Chapter 1
Epidemiology of Vasospastic Angina

Jun Takahashi and Hiroaki Shimokawa

Abstract Vasospastic angina (VSA) is one of the important functional cardiac disorders characterized by transient myocardial ischemia due to epicardial coronary artery spasm. The term of VSA is basically synonymous with the terms Prinzmetal's angina and variant angina, and is known to be associated with a wide variety of cardiac ischemic conditions, including stable angina, acute coronary syndrome, and life-threatening arrhythmic events. A number of studies have elucidated patient characteristics, outcomes, and prognostic factors of VSA, which led to a better understanding and management for this disorder. However, there remains to be insufficient data on the prevalence of VSA in both Eastern and Western countries, probably because it is difficult and cumbersome to examine coronary spasm during coronary angiography. On the other hand, it has been well known that age, smoking, high-sensitivity C-reactive protein, and remnant lipoprotein are significant risk factors for coronary spasm. Recently, the Japanese Coronary Spasm Association (JCSA) demonstrated that, in the temporary VSA patients, overall 5-year survival rate free from all-cause death or major adverse cardiac events was 98% and 91%, indicating the clinical outcome appears to be further improved as compared with the 1980s. Furthermore, the JCSA also developed a risk scoring system consisting of 7 predictive factors including history of out-of-hospital cardiac arrest and smoking, of which the average prediction rate was approximately 90%. In this chapter, we will briefly review the epidemiological data regarding VSA from a broad set of perspectives, including demographic characteristics, incidence and prognosis, risk and precipitating factors, and other recent clinical topics.

Keywords Prevalence · Prognosis · Risk factors · Predictive factors · Sudden cardiac death · Racial difference

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1.1 Coronary Artery Spasm and Coronary Ischemic Syndromes

Angina pectoris is a clinical syndrome caused by transient myocardial ischemia due to an imbalance between myocardial oxygen demand and supply [1]. For more than 200 years since the description by Heberdenk, its pathogenesis has been explained by increased myocardial oxygen demand in the presence of fixed organic stenosis of the epicardial coronary arteries. Angina caused by spasm of epicardial coronary arteries has been known as variant angina. By most strict definition, variant angina is a diagnosis given to patients having rest angina associated with reversible ST-segment elevation on electrocardiogram (ECG) but no evidence of myocardial necrosis as determined by serial ECGs and enzymatic analysis. This peculiar form of angina pectoris was systematically described for the first time by Myron Prinzmetal and colleagues in 1959, based on the observations of 32 patients with rest angina associated with transient ST elevation [2]. All characteristic clinical features that are at present well recognized were mostly reported in the Prinzmetal report. Namely, chest pain typically occurs at midnight or in the early hours of the morning and tends to be clustered. Night awakening with chest pain is also common. As compared with classical angina, chest pain in variant angina is usually longer in duration and severe in intensity, and frequently associated with autonomic symptoms such as nausea and cold sweating. In general, the patients do not develop angina on exertion unless obstructive coronary atherosclerosis is concomitantly present and exercise tolerance during daytime is usually preserved. Shortly after the Prinzmetal report, coronary artery spasm was angiographically documented by Gensini et al. in a patient with rest and effort angina [3]. Furthermore, in the 1970s, Yasue et al. demonstrated spasm of an epicardial coronary artery during an attack of variant angina systematically induced by methacholine or exercise in the early morning [4, 5]. Endo et al. also reported similar findings almost simultaneously [6]. Coronary angiography during anginal attacks in patients suffering from recurrent angina at rest revealed a wide range of coronary artery disease from normal coronaries to severe three-vessel disease. ST-segment elevation was caused by a transient occlusion of the major coronary artery, whereas ST depression was caused by incomplete occlusion of coronary branches and invariably associated with the extensive coronary artery disease and rich collateral networks. Coronary collaterals develop with or without coronary artery disease and can modify the extent and severity of myocardial ischemia [7, 8]. Spasm of large epicardial coronary arteries causes angina at rest associated with ST elevation [3] or depression [7, 9]. Then, variant angina is now regarded as one aspect of the wide spectrum of myocardial ischemic syndromes caused by coronary spasm, and angina pectoris caused by coronary spasm is generally called vasospastic angina (VSA).

