Highlights

This is the first international study examined ethnic differences in VSA patients.

Ethnic differences in clinical characteristics were present in the contemporary era.

The MACE-free survival rate was slightly but significantly lower in Caucasians.

The JCSA risk score was useful to predict the occurrence of MACE in both ethnics.

Abstract

Background: Possible ethnic differences in clinical characteristics and long-term prognosis of contemporary patients with vasospastic angina (VSA) remain to be elucidated.

Methods and results: The Japanese Coronary Spasm Association (JCSA) conducted an international, prospective, and multicenter registry study for VSA patients. A total of 1,457 VSA patients (Japanese/Caucasians, 1,339/118) were enrolled based on the same diagnostic criteria. Compared with Caucasian patients, Japanese patients were characterized by higher proportions of males (68 vs. 51%) and smoking history (60 vs. 49%). Japanese patients more often had angina especially during the night and early morning hours, compared with Caucasians. Ninety-five percent of Japanese and 84% of Caucasian patients underwent pharmacological provocation test. Importantly, no significant differences in the patterns of coronary spasm were apparent, with diffuse spasm most frequently noted in both ethnicities. The prescription rate of calcium-channel blockers was higher in Japanese (96 vs. 86%), whereas the uses of nitrates (46 vs. 59%), statins (43 vs. 65%), renin-angiotensin-system inhibitors (27 vs. 51%), and β-blockers (10 vs. 24%) were more common in Caucasian patients. Survival rate free from major adverse cardiac events (MACE) was slightly but significantly higher in Japanese than in Caucasians (86.7 vs. 76.6% at 5 years, $P<0.001$). Notably, multivariable analysis revealed that the JCSA risk score correlated with MACE rates not only in Japanese but also in Caucasian patients.

Conclusion: These results indicate that there are ethnic differences in clinical profiles and long-term prognosis of contemporary VSA patients.

(238/250 words)

Keywords: vasospastic angina, coronary spasm, ethnic difference, clinical characteristics, international cohort study

Clinical characteristics and long-term prognosis of contemporary patients with vasospastic angina
-Ethnic differences detected in an international comparative study-

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1. Introduction

Vasospastic angina (VSA) plays an important role in the pathogenesis of ischemic heart disease [1-3]. Since the first report of 'variant angina' by Prinzmetal et al. in 1959 [4], much has been learned regarding pathophysiology, diagnosis and treatment of VSA, where Japan has made significantly contributions, leading to the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina by the Japanese Circulation Society [5]. Indeed, the guidelines proposed by the Society defined for the first time the standards for the management of VSA based on currently available evidence, including the latest findings by the Japanese Coronary Spasm Association (JCSA) [6-9]. Furthermore, the Coronary Vasomotion Disorders International Study Group (COVADIS) has recently proposed diagnostic criteria for VSA to improve clinical diagnosis and facilitate research on the disorder [10].

Although it has long been suggested that the prevalence of VSA is lower in Caucasians than in Asians [11], recent studies demonstrated that the prevalence of coronary artery spasm in Caucasians may be higher than previously thought [12,13]. Moreover, early studies suggested ethnic differences in the clinical characteristics and long-term prognosis of VSA patients between Japanese and Caucasians [10,14]. However, whether these differences are present in contemporary VSA patients remains to be elucidated. To address these important clinical issues, the JCSA conducted an international, prospective, and multicenter registry study of VSA patients [10]. The objective of the present study was to compare baseline clinical characteristics and 5-year major adverse cardiac events (MACE) between Japanese and Caucasian patients with VSA.

2. Methods

JCSA conducted this multi-center, multi-national, observational, prospective, longitudinal cohort study of patients with VSA (UMIN000003304). This study was performed in accordance with the Declaration of Helsinki ethical principles, and the protocol was approved by the institutional review boards and/or ethics committees of all participating centers. Informed consent was obtained from all patients at the participating hospitals.

2.1. Study populations

This prospective study included consecutive patients first diagnosed with VSA after January 2010. From January 2010 to December 2014, a total of 1,661 VSA patients (Japanese, 1460 and Caucasians, 201) were enrolled from 42 participating hospitals. Of those, 204 were excluded for lack of follow-up data, and the final study population consists of 1,457 patients (Japanese/Caucasians, 1,339/118).

2.2 Diagnosis of VSA

The diagnosis of VSA was made based on the Guidelines of the Japanese Circulation Society [5], which subsequently was incorporated into the international criteria proposed by COVADIS in 2017 [10]. The diagnosis of 'definite' VSA was made when either spontaneous and/or pharmacologically induced coronary spasm was documented [5], and only patients with 'definite' VSA were enrolled in the present study. The definition of spontaneous VSA attacks was based on the occurrence of chest pain at rest and/or on effort with accompanying transient ischemic ECG changes (ST-segment elevation/ depression > 0.1 mV or the new appearance of negative U waves) that promptly responded to the administration of short-acting nitrates [5,10]. When ischemic ECG changes during a spontaneous angina episode could not be documented or they were equivocal, spasm provocation tests were performed. Pharmacological provocative testing involved the intracoronary administration of acetylcholine (ACh) or ergonovine (ER) during coronary angiography in accordance with the JCS guidelines [5]. The selection of the provocative agent and the decision as to whether the left coronary artery (LCA) or right coronary artery (RCA) was assessed first, were left to the discretion of the local clinician. The provocation test was performed after a washout period of at least 24 hours for calcium channel blockers (CCBs) and nitrates [5]. A positive provocation test was defined as a total or subtotal

(>90%) coronary artery narrowing accompanied by chest pain and/or ischemic ECG changes [5,10]. Types of coronary spasm observed during spasm provocation test were classified into focal, diffuse, and mixed types as previously described [8].

