded after the commencement of antiarrhythmic drugs or at 2-4 weeks after changing those drugs, while an ECG was recorded with a portable monitor at the time of the medical examination. Whenever palpitations occurred, ambulatory 24-h monitoring was conducted at the discretion of the attending physician to determine whether or not AF had recurred. In patients with chronic AF,  $\beta$ -blockers, Ca antagonists or digitalis were administered orally to control the heart rate.

### Antithrombotic therapy protocols

Antithrombotic therapy was generally performed according to the 2013 the Japanese Circulation Society (JCS) guidelines (8), but the decision to administer antithrombotic therapy was left to the physician. Warfarin was administered according to guidelines regulating international normalized ratios (INRs; target: 1.6-3.0), and direct oral anticoagulants were also prescribed on the basis of the patient's background.

### Protocols for FMD and NMD measurement

FMD was measured in the morning after 12 hours of fasting and no medications using standard techniques (7). All subjects were asked to refrain from smoking and consuming alcohol or beverages containing caffeine for at least 24 hours prior to the study. Subjects were asked to rest in a supine position on a bed for at least 10 minutes. The right brachial artery was visualized via high-resolution ultrasound on the anterior aspect of the arm (Unex, Nagoya, Japan; using a handheld 10-mHz vascular ultrasound probe). The position of the transducer relative to the antecubital fossa was recorded. The center of the artery was defined as the location with the clearest picture of both the anterior and posterior intimal layers. The focus zone was then adjusted to the depth of the anterior wall of the right brachial artery. Although images were subsequently magnified, no operating parameters were changed during the study. For arterial diameter measurements, the clearest defined section of the artery was identified via B-mode imaging, and an M-mode cursor was positioned over this location at an angle of 90° from the arterial lumen. The arterial diameter was then measured from the anterior to posterior "m" line (media-adventitia interface).

After baseline images were obtained, a pneumatic cuff was inflated to at least 30 mmHg greater than the subject's measured systolic pressure in order to occlude the arterial inflow for 5 minutes. Arterial image acquisition for diameter measurement was then performed at baseline and continuously from 30 seconds to 2 minutes after cuff deflation.

FMD was expressed as the percent change in the brachial artery diameter at end diastole, coincident with the R wave onset. After a 30-minute rest period in the supine position, new baseline images were obtained, and sublingual nitroglycerin (0.3 mg) was administered to facilitate the evaluation of endothelium-independent vasomotor responsiveness. NMD was recorded 4 minutes after drug administration. In this study, NMD was also measured in 185 (58%) of 316 subjects after obtaining their informed consent. For each individual, the baseline brachial artery diameter and response to FMD and NMD were calculated using the mean of five recordings during five cardiac cycles.

To assess the repeatability of this method, FMD and NMD were also measured twice in patients with sinus nodal rhythm (n=48). Changes in diameter were recorded continuously, and then vasodilatation was estimated as the percent change in diameter over the baseline value at the maximum dilatation after reactive hyperemia (FMD) and after the sublingual application of nitroglycerin. To assess the repeatability of the method used during AF, FMD and NMD were measured 5 times at end-diastole coincident with the R wave and 600 ms after the R wave, and 95% Bland-Altman bounds were obtained.

### Statistical analyses

The obtained values were expressed as the mean  $\pm$ 1 standard deviation. For the comparison of the patient characteristics and the FMD and NMD values among the three groups, a one-way analysis of variance (ANOVA) was used, followed by the post-hoc Bonferroni test. Patient percentages were compared with the chi-squared test. We used the SPSS 13.0 statistical software package (SPSS Japan, Tokyo, Japan) for the statistical analyses, with the level of significance set at  $p < 0.05$ .

### Ethical issues

The ethics committee at Iwate Medical University School of Medicine granted approval for this study, and all of the patients gave their informed consent.