In addition to rest angina, coronary artery spasm plays a pivotal role in a broad spectrum of coronary ischemic syndrome, including exercise-induced angina, silent myocardial ischemia, pre-infarction (unstable) angina, acute myocardial infarction, postinfarction angina, syncope, and sudden cardiac death (Fig. 1.1) [10]. Especially,

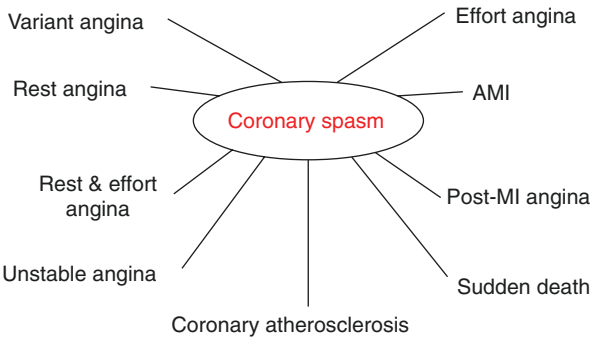


Fig. 1.1 Coronary artery spasm has been shown to play a key role in the pathogenesis of not only variant angina but also a number of related conditions in ischemic heart disease. (Reproduced from Takagi et al. [36])

coronary artery spasm can also be the cause of effort angina. It was generally believed that exercise-induced angina was caused by increased myocardial oxygen demand in the presence of flow-limiting organic stenosis and that ST elevation during exercise testing indicated the presence of severe organic stenosis. Coronary angiograms taken during exercise in the cardiac catheterization laboratory clearly demonstrated that exercise provoked coronary artery spasm, leading to total obstruction of major coronary artery at the site of no significant organic stenosis at baseline [11, 12]. The elevation or depression of ST-segment during exercise may be determined by the severity and extent of coronary artery spasm, the underlying coronary artery disease, or both [7, 13, 14].

It should be noted that patients with VSA often exhibit a marked variability of exercise capacity even in the same day. The circadian variation in angina threshold is an important diagnostic clue to suspect the involvement of coronary spasm in ischemic manifestations. It was shown that epicardial coronary artery tone as well as the sensitivity of coronary arteries to vasoconstrictor stimuli (e.g. ergonovine) varied substantially in the morning and in the afternoon [11, 15]. The underlying mechanism of the circadian variation is not fully understood, but may be related, at least partly, to the changes in the activity of autonomic nervous system [16, 17], endothelial function [18], and Rho-kinase activity [19]. The results based on the 24-h ambulatory ECG monitoring have shown that silent myocardial ischemia is frequently observed in patients with variant angina and approximately 80% of ischemia with transient ST elevation was asymptomatic [20]. Silent ischemia was associated with malignant ventricular tachyarrhythmias and may cause sudden cardiac death [21, 22].

In a subset of patients, coronary artery spasm is responsible for acute coronary thrombosis, resulting in pre-infarction unstable angina and acute myocardial infarction. It was previously reported that intracoronary nitroglycerin was effective to recanalize occluded vessel by relieving spasm in 6 out of 15 patients with acute myocardial infarction within 12 h after the onset [23]. In all the 6 patients, spasm was superimposed on the high-grade atherosclerotic stenosis. This result suggests that coronary spasm might be the primary cause of acute coronary occlusion or, at least, the secondary event to sustain flow impairment. Not rarely, myocardial infarction develops in the absence of significant organic stenosis [24, 25]. It was also shown that coronary spasm could be provoked at 4 weeks after the onset in 75% of patients with

