Risk Factors for Progression of Degenerative Aortic Valve Disease in the Japanese

– The Japanese Aortic Stenosis Study (JASS) Prospective Analysis –

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Background: Because of ethnic difference in the risk of degenerative aortic valve disease (DAVD), risk factors should be clarified in each race to establish prophylactic strategies for severe aortic valve stenosis (AS).

Methods and Results: This study prospectively followed 359 Japanese subjects with DAVD and age ≥ 50 years for 3 years. As both patients with peak aortic transvalvular flow velocity ≥ 2 m/s and < 2 m/s were enrolled, subgroup analysis was also conducted. Most patients were under treatment for their comorbidities. The use of warfarin, but none of the traditional risk factors for atherosclerosis, was related to greater reduction in aortic valve area indexed to body surface area (iAVA). In patients with peak aortic transvalvular flow velocity < 2 m/s, the use of an angiotensin-receptor blocker (ARB) was associated with less decrease in iAVA. In patients with peak velocity ≥ 2 m/s, changes in iAVA were not related to any baseline characteristics, but peak velocity was less increased under treatment with an angiotensin-converting enzyme inhibitor (ACEI).

Conclusions: In Japanese, the use of warfarin may exacerbate DAVD, and augmented management of atherosclerotic risk factors beyond the recommendations in the current guidelines is unlikely to exert additional benefit. The prescription of ARB for DAVD patients before the development of AS or ACEI after the development of AS may be useful. (*Circ J* 2015; **79**: 2050–2057)

Key Words: Angiotensin-converting enzyme inhibitor; Angiotensin-receptor blocker; Aortic valve; Degeneration; Warfarin

The prevalence of aortic valve stenosis (AS) increases with aging,¹ and the number of patients who undergo aortic valve replacement (AVR) has risen in developed countries.² Consequently, the number of surgical procedures for patients > 75 years old has grown.³ Postoperative mortality after AVR declined in the 1990s, but has not necessarily changed thereafter.³

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Degenerative aortic valve disease (DAVD) is the most common cause of AS, particularly in elderly subjects.⁴ The prevalence of AS patients with high operative risks is increased among the elderly and therefore, 73.5% of octogenarian

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patients with severe AS do not undergo AVR.⁵ Recently, in many countries, as well as Japan, transcatheter aortic valve replacement (TAVR) has become available as a procedure suitable for AS patients with high operative risks.^{6,7} However, it does not necessarily reduce the mortality as compared with conventional surgical AVR.^{8,9} Prevention of progression to severe AS may be ideal rather than invasive intervention at the advanced stage of severe AS, and it is valuable to identify the risk factors of progression.

Clinical studies report that the risk factors of DAVD are similar to those of atherosclerosis more than a decade ago.^{10,11} However, recent studies have concluded that risk factors for atherosclerosis, such as hypertension and diabetes mellitus, are not necessarily identified as those for AS.^{12,13} Clinical trials failed to show the beneficial effects of lipid-lowering therapy in AS patients, even though ischemic cardiovascular events were reduced in the same subjects.¹⁴ In addition, ethnic differences in the risk for developing AS are likely present.^{12,15} To establish a preventive strategy, identification of risk factors in each race and in the current era is required.

The aim of the Japanese Aortic Stenosis Study (JASS), a multicenter, hospital-based observational study that consists of retrospective and prospective studies, is to investigate the risk factors for progression of DAVD in Japanese subjects. The JASS Retrospective Analysis retrospectively assessed the risk factors with qualitative assessment of DAVD.¹⁶ In the current JASS Prospective Analysis, risk factors were prospectively assessed with quantitative evaluation of DAVD.

Methods

Subjects

The JASS Prospective Analysis enrolled 359 Japanese subjects who met the following criteria: (1) 50 years old or more; (2) markedly increased reflectivity (calcification) of any aortic valve leaflet or peak aortic transvalvular flow velocity of at least 2 m/s on echocardiography performed between 2007 and 2010; (3) agreement to participate in this study, and (4) to undergo annual echocardiography for 3 years. Subjects with rheumatic valvular disease or who had undergone AVR were excluded. The planned maximum follow-up period for each patient was 3 years, and Doppler echocardiography and blood sampling were conducted at study entry and annually thereafter. Phlebotomy was performed in the fasting or non-fasting state. The estimated glomerular filtration rate was calculated using a formula for the Japanese.¹⁷

This study was conducted in accordance with the principles stated in the Declaration of Helsinki and conforms with the guiding principles of the Ministry of Health, Labour and Welfare, Japan. The study was approved by the local ethics committee of each participating institution, and written informed consent was given by all patients before entry to the study. This study has been registered at <http://www.umin.ac.jp/ctr/list/j/> (UMIN000000707).