## Results

### A comparison of the clinical profiles among the SR, paroxysmal AF and chronic AF groups (Table 1)

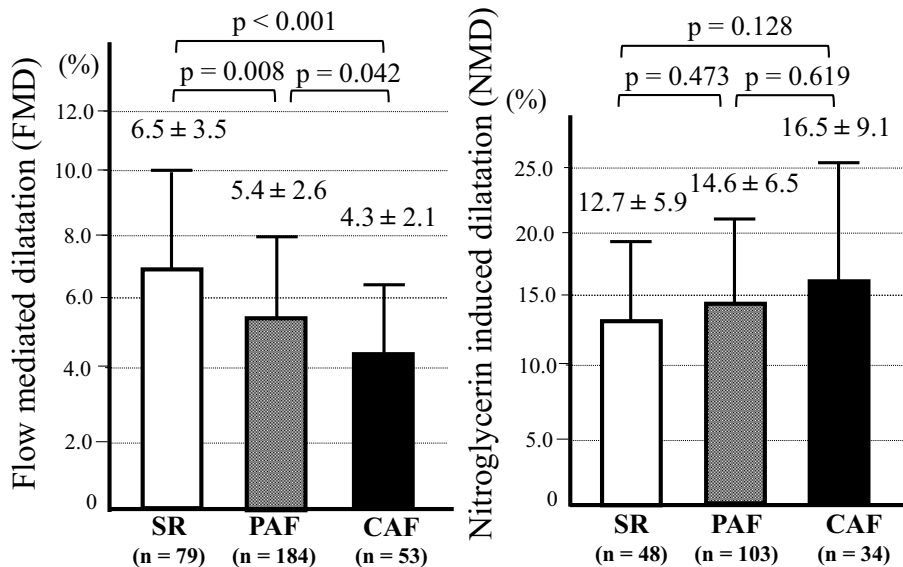
The left ventricular end diastolic dimension (LVDd) and left atrial dimension (LAD) were significantly higher in the chronic AF group than in the SR and paroxysmal AF groups ( $p < 0.01$ ). The left ventricular ejection fraction (LVEF) was significantly lower in the chronic AF group than in the SR and paroxysmal AF groups ( $p < 0.01$ ). There were otherwise no significant differences in demographic data among the three groups, including the percentage of administration of renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, Ca antagonist,  $\beta$ -blockers and organic heart disease (Table 1).

**Table 1. Clinical Profiles among SR, PAF and CAF.**

	SR	PAF	CAF	p value
Number	79	184	53	
Age (yrs)	64±11	64±10	64±8	0.823
Male : female	53:26	120:64	35:18	0.799
Hypertension	38 (48%)	93 (51%)	18 (34%)	0.102
Diabetes mellitus	8 (10%)	26 (14%)	5 (9%)	0.194
Dyslipidemia	23 (29%)	57 (31%)	16 (30%)	0.263
Smoking	10 (13%)	20 (11%)	6 (11%)	0.990
Alcohol habits	22 (28%)	51 (28%)	19 (36%)	0.268
Hyperuricemia	8 (10%)	14 (8%)	4 (8%)	0.945
Organic heart disease	17 (22%)	23 (13%)	16 (30%)	0.071
Organic pulmonary disease	3 (4%)	5 (3%)	0 (0%)	0.436
TTE parameters;				
LVDd (mm)	45.7±5.9	45.9±4.4	48.3±5.1	0.005
LAD (mm)	38.1±7.0	41.1±6.5	46.8±6.0	<0.001
LVEF (%)	68.3±9.8	68.2±7.3	63.7±9.6	0.002
RAAS inhibitors	23 (29%)	67 (36%)	19 (36%)	0.151
Statin	19 (24%)	53 (29%)	10 (19%)	0.232
Ca antagonist	21 (27%)	47 (26%)	16 (30%)	0.318
β-blocker	17 (22%)	51 (28%)	17 (32%)	0.209
CHA2DS2-VASc score	1.8±1.3	1.8±1.5	1.8±1.4	0.703

Continuous values are presented as the mean±SD. The values in parentheses are percentages.