acute myocardial infarction (AMI) and no significant organic stenosis in Japan [25]. These patients were characterized by the presence of pre-infarction and/or postinfarction angina at rest, the occurrence of multivessel spasm, and smaller infarct size. According to a recent study from Germany, in which the frequency of coronary spasm in patients with acute coronary syndrome (ACS) and unobstructed coronary arteries was examined by the intracoronary acetylcholine provocation test, every forth patients with ACS had no culprit lesion and almost 50% of the patients who underwent a provocation testing had proof of coronary spasm [26]. In general, postinfarction angina is a predictor of adverse outcomes after AMI [27]. However, coronary spasm is the cause of postinfarction angina in a subset of patients with cyclic ST elevation and they may have no critical stenosis on angiography [28, 29]. In almost of them, calcium channel blockers (e.g. diltiazem) are effective and the prognosis is generally favorable. Provocation testing frequently provokes coronary spasms in patients with AMI. When the relationship between provoked coronary spasm and clinical course in AMI patients was examined, the frequency of major adverse cardiac event-free survival was significantly higher in the positive group than in the negative group [30]. These results indicate that provoked coronary spasm is a significant independent predictor of poor prognosis in AMI patients.

1.2 Prevalence of Vasospastic Angina

There are insufficient data on the prevalence of VSA in both Eastern and Western countries, probably because it is difficult and cumbersome to examine coronary spasm during coronary angiography. To determine the prevalence of VSA, a survey was conducted on 2251 consecutive patients with angina (average age of 65.2 years) hospitalized in 15 major cardiovascular medical institutions in Japan in 1998 [31]. The survey showed that about 40% of patients with angina in Japan had VSA. Furthermore, analysis of the age group distribution of VSA revealed that the prevalence tended to be higher in relatively young patients than in elderly one. Recently, however, increase in use rate of calcium channel blockers (CCBs) for hypertension as well as decreasing rates of smoking might result in decreased morbidity of VSA in Japan [32]. It has been long believed that the prevalence of VSA patients is higher in Japanese than in Caucasian populations [33, 34]. This concept is consistent with a head-to-head controlled comparison of patients with acute ST elevation AMI (without a history of VSA) where Japanese patients were twice as likely to have inducible spasm than their Caucasian counterparts [35]. Furthermore, in Western studies, the diagnosis of VSA is primarily made on the basis of spontaneous episodes (i.e. anginal symptoms with ischemic ECG changes), whereas in Japan, it is more often based upon spasm provocation testing [36]. However, it has been recently demonstrated that the prevalence of coronary artery spasm in Caucasians may be higher than previously thought [37, 38]. Indeed, while previous Asian studies of patients without obstructive coronary artery disease have shown that the prevalence of coronary spasm was ~50% in patients with stable angina and

57% in patients with acute coronary syndrome [39, 40]; similar findings were demonstrated in Germany studies [26, 37]. Furthermore, Ong et al. demonstrated that, among 921 consecutive white patients with angina and nonobstructive coronary arteries, the overall frequency of epicardial spasm was 33.4%, and that of microvascular spasm was 24.2%, indicating that the morbidity of coronary functional disorder including VSA may be higher than we thought [41].