Echocardiography and Assessment of the Progression of DAVD

Doppler echocardiography was conducted using commercially available echocardiographic machines as previously described.¹⁶ In the routine echocardiographic examination, measurements were conducted on-line. Left ventricular mass (LVM) was calculated following a formula derived from data compiled by the American Society of Echocardiography,¹⁸ and the LVM index was calculated as a ratio of LVM to body surface area (BSA). Using the continuity equation, aortic valve area (AVA)

was calculated as previously described,¹⁹ and was indexed to BSA (iAVA). We calculated the annualized changes in iAVA (Δ iAVA, $\text{cm}^2 \cdot \text{m}^{-2} \cdot \text{year}^{-1}$) to assess the progression of DAVD as follows:

$$\frac{(\text{iAVA at final measurement} - \text{iAVA at study entry})}{\text{Duration of follow-up.}}$$

Because echocardiography may not be sensitive enough to reveal the changes in AVA in patients with a small AVA, we calculated the annualized changes in peak aortic transvalvular flow velocity as another marker of the progression of DAVD in patients with AS as follows:

$$\frac{(\text{Peak velocity at final measurement} - \text{peak velocity at study entry})}{\text{Duration of follow-up.}}$$

AS was defined as peak aortic transvalvular flow velocity ≥ 2 m/s.^{12,20–22}

In cases where the 3-year follow-up was not achieved, the latest data were utilized.

Statistical Analysis

Continuous data are summarized as means and standard deviations, whereas categorical variables were summarized as counts and percentages. To determine the association between progression of DAVD and variables at baseline, the scatter plot was used to assess the linear correlation for continuous variables, and Student's t-test (or 1-way analysis of variance) was used for categorical data. The means between groups were compared by Student's t-test.

Our previous retrospective study suggested that risk factors for the progression of DAVD differ according to disease stage.¹⁶ Therefore, in addition to analysis of all study subjects, subgroup analysis was conducted following the division of 359 subjects into 2 groups according to the degree of DAVD on baseline echocardiography. The group without AS comprised subjects with peak aortic transvalvular flow velocity < 2 m/s at baseline ($n=150$). The group with AS comprised subjects with peak aortic transvalvular flow velocity ≥ 2 m/s ($n=209$); 6 patients had a bicuspid aortic valve, but all met the criteria for AS and so were included in the group with AS.

All P values were 2-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SAS 9.3 (SAS Institute, Inc, Cary, NC, USA).

Results

Subjects Characteristics

Baseline characteristics are listed in [Tables 1–3](#). In each table, data of all subjects ($n=359$), data of the group without AS (peak aortic transvalvular flow velocity < 2 m/s, $n=150$), and data of the group with AS (peak aortic transvalvular flow velocity ≥ 2 m/s, $n=209$) are shown. Most patients were under treatment for their comorbidities.

Risk Factors for Progression of DAVD

The mean follow-up period was 2.4 years, and 67.7% of the study subjects were followed up for 3 years. In all subjects, there was no relation of Δ iAVA with any baseline characteristic listed in [Tables 1–3](#) except for the use of warfarin or β -blocker ([Table 4](#)). The use of warfarin or β -blocker was associated with the greater reduction of iAVA ([Table 5](#)). There was no significant difference in iAVA at baseline between patients with and without prescription of warfarin (1.26 ± 0.49 vs. $1.15 \pm 0.46 \text{ cm}^2/\text{m}^2$, $P=0.118$). Peak aortic transvalvular flow velocity at baseline was slightly but significantly higher

Table 1. Characteristics of Japanese Subjects With Degenerative Aortic Valve Disease