SR: sinus rhythm, PAF: paroxysmal atrial fibrillation, CAF: chronic atrial fibrillation, TTE: transthoracic echocardiography, LVDd: left ventricular end-diastolic dimension, LAD: left atrial dimension, LVEF: left ventricular ejection fraction, RAAS: renin-angiotensin-aldosterone system

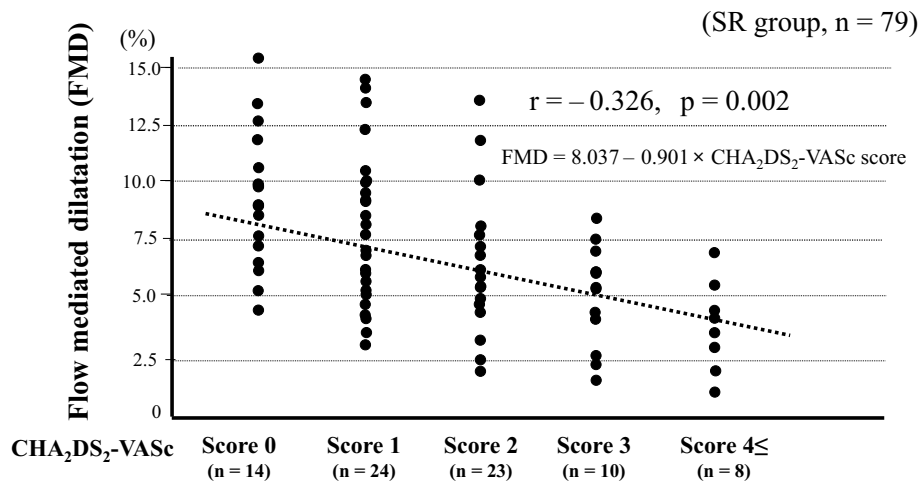


**Figure 1. Relationship between the heart rhythm status and flow-mediated dilatation/nitroglycerin-induced dilatation. SR: sinus rhythm, PAF: paroxysmal atrial fibrillation, CAF: chronic atrial fibrillation**

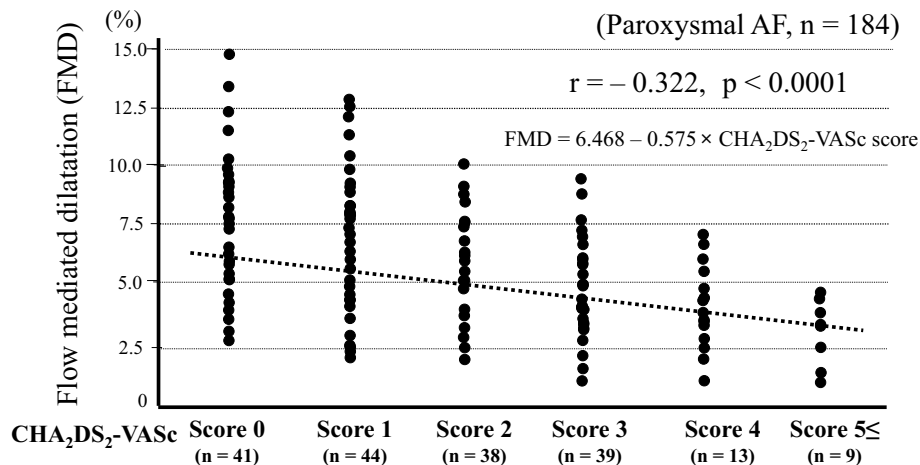
### Relationship between heart rhythm status and flow mediated dilatation/nitroglycerin induced dilatation

The FMD was 6.5%±3.5% in the SR group, 5.4%±2.6% in the paroxysmal AF group and 4.3%±2.1% in the chronic

AF group, showing significant differences among the 3 groups ( $p < 0.05$ ). The NMD was 12.7%±5.9% in the SR group, 14.6%±6.5% in the paroxysmal AF group and 16.5%±9.1% in the chronic AF group, with no significant differences among the 3 groups ( $p = \text{NS}$ ) (Fig. 1).



**Figure 2.** Relationship between the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and flow-mediated dilatation in the SR group. SR: sinus rhythm



**Figure 3.** Relationship between the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and flow-mediated dilatation in the paroxysmal AF group. PAF: paroxysmal atrial fibrillation

### Relationship between the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and FMD

In the SR group, the FMD was 6.1%±2.7% in the score 0 group, 5.9%±2.0% in the score 1 group, 5.4%±2.5% in the score 2 group, 4.2%±2.3% in the score 3 group and 3.7%±1.8% in the score ≥4 group based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, showing significant differences among the 5 groups (p<0.01). There were also significant negative correlations between the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and the FMD (r=-0.326, p<0.01) (Fig. 2).