2.3. Data collection

The patient de-identified demographic and clinical data were stored in a central database system. Hypertension, dyslipidemia, and diabetes mellitus were diagnosed based on the guidelines of the Japanese Society of Hypertension, Japan Atherosclerosis Society, and Japan Diabetes Society, respectively [15-17]. Significant coronary stenosis was defined as ≥70% of luminal narrowing of major coronary arteries evaluated by coronary angiography after intracoronary nitrate administration. Ventricular tachycardia (VT) was defined as 3 or more consecutive premature ventricular contractions (PVCs). Atrioventricular (AV) block consisted of second- and third-degree AV blocks and bradycardia was defined as sinus rhythm <50 beats/min. Out-of-hospital cardiac arrest (OHCA) was defined as cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation. Complications during spasm provocative testing included death, Q wave MI, non-Q wave MI, coronary perforation, temporary hypotension, electrical storm (VT/VF storm), cardiac tamponade, heart failure, and stroke. The JCSA risk score, which provide a comprehensive risk assessment and prognostic stratification for VSA patients, consists of 7 predictive factors of major adverse cardiac events (MACE), including history of OHCA (4 points), smoking, angina at rest alone, significant organic coronary stenosis, multivessel spasm (2 points each), and ST-segment elevation during an attack and beta-blocker use (1 point each) [9]. The risk score was calculated based on the sum of weighted predictors in the individual patient.

2.4. Endpoints and follow-up

The primary endpoint was MACE, which included cardiac death, non-fatal myocardial infarction (MI), appropriate ICD shocks, VT/VF episode in the patients without ICD, or hospitalization for unstable angina pectoris/heart failure over the 5-year follow-up period. The secondary endpoint was hard-MACE, consisting of cardiac death, non-fatal MI, and appropriate ICD shocks over the 5-year period. The follow-up data were obtained from each participating hospital annually until December, 2016.

2.5. Statistical analysis

Continuous variables are presented as medians and interquartile ranges (IQRs) and categorical variables as numerals and percentages. Group comparisons were made with Mann-Whitney test for continuous variables, Fisher's exact test for categorical variables, and log-rank test for survival curves. Survival free from MACE or hard-MACE was analyzed by the Kaplan-Meier method. To reduce confounding effects in this observational study, propensity score (PS) methods were used. For the calculation of PS, we used a logistic regression model in which the Caucasian VSA patient characteristics were regressed for the following 14 baseline features; age, sex, hypertension, diabetes mellitus, dyslipidemia, current smoking, previous MI, previous PCI, significant organic stenosis, use of CCBs, nitrates, beta-blockers, ACEI, ARB, and statins. Univariable and multivariable Cox proportional hazard models were applied for hazard ratio (HR) and 95% confidence interval (CI) for the risk of MACE between Japanese and Caucasian VSA patients. A P value <0.05 was considered to be statistically significant. The statistical analysis was performed with SPSS statistics 21 (IBM, NY, USA).

3. Results

3.1. Demographic characteristics

The patient characteristics by ethnicity are summarized in **Table 1**. Japanese VSA patients, as compared with Caucasian patients, were characterized by older age, higher prevalence of males and lower BMI. The proportion of patients with a smoking history was higher in Japanese patients. Additionally, Japanese patients less often had a family history of cardiovascular diseases. Similarly, patients with previous myocardial infarction (MI) were less prevalent among Japanese patients.

Of the entire cohort, 1,313 patients (90.1%) experienced spontaneous angina episodes at least once (**Table 1**). Caucasians had more frequently a combination of chest pain both at rest and on effort. Typical circadian variation of angina attacks with a peak incidence from night to early morning was noted more commonly in Japanese patients, whereas angina attacks occurred throughout the day in Caucasians.

3.2. Angiographic findings during spasm provocation test

Angiographic findings are shown in **Table 1**. The prevalence of a significant organic stenosis defined as ≥70% luminal narrowing by coronary angiography was similar between the 2 ethnic groups. Spasm provocative testing was performed in 1,364 patients (Japanese/ Caucasians, 1,266/98) with more tests undertaken in Japanese patients. Agents used for pharmacological provocation testing did not differ between the 2 ethnic groups, with ACh most commonly used in both. Importantly, the features of provoked spasm patterns, including focal, diffuse, and mixed type, was almost identical between the 2 ethnicities. Multivessel coronary spasm was documented more frequently in Japanese than in Caucasians. Caucasian patients had a higher incidence of bradycardia and atrioventricular block during the provocation test compared with Japanese patients. Thus, overall incidence of complications during provocation test, most of which was transient hypotension, was significantly higher in Caucasians than in Japanese. Overall, no serious complications related to spasm provocation test were observed except one Japanese case who developed non-Q wave MI. These results confirm that invasive pharmacological provocation test has an acceptable level of safety for diagnosis of VSA regardless of ethnicity, as reported in the recent Japanese and European studies [8,18].

3.3. Treatment after diagnosis

Regarding medical therapy following the diagnosis of VSA, prescription of CCBs was higher in Japanese patients (96 vs. 86%, P<0.001), whereas nitrates (46 vs. 59%, P=0.007), statins (43 vs. 65%, P<0.001), ACE-inhibitors/ARBs (27 vs. 51%, P<0.001), and β-blockers (10 vs. 24%, P<0.001) were more frequently prescribed in Caucasians. Implantation of ICD's was rare but more frequent in Japanese than in Caucasian patients (**Table S1**).