	All	Without AS	With AS
n	359	150	209
Age (years)	73.6±8.1	72.3±7.7	74.6±8.2
Male (%)	46.0	51.3	42.1
Body mass index (kg/m ²)	22.9±3.5	23.2±3.5	22.7±3.5
Waist circumference (cm)	84.5±11.0	85.6±9.9	83.5±11.8
Systolic BP (mmHg)	134±18	132±17	136±18
Diastolic BP (mmHg)	73±11	73±10	73±11
Heart rate (beats/min)	68±11	66±12	69±11
Prevalence of AF (%)	9.2	11.3	7.7
History of smoking (%)	35.4	43.3	29.7
Comorbidity (%)			
Hypertension	78.0	82.0	75.1
Diabetes mellitus	29.5	30.7	28.7
Dyslipidemia	54.6	65.3	46.9
Coronary artery disease	33.4	43.3	26.3
Cerebrovascular disease	10.0	10.0	10.1
Renal insufficiency	22.3	20.0	23.9
Hemodialysis	7.5	3.3	10.5
NYHA functional class (%)			
I	57.4	65.3	51.7
II	30.9	23.3	36.4
III	9.5	8.7	10.1
IV	0	0	0
Medications (%)			
ACEI	18.7	26.7	12.9
ARB	46.8	46.0	47.4
β -blocker	31.5	42.0	23.9
Calcium-channel blocker	54.0	54.7	53.6
Mineralocorticoid receptor blocker	6.7	7.3	6.2
Nonpotassium-sparing diuretics	21.2	18.0	23.4
Antiplatelet agents	43.5	46.0	41.6
Warfarin	16.4	22.7	12.0
Statins	40.1	48.7	34.0
Oral hypoglycemic medications	15.0	12.7	16.8
Insulin	6.7	8.0	5.7

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; AS, aortic valve stenosis; BP, blood pressure; NYHA, New York Heart Association.

in patients not taking warfarin than in those taking the drug (2.36 ± 0.96 vs. 2.08 ± 0.83 m/s, $P=0.043$). At baseline, iAVA was larger and peak aortic transvalvular flow velocity lower in patients taking a β -blocker than in those not (iAVA: 1.27 ± 0.48 vs. 1.12 ± 0.45 cm²/m², $P=0.007$, peak velocity: 2.01 ± 0.84 vs. 2.45 ± 0.96 m/s, $p<0.001$). In contrast, risk factors for atherosclerosis such as diabetes mellitus, dyslipidemia or hypertension were not related to progression of DAVD.

The subgroup analysis showed that the use of an ARB was associated with less decrease in iAVA in the group without AS (Tables 4,5), although iAVA at baseline was significantly smaller in patients treated with than without an ARB (1.51 ± 0.34 vs. 1.63 ± 0.31 cm²/m², $P=0.032$). Peak aortic transvalvular flow velocity at baseline was not different between the 2 groups (1.52 ± 0.27 vs. 1.49 ± 0.28 m/s, $P=0.587$). In the group with AS, none of the baseline characteristics listed in Tables 1–3 were related to Δ iAVA, but the use of an angiotensin-converting enzyme inhibitor (ACEI) was associated with less increase in peak aortic transvalvular flow velocity

(-0.03 m·s⁻¹·year⁻¹ in ACEI(+) vs. 0.11 m·s⁻¹·year⁻¹ in ACEI(-), $P=0.025$). There was no significant difference in iAVA or peak velocity at baseline between patients treated with and without ACEI (iAVA: 0.92 ± 0.47 vs. 0.90 ± 0.29 cm²/m², $P=0.771$, peak velocity: 2.91 ± 1.02 vs. 2.90 ± 0.79 m/s, $P=0.935$). The other factors were not related to changes in peak velocity.

Discussion

The JASS Prospective Analysis demonstrated that none of the traditional risk factors for atherosclerosis was related to progression of DAVD in these Japanese subjects. In all of the study subjects, the use of warfarin or β -blocker was associated with progression of DAVD. The prescription of an ARB before the development of AS and that of an ACEI after the development of AS was related to slowed progression of DAVD.