1.3 Risk Factors and Precipitating Factors for Coronary Artery Spasm

Age, smoking, high-sensitivity C-reactive protein (hsCRP), and remnant lipoprotein are significant risk factors for coronary spasm [42–45]. Generally, VSA is a disease of middle- and elderly aged men and postmenopausal women [42, 46]. Meanwhile, cigarette smoking, which has been identified as a risk factor for coronary artery spasm in various groups of patients including premenopausal women [47–49], has a strong effect on VSA development in younger than in their old counterparts [50, 51]. Nicotine potently upregulates Rho-kinase, which has been identified as one of the effectors of the small GTP-binding protein Rho and plays a key role in the molecular mechanisms of VSA, in human coronary artery smooth muscle cells, while estrogens potently downregulate it [52, 53]. Smoking is a controllable factor in preventing the development of coronary spasm and cessation of smoking is associated with spontaneous remission of angina [54]. High LDL cholesterol and insulin resistance were suggested to be a risk factor for VSA in selected patients [48, 55], but were not confirmed by others. Furthermore, it also has been suggested that oxidative stress may be associated with abnormalities of triglyceride metabolism and HDL cholesterol level reduction [20, 56]. However, the role of dyslipidemia as a risk factor for coronary spasm remains to be less clear. Thus, except for smoking, many conventional risk factors for atherosclerosis appear to be insignificant for VSA. On the other hand, it was reported that serum levels of hsCRP were elevated in VSA patients than in non-VSA patients [57] and that 6-month treatment with a statin could significantly reduce the disease activity of VSA along with the decrease in hsCRP levels [58]. These results suggest that low-grade inflammation caused by risk factors including smoking and hyperlipidemia is involved in the pathogenesis of VSA and that hsCRP is useful for disease activity assessment of VSA.

1.4 Prognosis and Predictive Factors for Vasospastic Angina

The prevalence of major adverse cardiac events (MACE) in VSA is difficult to define because of the variation in defining the disorder. Several important prognostic studies with a few hundreds of patients were performed in the 1980s. Shimokawa et al. reported that overall survival rates at 1, 3, and 5 years among consecutive 158

Japanese patients with variant angina were 99, 96, and 93%, respectively, and survival rates without AMI at 1, 3, and 5 years were 94, 92, and 87%, respectively [59]. Yasue et al. also reported that 5-year survival rate free from death or myocardial infarction was 97% and 83% in 245 patients [60]. On the other hand, the prognosis of Caucasian population of the day was much worse, demonstrating that 5-year survival rate free from death or myocardial infarction was 89% and 69%, respectively [61]. In association with the epidemics of obesity and metabolic syndrome, the general population has been rapidly growing older and the Westernization of lifestyle has been progressing, especially in Japan [62]. Thus, we conducted the nationwide multicenter retrospective registry study by the Japanese Coronary Spasm Association (JCSA), which focused on the clinical characteristics and outcomes of VSA patients in the 2000s (Fig. 1.2) [36]. During the median follow-up period of 32 months, among 1429 patients with VSA, 19 (1.3%) died, in which 6 had cardiac death. MACE occurred in 85 patients (5.9%), including AMI (n = 9), hospitalization for unstable angina (n = 68) and heart failure (n = 4), and appropriate ICD shocks (n = 2). Overall 5-year survival rate free from all cause death or MACE was 98% and 91%, respectively (Fig. 1.3) [36]. Especially, 5-year survival rate free from nonfatal AMI was high (99%). Moreover, Ong et al. reported that ACS patients without culprit lesion and proven coronary spasm have an excellent prognosis for survival and coronary events after 3 years compared with those with obstructive