3.4. Clinical outcomes and prognostic factors for MACE

During the median follow-up period of 39 months (IQR: 24-51 months), 119 Japanese patients (9.0%) and 27 Caucasian patients (23%) reached the primary MACE endpoint (**Table S2**). The 5-year MACE-free survival rate was marginally better in Japanese VSA patients compared with Caucasians (86.7 vs. 76.6%, P<0.001), whereas those free from the hard-MACE endpoint was similar (96.5 vs. 97.7%, P=0.66; **Figure 1**). After performing PS matching for the entire population, 114 matched pairs of patients were identified (**Table S3**), showing that the long-term prognosis still remained better in the Japanese than in the Caucasians (87.9 vs. 76.7%, P=0.012) (**Figure S2**). When patients were classified into 3 risk strata based upon their JCSA score, (i.e. low = 0-2, intermediate = 3-5, and high ≥ 6), Kaplan-Meier curves for MACE among the 3 risk groups showed a clear prognostic difference throughout the follow-up period in both Japanese and Caucasian patients (**Figure 2**). Moreover, in the multivariable model, the JCSA risk score was significantly correlated with future occurrence of MACE in both ethnicities (**Table 2**).

4. Discussion

This is the first international large-scale study that examined ethnic differences in contemporary VSA patients between Japanese and Caucasians using the same diagnostic criteria [5,10]. The major findings of the present study were as follows. (1) Ethnic differences in clinical characteristics of VSA patients, including demographics and spontaneous angina features, were present in the modern era with contemporary therapies. (2) The results of spasm provocation testing did not differ between the 2 ethnicities. (3) There was considerable variation in the therapies employed for the treatment of VSA between Japanese and Caucasians. (4) The 5-year MACE-free survival rate was slightly but significantly lower in Caucasian compared with Japanese patients, and the JCSA risk score was useful to predict the occurrence of future MACE in both Japanese and Caucasian patients.

4.1. Demographics and clinical ethnic differences

It has been long believed that the prevalence of VSA patients is higher in Japanese than in Caucasian populations [19,20]. This concept of a higher coronary vasomotor reactivity among Japanese is consistent with a head-to-head controlled comparison of patients with acute ST elevation myocardial infarction (without a clinical history of VSA) where Japanese patients were twice as likely to have inducible spasm than their Caucasian counterparts [21]. Furthermore, it has been described in patients with VSA, that the Japanese have a higher prevalence of diffuse and multivessel coronary spasm although a lower prevalence of significant coronary artery disease compared with Caucasians [11]. However, in Western studies, the diagnosis of VSA was more commonly made on the basis of spontaneous episodes (i.e. anginal symptoms with ischemic ECG changes) [22], whereas in Japan, it is more often based upon spasm provocation testing [7].

The present study demonstrates that demographics of VSA patients may have evolved over time. Indeed, VSA patients in this study were more likely to be elderly female with higher prevalence of hypertension and dyslipidemia, but less likely to have smoking history compared with those evaluated 30 years ago [14]. A similar tendency was also noted in a recent report from Japan that examined the transition of factors related to coronary spasm during the last 2 decades [23]. The present study also demonstrates that some differences are still present in the clinical features of VSA patients between the 2 ethnicities as reported

previously, such as male-preponderance and higher prevalence of smoking history in Japanese patients, whereas a history of prior MI was more common in Caucasian VSA patients.

Classical clinical manifestations of VSA include rest angina readily relieved by short-acting nitrate and a circadian pattern of ischemic episodes with a peak from midnight to early morning, which are important diagnostic criteria for definitive VSA [5,10]. However, importantly, the present study demonstrates that the clinical presentations of spontaneous VSA attacks are significantly different between the 2 ethnic groups. Indeed, although Japanese patients more often presented the above typical clinical manifestations of VSA, that was not the case in Caucasian patients. One of the interesting manifestations of Caucasian patients was that 39% of angina symptoms occurred during exercise. A potential explanation could be that concomitant coronary microvascular dysfunction may account for exertional symptoms in patients with documented epicardial spasm. It has been shown that coronary vasomotor abnormalities may be found in patients with exertional angina and unobstructed coronary artery disease [12], another explanation could be an increased activity of the sympathetic nervous system associated with parasympathetic withdrawal during exercise which has been proposed as a potential trigger for epicardial coronary artery spasm [24]. Additionally, autonomic dysfunction has also been postulated as one of the most important mechanisms of circadian variation of VSA [25]. Thus, it is possible that there could be a fundamental ethnic difference in autonomic nervous system activity in VSA patients.

4.2. Ethnic differences in angiographic findings

There are different patterns of coronary spasm during provocation testing, including focal, diffuse, and mixed-pattern spasm [8]. Notably, the spasm pattern is not only a surrogate marker reflecting coronary vasomotor reactivity but also a predictor of long-term prognosis of VSA patients [8,26], indicating that the spasm provocation test could provide useful information for the management of VSA patients. Indeed, in the present study, 84% of Caucasian patients and 95% of Japanese patients underwent invasive provocation test to ensure a confirmed diagnosis of VSA. Importantly, in both ethnic groups, two-thirds of the patients had diffuse spasm and ~20% focal spasm during the provocation test. These results are consistent with the previous studies showing that diffuse spasm is frequent in contemporary Caucasian patients with angina and non-obstructive coronary artery disease [12,27]. As demonstrated in a population-based autopsy study, the prevalence and severity of coronary artery disease has been decreasing in Caucasians [28]. Indeed, about 30 years

ago, Bertrand et al. reported that 60% of focal coronary spasm occurred in pre-existing atherosclerotic lesions in a large French cohort study [19], whilst in the present study we found that only 13% of the contemporary Caucasian VSA patients had significant fixed coronary atherosclerosis. Thus, in contemporary Caucasian VSA patients, the decline in the extent of coronary atherosclerosis could be associated with the alteration in coronary vasomotor responses.