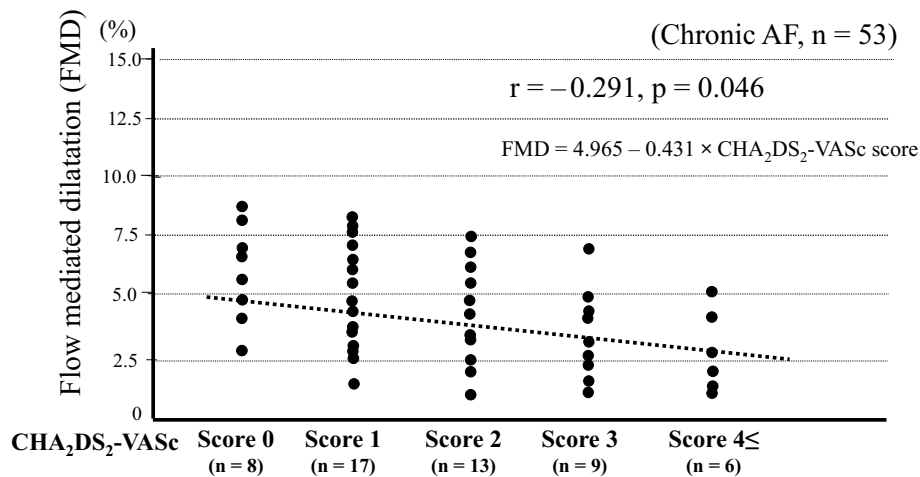
In the paroxysmal AF group, the FMD was 6.1%±2.7% in the score 0 group, 5.9%±2.0% in the score 1 group, 5.4%±2.5% in the score 2 group, 4.7%±2.3% in the score 3 group, 4.1%±1.8% in the score 4 group, and 3.6%±2.0% in the score ≥5 group based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, showing significant differences among the 6 groups (p<0.01). The relationships between the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and the FMD were significant in this group (r=-0.322, p<0.01) (Fig. 3).

In the chronic AF group, the FMD was 5.3%±2.2% in the score 0 group, 4.7%±2.1% in the score 1 group, 4.4%±3.0% in the score 2 group, 4.0%±2.1% in the score 3 group, and 3.4%±2.2% in the score ≥4 group based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, showing significant differences among the 5 groups (p<0.01). Once again, higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were correlated with lower FMD values in the chronic AF group. CHA<sub>2</sub>DS<sub>2</sub>-VASc scores also had a significant negative correlation with the FMD (r=-0.291, p<0.05) (Fig. 4).

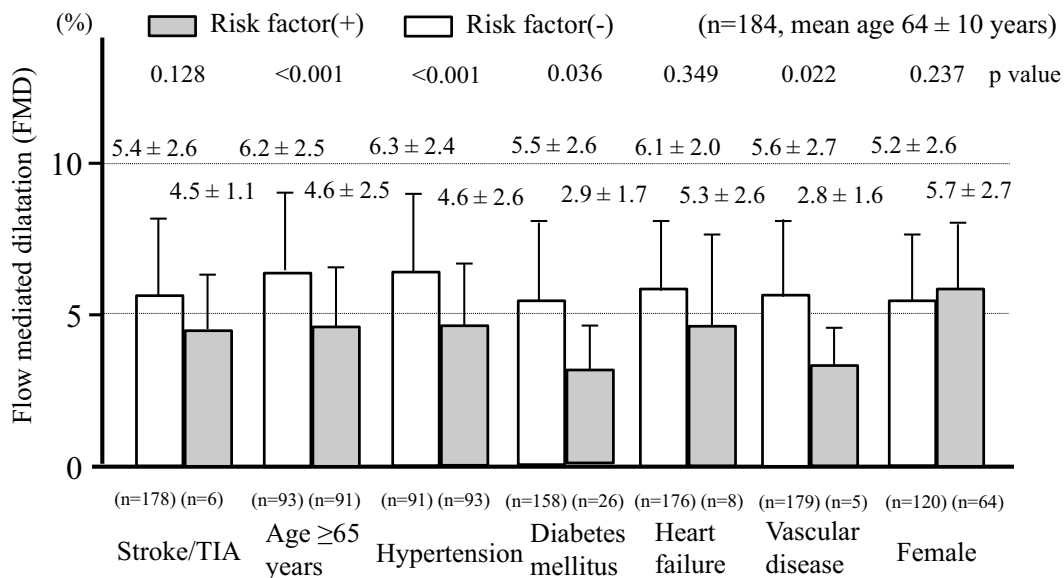
### Relationship between individual risk factors comprising the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and the FMD in patients with AF