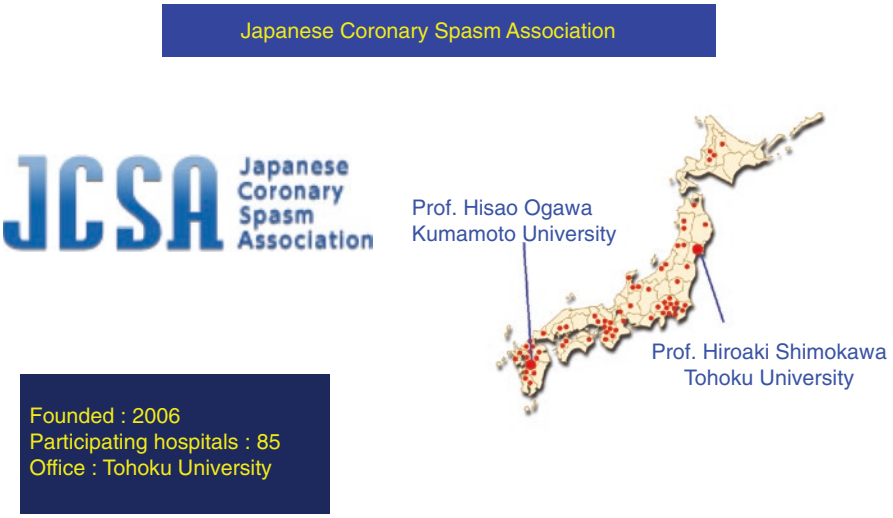


Fig. 1.2 The Japanese Coronary Spasm Association (JCSA) was established in 2006 by Prof. Shimokawa and Ogawa to elucidate the clinical characteristics and outcomes of patients with VSA in the current era and conducted the nationwide multicenter registry study of VSA

	No. of events (%)
All cause death	19 (1.3)
MACE	85 (5.9)
Cardiac death	6 (0.5)
Non-fatal MI	9 (0.6)
Unstable angina	68 (4.9)
Heart failure	4 (0.3)
Appropriate ICD shock	2 (0.1)

MACE, major adverse cardiac events; MI, myocardial infarction; ICD, implantable cardioverter defibrillator.

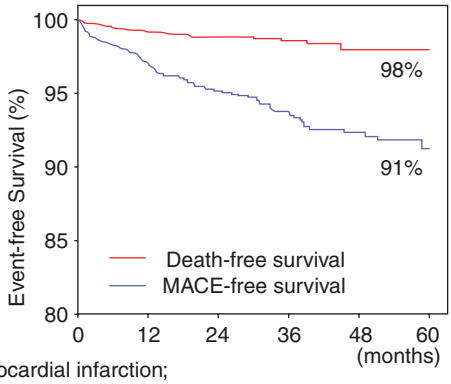


Fig. 1.3 Clinical outcomes of 1429 VSA patients enrolled into the nationwide multicenter retrospective registry study by the Japanese Coronary Spasm Association. During the median follow-up period of 32 months, 19 patients (1.3%) died and MACE occurred in 85 patients. Overall 5-year survival rate free from all cause death or MACE was 98% and 91%, respectively. (Reproduced from Takagi et al. [36])

ACS [63]. Taken together, in the current era, the clinical outcome of VSA patients appears to be further improved as compared with the 1980s. It is important to continue medical treatments with CCB for VSA, since silent myocardial ischemia with fatal arrhythmia and a rebound phenomenon of the spasm could occur after withdrawal of CCB [21, 64].

Several prognostic factors for VSA, such as smoking, organic coronary stenosis, and multivessel spasm, have been established since the 1980s [59–61, 65–67]. Recently, in addition to the aforementioned prognostic factors, we newly identified the prognostic impact of history of out-of-hospital cardiac arrest (OHCA) [36] and specific angiographic findings during the diagnostic provocation tests [68]. However, in order to apply such prognostic findings to clinical practice, the accumulation of various prognostic factors in individual patients should be taken into consideration. Additionally, it is conceivable that potential interactions among those prognostic factors exist, making it difficult to assess individual prognosis. Thus, we developed the JCSA risk scoring system as a comprehensive assessment tool that provides the valid risk prediction in individual patients [69]. This JCSA risk score, which consists of 7 predictive factors, including history of OHCA, smoking, angina at rest alone, significant organic stenosis, multivessel spasm, ST-segment elevation during angina, and β-blocker use, showed a significant correlation with the prognosis of VSA patients (see Chap. 4**,** Fig. 4.3a, b). The average prediction rate of the scoring system was approximately 90%, suggesting that the risk scoring system could accurately estimate future adverse cardiac events in individual VSA patient. Since the clinical information required for the scoring system is readily available from routine practice, it should help clinicians predict patient outcomes easily. The information on the prognostic stratification may lead to personalized management, including the judgment of necessity for intensive medical treatment and close follow-up. In

addition, because the outcomes of VSA patients could be aggravated by a rebound phenomenon after careless discontinuation of medications [36, 64], it is of clinical significance that the adherence in high-risk patients should be improved through the awareness with this risk score.