4.3. Ethnic differences in medical treatment and long-term prognosis

We previously demonstrated that Caucasian VSA patients had a higher incidence of death or MI than Japanese VSA patients, which might relate to their more extensive coronary artery disease [11,14]. However, in the present study, the incidence of hard-MACE in Caucasian patients, including cardiac death, non-fatal MI, and ICD shocks, was comparable to that in Japanese patients (Caucasians 1.6% vs. Japanese 2.0% at 5 years, P=0.81), a finding in line with other recent studies [9,29]. The decline in the extent of coronary atherosclerosis in contemporary Caucasians may have contributed to the improvement in the long-term prognosis of these patients. However, hospitalization for unstable angina still developed more frequently in Caucasian patients during the follow-up, resulting in a higher incidence of MACE as compared with Japanese patients. There may be 2 reasons for the prognostic differences between the two ethnicities in the modern era. First, the use of CCBs was lower in Caucasian than in Japanese patients (86 vs. 96%, P<0.001). CCBs are the established first-line therapy for VSA [5]. Indeed, it is important to note in the present study that MACE occurred mainly in the first few months of follow-up in Caucasian patients as was the case in the previous study [22]. Second, age and gender are important prognostic factors in VSA patients. We have previously shown that younger age (<50 years) was a significant negative prognostic factor in female but not in male VSA patients [30]. In the present study, the prevalence of young female patients was significantly higher in Caucasians than in Japanese (9.3 vs. 2.5%, P<0.001) (**Figure S1**). Importantly, in the present study, multivariable analysis also showed that younger age was associated with increased occurrence of MACE in Caucasian patients, but older age was so in Japanese patients (**Table 2**). As shown in **Figure S2**, the 5-year MACE-free survival rate was still better in Japanese VSA patients compared with Caucasians even after performing the PS matching. This finding suggests that ethnicity has a prognostic impact in VSA patients, although the sample size of the PS-matching cohort was small. Of interest, the present study confirmed the usefulness of the JCSA risk score not only in Japanese VSA patients but also in Caucasian VSA patients.

Since individual prognostic stratification is important for personalized medicine, the JCSA score should help physicians improve the management of VSA patients in clinical practice worldwide.

4.4. Study limitations

Several limitations should be considered in interpreting the results reported in the present study. First, the number of Caucasian patients with VSA was relatively small compared with Japanese patients. However, we were able to demonstrate the important differences in the clinical characteristics and long-term prognosis between the 2 ethnicities. Second, in the present study, spasm provocation tests were not performed for both left and right coronary arteries in all subjects for various reasons. Only a half of Japanese patients and 15% of Caucasians underwent provocation tests in both coronary arteries. Thus, it is possible that the frequency of multivessel spasm was underestimated. Third, in the present study, we exclusively examined epicardial coronary spasm but coronary microvascular dysfunction remains to be evaluated. Fourth, since there was no information available on the use of temporary pacing during spasm provocation test, the incidence of brady-arrhythmias may have been underestimated. Fifth, the information on medications was obtained at the beginning of follow-up, and additional information on the changes in medications during follow-up was not available. Sixth, we did not use a core lab for analysis of angiographic data, which were left to visual judgement by the attending experienced cardiologists in each institution. Seventh, the composite primary and secondary endpoints were used. However, despite these limitations, the present findings should merit emphasis for a better understanding of the differences and similarities between Caucasians and Japanese VSA patients in the modern era.

4.5. Conclusions

This is the largest international and prospective study in VSA patients diagnosed based on the same criteria. It provides the first evidence that there are ethnic differences in clinical characteristics and long-term prognosis between contemporary Caucasian and Japanese VSA patients.

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Conflict of interest

We have no conflict of interest.

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https://doi.org/10.1253/circj.CJ-12-1486

Figure legends

Figure 1. (**A**) Kaplan-Meier curves by ethnics for MACE in VSA patients. MACE included cardiac death, non-fatal myocardial infarction, hospitalization for heart failure and unstable angina pectoris, appropriate ICD shocks, and VT/VF in the patients without ICD. (**B**) Kaplan-Meier curves by ethnics for hard-MACE in VSA patients. Hard-MACE included cardiac death, non-fatal myocardial infarction, VT/VF, and appropriate ICD shocks.

Figure 2. Kaplan-Meier curves for MACE in Caucasian and Japanese VSA patients according to 3 risk strata divided by the JCSA risk score.
(**A**) Caucasians, (**B**) Japanese.