In the paroxysmal AF group, the FMD was 4.6%±2.5% in those ≥65 years of age and 6.2%±2.5% in those <65 years of age, 4.6%±2.6% in those with hypertension and 6.3%±2.4% in those without hypertension, 2.9%±1.7% in those with diabetes mellitus and 5.5%±2.6% in those without diabetes mellitus and 2.8%±1.6% in those with vascular disease and 5.6%±2.7% in those without vascular disease, showing





**Figure 4.** Relationship between the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and flow-mediated dilatation in the chronic AF group. CAF: chronic atrial fibrillation



**Figure 5.** Relationship between individual risk factors comprising the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and flow-mediated dilatation in patients with paroxysmal AF.

significant differences between each pair of individual risk factors comprising the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ( $p < 0.05$ ) (Fig. 5).

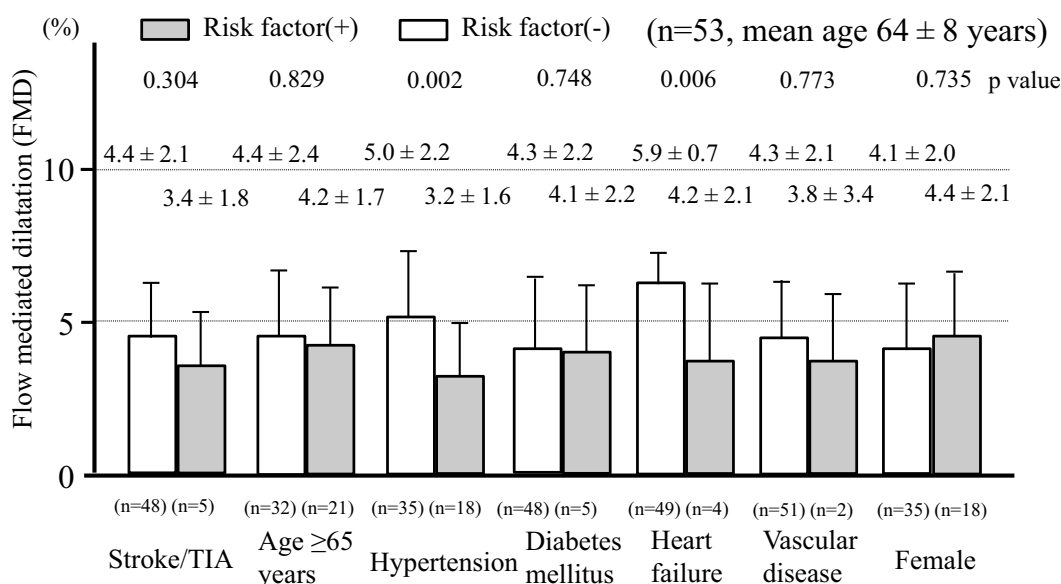
In the chronic AF group, the FMD was  $3.2\% \pm 1.6\%$  in the group with hypertension and  $5.0\% \pm 2.2\%$  in those without hypertension and  $4.2\% \pm 2.1\%$  in those with heart failure and  $5.9\% \pm 0.7\%$  in those without heart failure, showing significant differences between each pair of individual risk factors comprising the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ( $p < 0.05$ ) (Fig. 6).