1.5 Sudden Cardiac Death in Vasospastic Angina

Syncope is an important manifestation of VSA and is caused by ventricular tachyarrhythmias or bradycardia due to transient conduction disturbances. It is commonly preceded by anginal pain, although not in all cases [70]. The development of arrhythmias is not related to the frequency of angina and concurs with symptomatic as well as asymptomatic myocardial ischemia [20, 21]. More importantly, sudden cardiac death can ensue as a result of coronary artery spasm [71, 72], even in patients with silent myocardial ischemia [21, 22]. In a subgroup of survivors of OHCA, coronary spasm and silent myocardial ischemia were identified as a likely cause of their fatal arrhythmias [21, 22]. Additionally, in the current era, a substantial portion of patients with OHCA survived without neurological deficits by the contribution of increasing use of bystander cardiopulmonary resuscitation, implantable cardioverter-defibrillator (ICD), and hypothermia therapy and a certain number of them have coronary spasm [73]. VSA patients who survived OHCA are particularly high-risk population even in the current era with long-acting CCBs [36]. Implantation of an ICD with medication for VSA might be appropriate for this high-risk population [74]. Recently, we examined the long-term prognosis of patients with OHCA classified based on the results of the dual induction tests for coronary artery spasm and lethal ventricular arrhythmias and evaluated the necessity of ICD by the underlying mechanisms involved (Fig. 1.4) [75]. We found that among OHCA survivors without structural heart disease, provokable coronary spasm and ventricular arrhythmias are common and can be seen in Brugada syndrome (Fig. 1.5a). Then, coronary spasm alone without Brugada syndrome who are treated by CCBs may be a low-risk group (Fig. 1.5b), indicating that ICD may not be essential for OHCA survivors in this low-risk group [75].

1.6 Racial Difference in Vasospastic Angina

For decades, many researchers considered that there may be a racial difference in the prevalence of coronary artery spasm and VSA [76]. For example, variant angina appears to be relatively common in Japan [76]. However, there have been very few studies to systematically examine possible ethnic differences in clinical characteristics and long-term prognosis of VSA patients [59]. Recently, the JCSA conducted