Figure 1

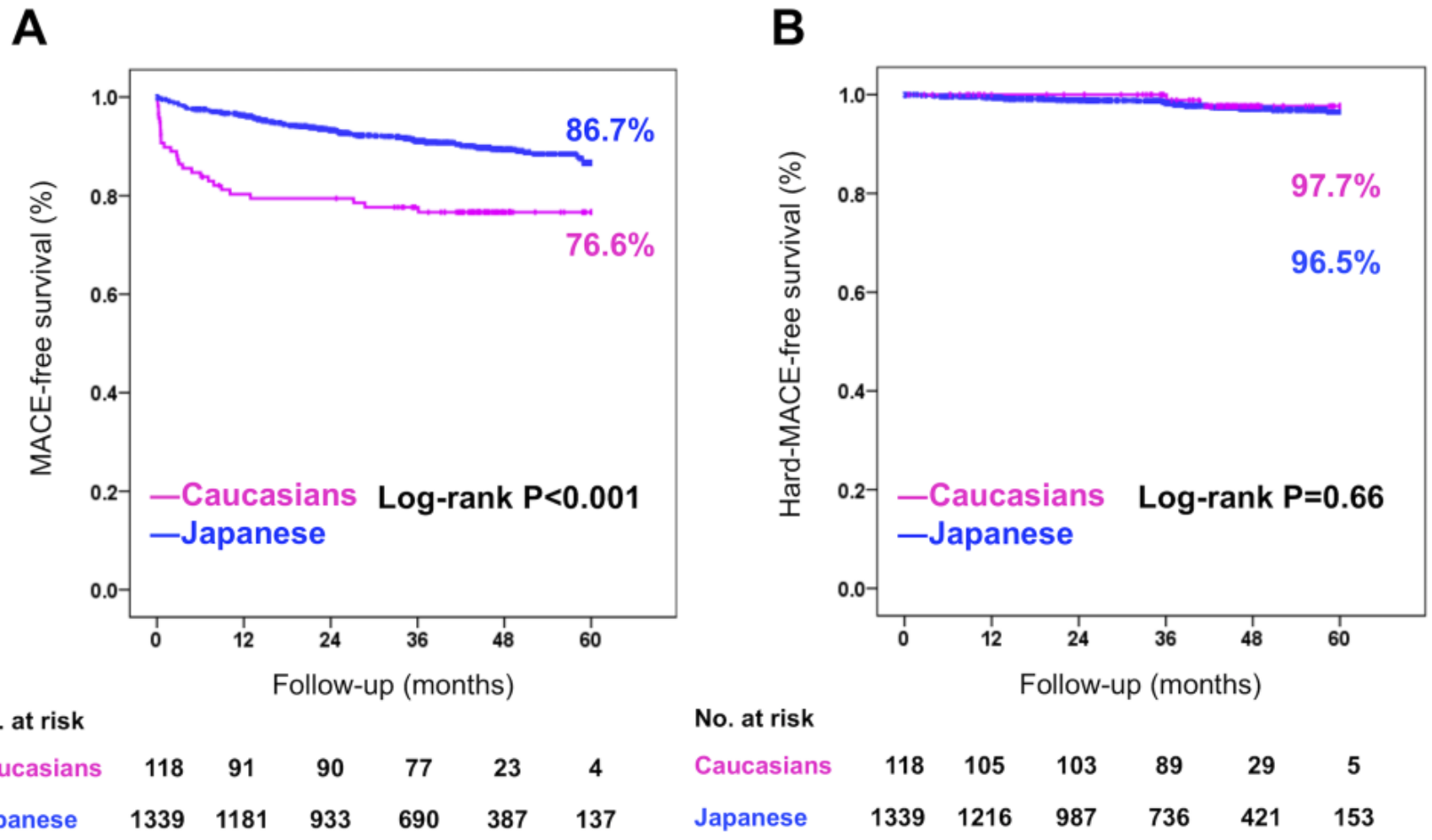
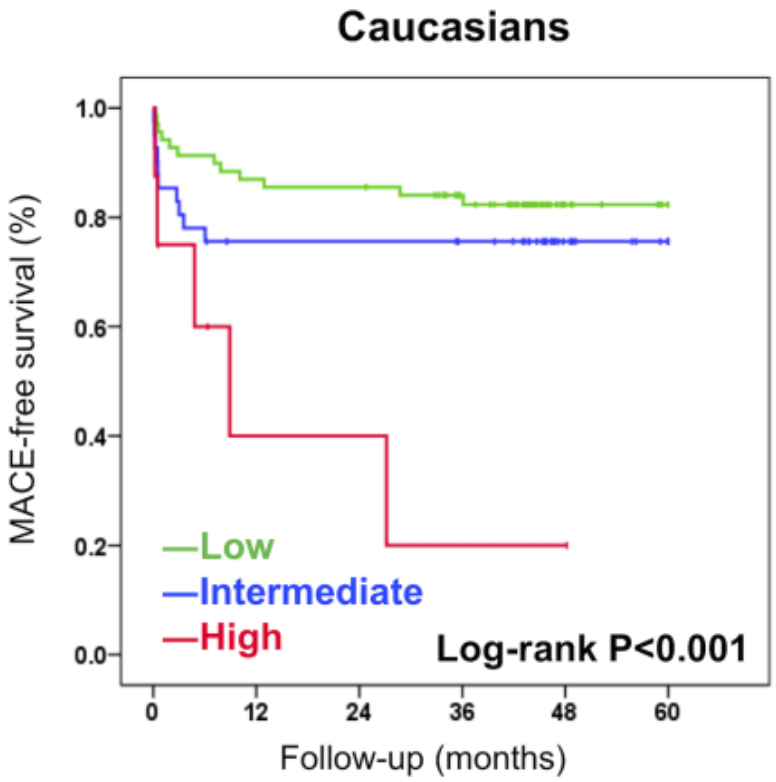
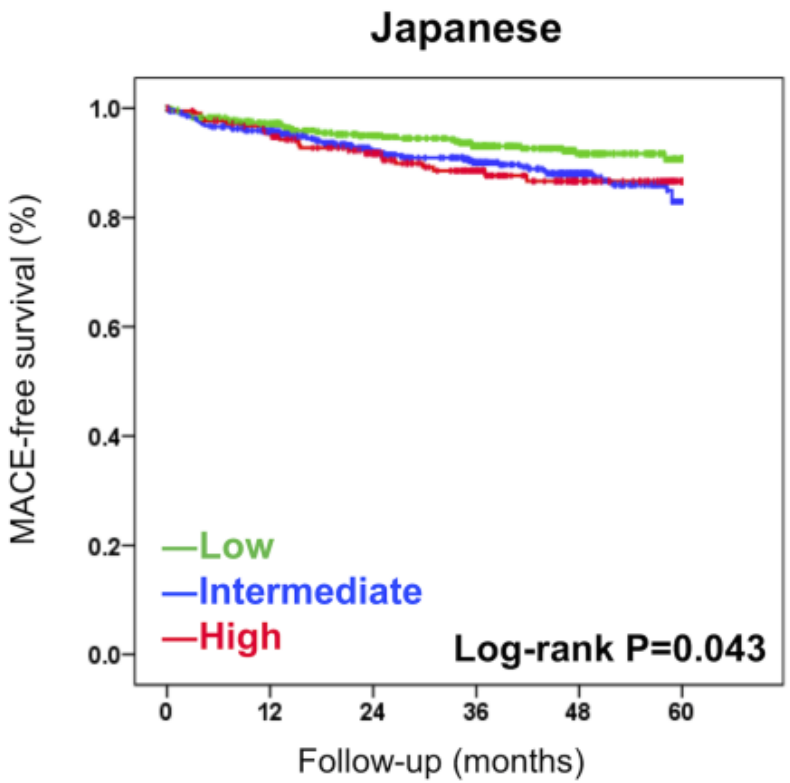