The Cardiovascular Health Study demonstrated an agree-

Table 2. Baseline Echocardiographic Data of Japanese Subjects With Degenerative Aortic Valve Disease

	All	Without AS	With AS
Left atrial dimension (mm)	41±7	40±7	41±7
LV end-diastolic dimension (mm)	47±6	48±6	46±6
LV end-systolic dimension (mm)	29±7	30±7	28±6
Ejection fraction (%)	65±12	64±13	66±11
LV mass index (g/m ²)	109.9±33.0	98.4±29.2	118.1±33.2
Relative wall thickness	0.43±0.11	0.39±0.09	0.46±0.12
AVA (cm ²)	1.8±0.8	2.5±0.6	1.4±0.5
iAVA (cm ² /m ²)	1.17±0.46	1.57±0.33	0.90±0.32
Peak aortic transvalvular flow velocity (m/s)	2.3±0.9	1.5±0.3	2.9±0.8
Sinus of Valsalva (mm)	32.8±4.4	34.0±3.9	31.8±4.4
Sinotubular junction (mm)	27.5±4.3	28.1±3.8	27.1±4.6
Prevalence of aortic annular calcification (%)	58.5	38.0	73.2
Prevalence of sinotubular junction calcification (%)	38.4	23.3	49.3
Degree of aortic regurgitation (%)			
0	39.6	51.3	31.1
I	39.3	28.0	47.4
II	17.6	16.0	18.7
III	3.1	4.7	1.9
IV	0.6	0	1.0
Degree of mitral regurgitation (%)			
0	35.7	38.0	34.0
I	47.6	40.0	53.1
II	14.8	20.0	11.0
III	1.4	0.7	1.9
IV	0.6	1.3	0.0

AS, aortic valve stenosis; AVA, aortic valve area; iAVA, AVA indexed to body surface area; LV, left ventricular.

Table 3. Baseline Laboratory Data of Japanese Subjects With Degenerative Aortic Valve Disease

	All	Without AS	With AS
Hemoglobin (g/dl)	12.4±1.8	12.9±1.7	12.0±1.8
White blood cell count (/μl)	5,863±1,638	5,938±1,622	5,808±1,650
Platelets (10 ⁴ /μl)	20.2±6.6	21.0±6.9	19.5±6.4
Serum glucose (mg/dl)	118±37	113±29	121±42
HbA1c (JDS) (%)	5.8±0.9	5.8±1.0	5.7±0.8
Total cholesterol (mg/dl)	188±36	192±34	185±37
HDL-C (mg/dl)	56±16	57±17	55±16
Non-HDL-C (mg/dl)	133±32	135±29	131±34
LDL-C (mg/dl)	109±29	110±28	109±30
Triglyceride (mg/dl)	120±67	123±60	118±72
Creatinine (mg/dl)	1.5±2.3	1.2±1.6	1.8±2.7
eGFR (ml/min/1.73 m ²)	61.9±19.6	62.5±18.0	61.4±20.9
Uric acid (mg/dl)	5.7±1.5	5.6±1.4	5.7±1.6
BNP (pg/ml)	159±356	119±259	189±414

AS, aortic valve stenosis; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; JDS, Japanese Diabetes Society; LDL-C, low-density lipoprotein cholesterol.

ment of the risks of atherosclerosis and DAVD in the 1990s.¹⁰ The Framingham Offspring Study enrolled study subjects with a mean age of 34 years between 1971 and 1975, followed them for 27 years, and concluded that exposure to multiple atherosclerotic risk factors starting in early to mid-adulthood was associated with aortic valve calcification.²³ However, adherence to guideline-based treatment has improved in the

past 2 decades, and the current and other recent studies have shown that traditional risk factors for atherosclerosis such as hypertension and diabetes mellitus are not associated with progression of DAVD.^{12,13,16} Several clinical studies have reported the absence of benefits of statins against progression of AS.^{24,25} The lack of a beneficial effect of lipid-lowering therapy was observed even when the risk of ischemic heart

Table 4. P Value for Association of Medication With Δ iAVA in Japanese Subjects With Degenerative Aortic Valve Disease

	All	Without AS	With AS
ACEI	0.382	0.869	0.401
ARB	0.396	0.039	0.564
β -blocker	0.042	0.013	0.274
Calcium-channel blocker	0.799	0.953	0.676
Mineralocorticoid receptor blocker	0.370	0.848	0.166
Nonpotassium-sparing diuretics	0.679	0.790	0.504
Antiplatelet agents	0.524	0.914	0.510
Warfarin	0.026	0.054	0.116
Statins	0.409	0.339	0.763
Oral hypoglycemic medications	0.553	0.692	0.669
Insulin	0.730	0.713	0.309

Abbreviations as in Tables 1,2.