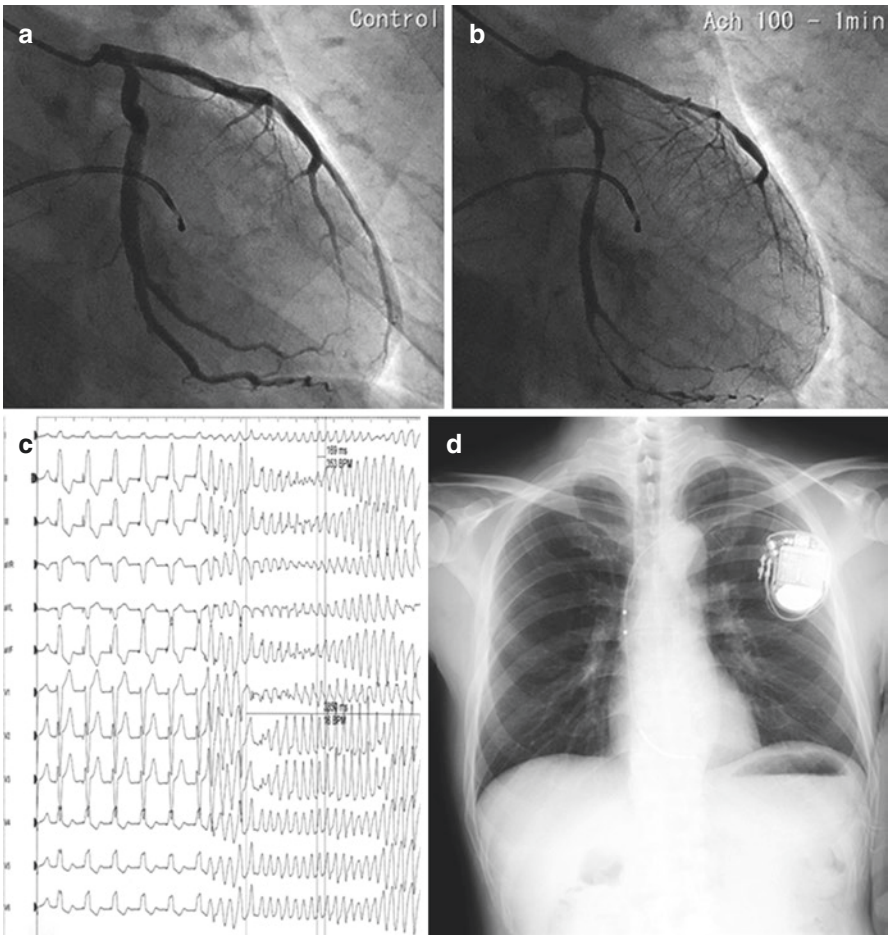


Fig. 1.4 A representative case in the group with both coronary spasm and idiopathic ventricular fibrillation by the dual induction tests. (**a**) Coronary angiogram before spasm provocation test. (**b**) Coronary artery spasm induced by intracoronary acetylcholine. (**c**) Ventricular fibrillation induced by electrophysiological study. (**d**) Subsequent implantation of implantable cardioverter-defibrillator. (Reproduced from Komatsu et al. [75])

an international, prospective, and multicenter registry study, in which a total of 1457 VSA patients (Japanese/Caucasians, 1339/118) were enrolled based on the same diagnostic criteria [77]. 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.