A
MACE-free survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
86.7%
76.6%
—Caucasians
—Japanese
Log-rank P<0.001
0
12
24
36
48
60
Follow-up (months)
No. at risk
Caucasians 118 91 90 77 23 4
Japanese 1339 1181 933 690 387 137
B
Hard-MACE-free survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
97.7%
96.5%
—Caucasians
—Japanese
Log-rank P=0.66
0
12
24
36
48
60
Follow-up (months)
No. at risk
Caucasians 118 105 103 89 29 5
Japanese 1339 1216 987 736 421 153

Figure 2



No. at risk						
Low	69	60	59	49	12	1
Intermediate	41	29	29	27	10	3
High	8	2	2	1	1	0



No. at risk						
Low	552	485	387	299	168	58
Intermediate	571	499	383	277	159	58
High	216	197	163	114	60	21

Table1. Demographic patient characteristics

	Caucasians (n=118)	Japanese (n=1,339)	*P*-value
Demographic features			
Age (mean±SD), yrs.	61±12	64±12	0.007
Male, n(%)	60(51)	913(68)	<0.001
BMI, (kg/m^2)	28±5	24±12	<0.001
Coronary risk factors, n(%)			
Hypertension	66(56)	757(57)	0.98
Dyslipidemia	66(56)	717(54)	0.55
Diabetes mellitus	19(16)	257(19)	0.46
Smoking history	57(49)	801(60)	0.019
Family history of IHD	60(51)	307(23)	<0.001
Previous history of CVD, n(%)			
Overall	52(44)	400(30)	0.001
Myocardial infarction	18(15)	89(7)	0.001
Previous PCI	21(18)	179(13)	0.18
OHCA	0(0)	46(3)	0.041
Features of spontaneous angina episodes [a)]			
Angina pattern, n(%)			
Rest	46(60)	808(67)	0.17
Effort angina	9(12)	180(15)	0.43
Mixed pattern (Rest and effort)	21(27)	141(12)	<0.001
Unknown	1(1)	71(6)	0.089
Circadian pattern, n(%)			
Daytime (6 AM~6 PM)	16(22)	389(34)	0.033
Night to morning (6 PM~6 AM)	9(12)	396(34)	<0.001
Throughout the day (no circadian pattern)	49(66)	371(32)	<0.001
Ischemic ST-segment change during spontaneous attack, n(%)			
ST elevation	12(16)	168(14)	0.55
ST depression	22(30)	107(9)	<0.001
Associated arrhythmic events during spontaneous attack, n(%)			
PVC	2(3)	18(2)	0.43

VT/VF	1(1)	40(3)	0.34
Bradycardia	5(7)	10(1)	<0.001
AV block	1(1)	11(1)	0.72

Angiographic findings and safety of provocation testing

Coronary angiography[b], n(%)	109(93.2)	1333(99.6)	
Organic stenosis 70%	6(5.5)	156(11.7)	0.049
Organic stenosis 90%	9(8.3)	65(4.9)	0.12
Organic stenosis ≥99%	2(1.8)	14(1.1)	0.45
2-vessel disease	2(1.8)	21(1.6)	0.84
3-vessel disease	1(0.9)	7(0.5)	0.60
Provocation test, n(%)	98(84)	1266(95)	<0.001
Provocation agent (ACh/ER/others), n(%)	90(92)/8(8) /0(0)	1108(88)/144(11) /8(1)	0.44
Target vessel of provocation test, n(%)			
LCA	69(70)	417(33)	<0.001
RCA	14(14)	183(14)	0.97
Both LCA and RCA	15(15)	666(53)	<0.001
Type of provoked spasm, n(%) [c]			
Diffuse	66(70)	839(68)	0.77
Focal	20(21)	228(19)	0.54
Mixed	9(10)	167(14)	0.26
Multivessel, n(%)	4(3)	239(18)	<0.001
Arrhythmias during provocation test, n(%)			
Overall	29(28)	161(13)	<0.001
PVC	1(1)	26(2)	0.48
VT/VF	1(1)	24(2)	0.53
AV block	5(5)	18(2)	0.006
Bradycardia	15(16)	38(3)	<0.001
Cardiac arrest	0(0)	1(0.1)	0.78
PAF	3(3)	43(4)	0.86
Complications, n (%)			
Overall	7(7)	19(2)	<0.001
Transient hypotension	7(7)	12(1)	<0.001
Non-Q wave MI	0	1(0.1)	0.78
Others	0	6(0.4)	0.47