In a multivariate logistic regression analysis, hypertension [odds ratio (OR) 0.221, 95% confidence interval (CI) 0.114-0.428,  $p < 0.001$ ] and vascular disease (OR 0.112, 95% CI 0.016-0.776,  $p = 0.027$ ) were associated with vascular endothelial dysfunction (VED) among individual risk factors comprising the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores when VED was defined as an FMD of  $< 3.0\%$  (Table 2).

## Discussion

### Major findings

The present study found that AF episodes appear to cause deterioration in the vascular endothelial function compared with SR, and a long AF duration also seems to impair the endothelium-dependent vasodilatation when matched for age, gender and CHA<sub>2</sub>DS<sub>2</sub>-VASc score. In addition, higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were found to be correlated with lower endothelium-dependent vasodilatation among SR and paroxysmal and chronic AF patients.



**Figure 6.** Relationship between individual risk factors comprising the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and flow-mediated dilatation in patients with chronic AF.

**Table 2.** Predictors for Detecting Vascular Endothelial Dysfunction among Individual Risk Factors Comprising the CHA<sub>2</sub>DS<sub>2</sub>-VASc Score.

(N=237, mean age 65±10 years)			
Variable	$\beta$	Odds ratio (95%CI)	p value
Hypertension	-1.510	0.221 (0.114 - 0.428)	<0.001
Vascular disease	-2.186	0.112 (0.016 - 0.776)	0.027
Female	-0.468	0.626 (0.332 - 1.217)	0.167
Age ≥ 65 years	-0.508	0.602 (0.282 - 1.217)	0.189
Diabetes mellitus	0.446	2.535 (0.659 - 3.706)	0.311
Prior stroke/TIA	0.710	2.034 (0.318 - 12.98)	0.453
Congestive heart failure	19.82	406.1 (0.001 - 65,478)	0.998

CI: confidence interval, TIA: transient ischemic attack

### Relationship between CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and endothelial dysfunction in patients with non-valvular AF

Previous studies have reported that an irregular blood flow due to AF reduces the expression of endocardial nitric oxide (NO) production enzyme and nitric oxide synthase (NOS) gene originating from the left atrium and appendage (15). It has also been reported that longstanding AF increases the oxidative stress and inflammation of atrial endothelial cells (16). The formation of atrial thrombus may be accelerated by this malignant cycle. In addition, the NO system is known to perform various anti-arteriosclerotic actions, including not only vasodilation but also the inhibition of platelet aggregation, inhibition of vascular smooth muscle cell growth, elimination of superoxides and suppression of adhesion factor (17). However, risk factors for cardiovascular disease, such as aging, diabetes mellitus, hypertension and heart failure (CHA<sub>2</sub>DS<sub>2</sub>-VASc score) further attenuate the vascular NO system (18-21).

In contrast, in an animal model of rapid pacing, AF reduced the expression of thrombomodulin (TM), which is a control factor for blood coagulation produced by vascular endothelial cells, and tissue factor pathway inhibitor (TFPI) (22) and increased the blood concentrations of plasminogen activator inhibitor (PAI-1) (16). There are several experimental reports that AF easily causes thrombogenesis. Furthermore, reports based on clinical practice indicate that paroxysmal AF accelerated the local platelet aggregation derived from vascular endothelial damage (23) and activation of coagulation factor (24). In addition, some studies have shown that chronic AF accelerated the infiltration of leukocytes and the expression of von Willebrand factor (vWF) and tissue factor (TF) based on pathologic specimens of atrium obtained from surgery (25, 26). Taken together, these findings suggest the acceleration of the intra-cardiac thrombogenic system, with endothelial damage in patients with AF possibly leading to the deterioration of both endothelium-dependent vasodilatation and anti-thrombogenic activity.

Previous studies have shown that the FMD values in patients with AF were lower than those in patients with SR (27, 28). To our knowledge, however, the relationship between the degree of vascular endothelial damage and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score reflecting risk stratification for stroke remains unclear in patients with non-valvular AF. In the present study, a significant negative correlation was noted between the FMD and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in subjects with non-valvular AF. Based on our findings, the frequency and duration of AF episode appear to cause deterioration in the vascular endothelial function. In addition, hypertension and vascular disease seemed to be significant independent predictors for VED among individual risk factors comprising the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in our study. These findings suggest that not only hypertension but also CHA<sub>2</sub>DS<sub>2</sub>-VASc scores are required to evaluate VED in subjects with non-valvular AF.