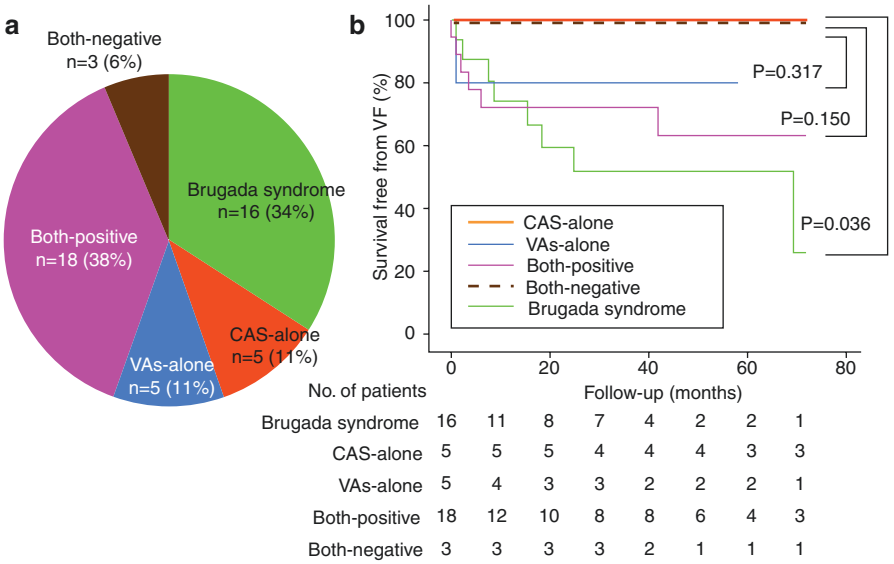
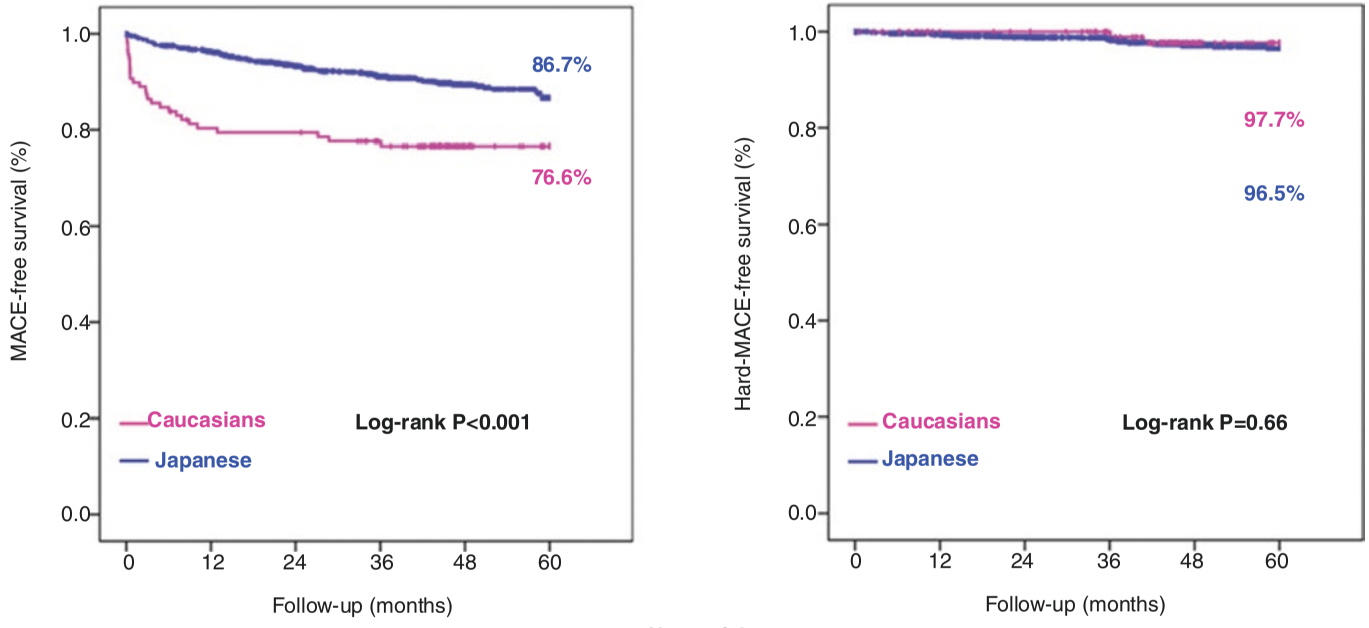


Fig. 1.5 Classification of OHCA survivors when analyzing the patients with Brugada syndrome as a separate group. (**a**) Distribution of patients when the patients with Brugada syndrome were separated as a different group. (**b**) Kaplan–Meier curves for sudden cardiac death by the groups classified by the presence or absence of Brugada syndrome and the dual induction tests. (Reproduced from Komatsu et al. [75])

Importantly, there were no significant differences in the patterns of coronary spasm, with diffuse spasm most frequently noted in both ethnicities. The prescription rate of CCBs 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 MACE was slightly but significantly higher in Japanese than in Caucasians (86.7 vs. 76.6% at 5 years, $P < 0.001$), whereas that free from the hard MACE endpoint was similar (96.5 vs. 97.7%, $P = 0.66$) (Fig. 1.6). Notably, multivariable analysis revealed that the JCSA risk score well correlated with MACE rates not only in Japanese but also in Caucasian patients. These results indicate that there are ethnic differences in clinical profiles and long-term prognosis of contemporary VSA patients [77].



No. at risk						
Caucasians	118	91	90	77	23	4
Japanese	1339	1181	933	690	387	137

No. at risk						
Caucasians	118	105	103	89	29	5
Japanese	1339	1216	987	736	421	153

Fig. 1.6 Clinical outcomes of the contemporary Japanese and Caucasians VSA patients. (**a**) Kaplan–Meier curves by ethnics for MACE in VSA patients. MACE included cardiac death, nonfatal 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, nonfatal myocardial infarction, VT/VF, and appropriate ICD shocks. (Reproduced from Sato et al. [77])

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