a) Data of spontaneous angina attack were available for 77 Caucasian and 1236 Japanese patients.
b) Coronary angiography was performed in 109 Caucasians and 1333 Japanese patients.
c) Data of type of provoked spasm were available for 98 Caucasians and1266 Japanese patients.
ACh=acetylcholine, AV block=atrioventricular block, BMI=body mass index, CVD=cardiovascular disease, ER=ergonovine, IHD=ischemic heart disease, LCA=left coronary artery, MI=myocardial infarction, PAF=paroxysmal atrial fibrillation, PCI=percutaneous coronary intervention, PVC=premature ventricular contraction, OHCA=out-of-hospital cardiac arrest, RCA=right coronary artery, VT=ventricular tachycardia, VF=ventricular fibrillation.

Table 2. Correlated factors for MACE in VSA patients

	Univariable analysis			Multivariable analysis		
	HR	**95%CI**	***P*-value**	**HR**	**95%CI**	***P*-value**
Caucasians						
Age	0.94	0.91-0.97	0.001	0.95	0.92-0.99	0.008
Men	1.27	0.60-2.72	0.54			
Hypertension	0.43	0.20-0.94	0.034			
Dyslipidemia	0.92	0.43-1.96	0.84			
DM	1.21	0.46-3.19	0.71			
MI	1.34	0.50-3.50	0.57			
JCSA risk score	1.362	1.12-1.66	0.002	1.29	1.04-1.60	0.019
Japanese						
Age	1.03	1.01-1.05	0.002	1.03	1.01-1.05	0.001
Men	1.23	0.82-1.83	0.32			
Hypertension	1.57	1.08-2.30	0.020			
Dyslipidemia	1.25	0.87-1.80	0.24			
DM	1.15	0.75-1.78	0.52			
MI	2.15	1.25-3.70	0.006	1.96	1.13-3.37	0.016
JCSA risk score	1.10	1.01-1.19	0.032	1.12	1.03-1.21	0.011

DM= Diabetes mellitus, MI= Myocardial infarction, JCSA= Japanese Coronary Spasm Association.

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

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Conflict of interest

We have no conflict of interest.

Clinical characteristics and long-term prognosis of contemporary patients with vasospastic angina
-Ethnic differences detected in an international comparative study-

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on behalf of the Japanese Coronary Spasm Association*

Supplementary materials

Table S1. Treatments of VSA patients

	Caucasians (n=118)	**Japanese (n=1339)**	***P*-value**
Medications, n(%)			
CCB	101(86)	1282(96)	<0.001
Nitrate	69(59)	609(46)	0.007
Statin	77(65)	580(43)	<0.001
ACE-I/ARB	60(51)	366(27)	<0.001
Antiplatelet	62(53)	533(40)	0.007
β-blocker	28(24)	130(10)	<0.001
Non-medical therapy, n(%)			
ICD implantation	0(0)	33(3)	0.092

CCB=calcium channel blocker, ACE-I=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, ICD=implantable cardioverter-defibrillator

Table S2. Primary outcomes in VSA patients

	Caucasians (n=118)	**Japanese (n=1339)**	***P*-value**
MACE, n(%)	27(23)	119(9)	<0.001
Cardiac death	1(1)	5(0.4)	0.44
Non-fatal MI	1(1)	18(1)	0.65
VF/appropriate ICD shock	0(0)	5(0.4)	0.51
Hospitalization for unstable angina	26(22)	85(6)	<0.001
Hospitalization for heart failure	0(0)	16(1)	0.23
Hard-MACE, n(%)	2(2)	27(2)	0.81

ICD=implantable cardioverter defibrillator, MACE=major adverse cardiac events, MI=myocardial infarction, VF=ventricular fibrillation.

Table S3. Clinical characteristics of the entire and propensity score-matched populations

	Entire population			Propensity score matched population		
	Caucasians (n=118)	**Japanese (n=1339)**	***P*-value**	**Caucasians (n=114)**	**Japanese (n=114)**	***P*-value**
Age (mean±SD), yrs.	61±12	64±12	0.007	61±12	61±13	0.88
Male, n(%)	60(51)	913(68)	<0.001	57(50)	54(47)	0.69
Coronary risk factors, n(%)						
Hypertension	66(56)	757(57)	0.98	64(56)	70(61)	0.42
Dyslipidemia	66(56)	717(54)	0.55	64(56)	61(54)	0.69
Diabetes mellitus	19(16)	257(19)	0.46	19(17)	17(15)	0.72
Smoking history	57(49)	801(60)	0.019	55(48)	55(48)	1.00
Myocardial infarction	18(15)	89(7)	0.001	16(14)	13(11)	0.55
Previous PCI	21(18)	179(13)	0.18	20(18)	22(19)	0.73
Significant organic stenosis ≥70%, n(%)	15(14)	219(16)	0.47	14(12)	18(16)	0.45
CCB	101(86)	1282(96)	<0.001	99(87)	100(88)	0.84
Nitrate	69(59)	609(46)	0.007	67(59)	65(57)	0.79
Statin	77(65)	580(43)	<0.001	74(65)	72(63)	0.78
ACE-I/ARB	60(51)	366(27)	<0.001	59(52)	66(58)	0.35
β-blocker	28(24)	130(10)	<0.001	27(24)	24(21)	0.63