Table 5. Effects of Medication on Δ iAVA ($\text{cm}^2 \cdot \text{m}^{-2} \cdot \text{year}^{-1}$) in Japanese Subjects With Degenerative Aortic Valve Disease

	All	Without AS	With AS
ARB			
+	-0.037 $\pm$ 0.117	-0.004 $\pm$ 0.111	-0.060 $\pm$ 0.117
-	-0.047 $\pm$ 0.096	-0.044 $\pm$ 0.104*	-0.051 $\pm$ 0.089
β -blocker			
+	-0.062 $\pm$ 0.121	-0.054 $\pm$ 0.113	-0.072 $\pm$ 0.132
-	-0.034 $\pm$ 0.100*	-0.006 $\pm$ 0.102*	-0.051 $\pm$ 0.095
Warfarin			
+	-0.075 $\pm$ 0.157	-0.063 $\pm$ 0.117	-0.090 $\pm$ 0.197
-	-0.036 $\pm$ 0.095*	-0.016 $\pm$ 0.106*	-0.051 $\pm$ 0.084

*P<0.05 vs. +. Abbreviations as in Tables 1,2.

disease was reduced in the same subjects.¹⁴ In addition, we have to take into account that atherosclerosis and DAVD have different pathophysiology.^{26–28} Although uncontrolled or long-term or early exposure to atherosclerotic risks are likely to contribute to progression of DAVD, additional management of atherosclerotic risk factors beyond that recommended in the current guidelines may not provide any further benefits against progression of DAVD. Our and the previous studies also indicate that it is currently difficult to predict progression of DAVD, and careful, periodic follow-up is required in patients with DAVD regardless of their clinical characteristics. The guidelines have recommended the follow-up strategy for asymptomatic patients with severe AS, but we have to keep in mind the progression of DAVD in a substantial number of elderly subjects without AS.^{12,29} Although echocardiography is the most useful tool to detect progression of DAVD, we have to take health economics into account, and the appropriate interval of echocardiographic examination of patients with DAVD but without severe AS should be discussed in the future. At least, we may be able to recommend routine auscultation to physicians.

The current prospective study demonstrated that the use of warfarin was associated with progression of DAVD, which is at least partly compatible with the results of our previous retrospective study.¹⁶ Warfarin attenuates the synthesis and function of matrix γ -carboxyglutamic acid protein, a potent inhibitor of tissue calcification, through its incom-

plete γ -carboxylation by antagonization of vitamin K.³⁰ Another possible mechanism of the contribution of warfarin to the progression of DAVD is hemorrhage in the leaflets facilitated by warfarin, because Akahori et al reported a frequent association between intraleaflet hemorrhage and a rapid progression of AS in patients with severe AS.^{31,32} Although the relationship of progression of DAVD to the use of warfarin can be theoretically understandable, it is difficult to explain the relation of β -blocker to DAVD and further studies are necessary.

In the subgroup without AS, the non-use of ARBs was raised as a risk for progression of DAVD, which is compatible with the results of our previous retrospective study.¹⁶ ACE, chymase and angiotensin II type 1 receptor are upregulated in the calcified human aortic valve compared with the normal valve,^{33,34} suggesting activation of the angiotensin II-angiotensin-receptor axis in DAVD. AS is associated with enhanced inflammatory changes in the aortic valve in the early stage, but with a ‘burnt-out’ condition in the late stage.³⁵ As the expression of ACE and chymase colocalizes with inflammatory cells,³⁴ a metabolic response to ARBs may be expected only during active inflammation of the aortic valve and may be small or absent after the reduction of inflammatory activity (ie, after the development of AS).

In patients with peak aortic transvalvular flow velocity ≥ 2 m/s, no factors were related to Δ iAVA in the current study. However, iAVA was significantly smaller in those patients