Further studies are needed to clarify whether or not the endothelial function index can improve the risk stratification value for stroke in patients with non-valvular AF.

### Limitations

Several limitations associated with the present study warrant mention. First, the relationship between FMD and the cardiovascular prognosis in patients with non-valvular AF remains unclear. According to previous studies in Europe and the U.S., there is a close relationship between the FMD values and ischemic heart disease (29) and peripheral vascular disease (30). Second, we did not measure the levels of inflammation biomarkers in patients with non-valvular AF. However, endothelium-dependent vasodilatation is generally considered to be an index indicating the degree of arteriosclerosis caused by chronic inflammation of blood vessels. A previous study showed that the blood C-reactive protein values were related to endothelium-dependent vasodilatation, as chronic inflammation is related to the development of atherosclerosis (31). Third, the reliability of blood flow measurements in AF may be questionable, given the known beat-to-beat variations associated with AF rhythm. However, because each point on the FBF curve is based on the angle of the plethysmographic curve over five cardiac cycles, this averaging effect may attenuate the beat-to-beat variations and limit their influence. Fourth, the types of antihypertensive (32) and antiarrhythmic drugs (33) and the dosage of statins (34) may have influenced the FMD values in patients with non-valvular AF. Fifth, the present study is a retrospective study analyzing the FMD, and we cannot completely exclude the possibility of bias despite carefully matching for age, gender and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores among the three groups. Finally, the patient population in this study was relatively small. A large, multicenter, prospective study will be required to determine whether or not including the FMD might improve the predictive abilities of the score for systemic thromboembolism in patients with non-valvular AF.

### Conclusion

The present study found that the frequency and duration of AF episodes appeared to cause deterioration in the endothelial function compared with SR and that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in not only patients with non-valvular AF but also those with SR seemed to affect the impairment of endothelium-dependent vasodilatation.

### Author's disclosure of potential Conflicts of Interest (COI).

Takashi Komatsu: Honoraria, Daiichi-Sankyo and Nippon Behringer.

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### References

1. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation. *J Am Coll Cardiol* **37**: 371-378, 2001.
2. Ohsawa M, Okayama A, Sakata K, et al. Rapid increase in estimated number of persons with atrial fibrillation in Japan: an analysis from national surveys on cardiovascular disease in 1980, 1990 and 2000. *J Epidemiol* **15**: 194-196, 2005.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. *Arch Intern Med* **147**: 1561-1564, 1987.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* **22**: 983-988, 1991.
5. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* **373**: 155-166, 2009.
6. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation-developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* **33**: 2719-2747, 2012.
7. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guideline for the ultrasound assessment of endothelial-dependent flow-mediated vasodilatation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* **39**: 257-265, 2002.
8. Inoue H, Atarashi H, Okumura K, et al; for the JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). *Circ J* **78**: 1997-2021, 2014.
9. Sopher SM, Camm AJ. Atrial fibrillation: maintenance of sinus rhythm versus rate control. *Am J Cardiol* **77**: 24A-37A, 1996.
10. Ogihara T, Kikuchi K, Matsuoka H, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009). *Hypertens Res* **32**: 3-107, 2009.
11. Investigating Committee of Guideline for Diagnosis and Treatment of Hyperlipidemias. Guidelines for diagnosis and treatment of hyperlipidemia in adults. *J Jpn Atheroscler Soc* **25**: 1-34, 1997.
12. Kuzuya T, Nakagawa S, Satoh J, et al. The Committee of Japan Diabetes Society for the diagnostic criteria of diabetes mellitus. *J Jpn Diabetes Soc* **42**: 385-404, 1999.