MI=myocardial infarction, PCI=percutaneous coronary
CCB=calcium channel blocker, ACE-I=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker,

Figure S1. Age groups of VSA patients by ethnicity

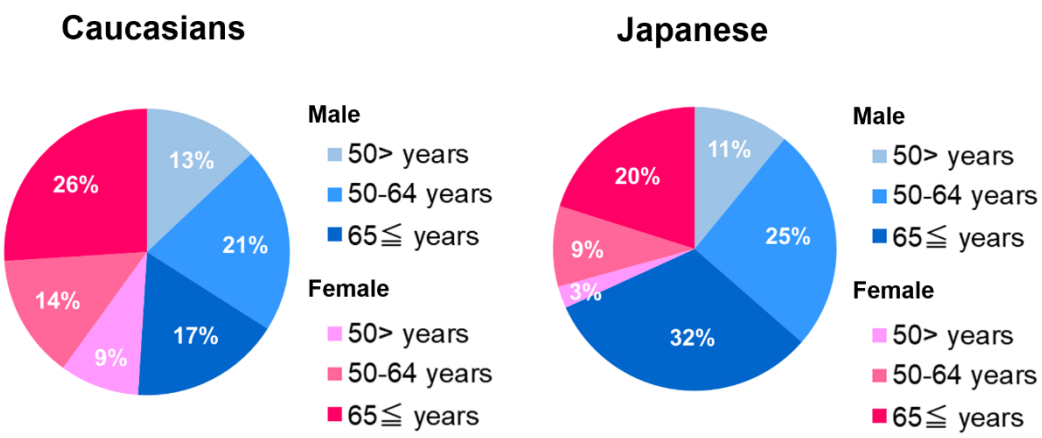
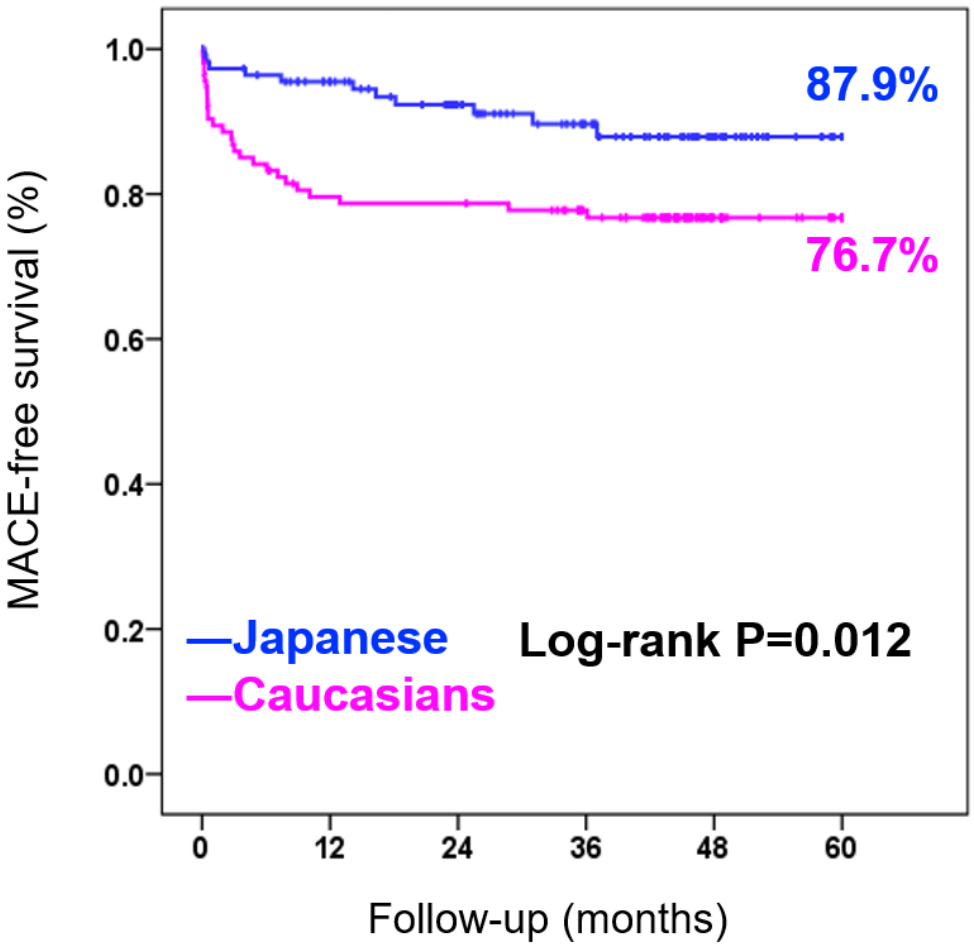


Figure S2. Kaplan-Meier curves by ethnicity for MACE in VSA patients after propensity score (PS) matching analysis



No. at risk						
Japanese	114	96	76	55	29	12
Caucasian	114	87	86	74	21	4