than in patients with peak velocity <2 m/s (Table 2), and echocardiography may not be sensitive enough to reveal the changes in AVA in patients with a small AVA. Therefore, we also assessed the changes in peak aortic transvalvular flow velocity, and found that the administration of ACEI was associated with less increase in velocity than non-use of ACEIs. This result is compatible with our preliminary study that showed an association of the prescription of ACEI with slow increase of the aortic transvalvular flow velocity in patients with a baseline peak velocity ≥ 2 m/s.³⁶ O'Brien et al reported that ACEIs attenuate the progression of aortic valve calcification as measured by electron beam computed tomography.³⁷ Nadir et al reported in a retrospective, population-based longitudinal cohort study that the use of an ACEI or ARB resulted in improved clinical outcomes for patients with AS,³⁸ although it is unclear whether the benefits were exerted through effects on the aortic valve or on LV myocardium exposed to AS-induced pressure overload. In that study, 87% of the patients in the ACEI/ARB group were treated with an ACEI. In contrast, Rosenhek et al failed to find benefits of ACEI therapy.³⁹ These discrepancies may be partly explained by differences in the severity of DAVD among the study subjects. The mean peak aortic transvalvular flow velocity was 2.9 m/s in the current study's subjects with a baseline peak velocity ≥ 2 m/s, 2.4 m/s in Wakabayashi's study, 3.3 m/s in Nadir's study, and 3.9 m/s in Rosenhek's study. Although echocardiographic data were lacking in O'Brien's study, these results suggest that ACEIs exert beneficial effects at a relatively early stage after the development of AS but not at the very advanced stage. Helseke et al demonstrated that bradykinin type 1 and 2 receptors were expressed in the aortic valves of patients who underwent AVR.⁴⁰ The type 1 receptor mediates fibrotic changes, and the type 2 receptor exerts antifibrotic effects. The balance of the expression of these receptors may vary according to the disease stage, resulting in the inconsistent effects of ACEIs among patients with AS.

DAVD is common and progressive in elderly subjects,^{12,29} and is related to poor prognosis.⁴¹ The prevention of its progression may well contribute to improvements in the activities of daily life, morbidity and mortality of the elder population. Advanced DAVD requires AVR, and thus, prevention of the progression of DAVD may have socioeconomic merit through avoidance of AVR. The prevalence of atrial fibrillation increases with aging,⁴² and anticoagulation therapy is suggested by guideline-based treatment in many elder patients with atrial fibrillation to prevent thromboembolic events.⁴³ Warfarin has been principally used for anticoagulation therapy; however, the risk of warfarin in promoting calcification of soft tissue has not been widely recognized. Several cross-sectional studies have reported the increased ratio of valvular or coronary calcification in patients treated with warfarin.^{44,45} The current study confirmed this phenomenon in a prospective observation. Recently, several new anticoagulants that exert their effects independent of vitamin K antagonization are available, and their benefits in preventing thromboembolic events are not inferior to that of warfarin.⁴³ As warfarin-induced calcification is likely promoted in patients with chronic usage or in elderly patients,⁴⁵ the results of the current and previous studies call attention to the use of warfarin in patients with atrial fibrillation, in particular those who need anticoagulation chronically or elderly patients. It is interesting whether ARBs or ACEIs can cancel such effects of warfarin on DAVD, however, the number of the subjects treated with both warfarin and ARB/ACEI was small in the current study, and the ongoing JASS-2 study (UMIN ID; 000003007, <https://>

upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000003642&language=J) is awaited.

Study Limitations

First, this was an observational and hospital-based study, and thus the selection of study subjects might be biased. In particular, the baseline characteristics of patients treated with and without each medicine were not comparable. To assess the effects of each medicine on the progression of DAVD, propensity matching is preferable; however, the number of the study subjects was not large enough to adjust their characteristics. In this study, peak aortic transvalvular flow velocity at baseline was lower in patients treated with than without warfarin, and iAVA at baseline was larger in patients treated without than with an ARB. Previous studies showed that progression of AS is more rapid in patients with more severe AS.^{46,47} Thus, lower peak velocity at baseline in patients treated with warfarin or larger iAVA at baseline in patients treated without ARB is unlikely to explain the greater reduction of iAVA in association with the use of warfarin or non-use of ARBs in this study. Future studies with larger numbers of subjects are required. Second, the duration of exposure to atherosclerotic risk factors such as hypertension and diabetes mellitus was not taken into account, and its effects on progression of DAVD cannot be discussed in this study.

Conclusions

In a Japanese study, atherosclerotic risk factors were not associated with progression of DAVD. As most patients were under treatment for their comorbidities in this study, the current results suggest that management of risk factors beyond the current guidelines does not provide any additional benefits against progression of DAVD. In DAVD patients, the use of warfarin is likely a risk for progression of DAVD. The prescription of ARBs for DAVD patients before the development of AS or that of ACEIs early after the development of AS may be useful.

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Appendix

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