13. Komatsu T, Tachibana H, Sato Y, Ozawa M, Nakamura M, Okumura K. Efficacy of amiodarone for preventing the recurrence of symptomatic paroxysmal and persistent atrial fibrillation after cardioversion. *Circ J* **71**: 46-51, 2007.
14. Komatsu T, Sato Y, Tachibana H, et al. Relationship between CHADS<sub>2</sub> score and efficacy of antiarrhythmic drug therapy in patients with paroxysmal atrial fibrillation. *Circ J* **77**: 639-645, 2013.
15. Cai H, Li Z, Goette A, et al. Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation: potential mechanisms for atrial thrombosis and stroke. *Circulation* **106**: 2854-2858, 2002.
16. Dudley SC, Hoch NE, McCann LA, et al. Atrial fibrillation increases production of superoxide by the left atrium and left atrial appendage. role of the nadph and xanthine oxidases. *Circulation* **112**: 1266-1273, 2005.
17. Vita JA, Treasure CB, Nabel EG, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. *Circulation* **81**: 491-497, 1990.
18. Skyrme-Jones RA, O'Brien RC, Luo M, Meredith IT. Endothelial vasodilator function is related to low-density lipoprotein particle size and low-density lipoprotein vitamin E content in type 1 diabetes. *J Am Coll Cardiol* **35**: 292-299, 2000.
19. Starr ME, Ueda J, Takahashi H, et al. Age-dependent vulnerability to endotoxemia is associated with reduction of anticoagulant factors activated protein C and thrombomodulin. *Blood* **115**: 4886-4893, 2010.
20. Lloyd-Jones DM, Bloch KD. The vascular biology of nitric oxide and its role in atherogenesis. *Annu Rev Med* **47**: 365-375, 1996.
21. Vane JR, Anggard EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med* **323**: 27-36, 1990.
22. Yamashita T, Sekiguchi A, Iwasaki YK, et al. Thrombomodulin and tissue factor pathway inhibitor in endocardium of rapidly paced rat atria. *Circulation* **108**: 2450-2452, 2003.
23. Akar JG, Jeske W, Wilber DJ. Acute onset human atrial fibrillation is associated with local cardiac platelet activation and endothelial dysfunction. *J Am Coll Cardiol* **51**: 1790-1793, 2008.
24. Freestone B, Chong AY, Nuttall S, Blann AD, Lip GY. Soluble E selectin, von Willebrand factor, soluble thrombomodulin, and total body nitrate/nitrite product as indices of endothelial damage/dysfunction in paroxysmal, persistent, and permanent atrial fibrillation. *Chest* **132**: 1253-1258, 2007.
25. Nakamura Y, Nakamura K, Fukushima-Kusano K, et al. Tissue factor expression in atrial endothelia associated with nonvalvular atrial fibrillation: possible involvement in intracardiac thrombogenesis. *Thromb Res* **111**: 137-142, 2003.
26. Fukuchi M, Watanabe J, Kumagai K, et al. Increased von Willebrand factor in the endocardium as a local predisposing factor for thrombogenesis in overloaded human atrial appendage. *J Am Coll Cardiol* **37**: 1436-1442, 2001.
27. Skolidis EI, Zacharis EA, Tsetis DK, et al. Endothelial cell function during atrial fibrillation and after restoration of sinus rhythm. *Am J Cardiol* **99**: 1258-1262, 2007.
28. Takahashi N, Ishibashi Y, Shimada T, et al. Atrial fibrillation impairs endothelial function of forearm vessels in humans. *J Card Fail* **7**: 45-54, 2001.
29. Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation* **120**: 502-509, 2009.
30. Gokce N, Keaney JF Jr, Hunter LM, et al. Predictive value of non-invasively determined endothelial dysfunction for long-term cardiovascular events in patients with peripheral vascular disease. *J Am Coll Cardiol* **41**: 1769-1775, 2003.
31. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation* **102**: 1000-1006, 2000.
32. Morimoto S, Yano Y, Maki K, Sawada K. Renal and vascular protective effects of telmisartan in patients with essential hypertension. *Hypertens Res* **29**: 567-572, 2006.
33. Jewitt D. Hemodynamic effects of newer antiarrhythmic drugs. *Am Heart J* **100**: 984-989, 1980.
34. Ostad MA, Eggeling S, Tschentscher P, et al. Flow-mediated dilation in patients with coronary artery disease is enhanced by high dose atorvastatin compared to combined low dose atorvastatin and ezetimibe: results of the CEZAR study. *Atherosclerosis* **205**: 227-232, 2009.

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