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Prognostic impact of chronic nitrate therapy in patients with vasospastic angina: multicentre registry study of the Japanese coronary spasm association

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Aims Although nitrates are widely used as a concomitant therapy with calcium channel blockers (CCBs) for vasospastic angina (VSA), their prognostic contribution remains unclear. The present study aimed to examine the prognostic impact of chronic nitrate therapy in patients with VSA.

Methods and results A total of 1429 VSA patients (median 66 years; male/female, 1090/339) were enrolled. The primary endpoint was defined as major adverse cardiac events (MACE). The propensity score matching and multivariable Cox proportional hazard model were used to adjust for selection bias for treatment and potential confounding factors. Among the study patients, 695 (49%) were treated with nitrates, including conventional nitrates [e.g. nitroglycerin (GTN), isosorbide mono- and dinitrate] in 551 and nicorandil in 306. Calcium channel blockers were used in >90% of patients. During the median follow-up period of 32 months, 85 patients (5.9%) reached the primary endpoint. Propensity score-matched analysis demonstrated that the cumulative incidence of MACE was comparable between the patients with and those without nitrates [11 vs. 8% at 5 years; hazard ratio (HR): 1.28; 95% confidence interval (CI): 0.72–2.28, $P = 0.40$]. Although nicorandil itself had a neutral prognostic effect on VSA (HR: 0.80; 95% CI: 0.28–2.27, $P = 0.67$), multivariable Cox model revealed the potential harm of concomitant use of conventional nitrates and nicorandil (HR: 2.14; 95% CI: 1.02–4.47; $P = 0.044$), particularly when GTN and nicorandil were simultaneously administered.

Conclusions Chronic nitrate therapy did not improve the long-term prognosis of VSA patients when combined with CCBs. Furthermore, the VSA patients with multiple nitrates would have increased risk for cardiac events.

Keywords Vasospastic angina • Coronary vasospasm • Nitrate • Nicorandil • Prognosis

Introduction

Nitrates are one of the classical drugs that have been widely used for cardiovascular diseases. Nitrates act via nitric oxide signalling pathways and exert endothelium-independent vasodilatation, leading to an increase in coronary perfusion and reductions in cardiac pre- and post-load.[1,2] With these pharmacological features, nitrates acutely improve cardiac conditions, such as angina attacks

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and acute heart failure. However, their long-term prognostic effects have been controversial. The chronic exposure to nitrates results in a rapid development of tolerance, blunting their anti-ischaemic and haemodynamic efficacy.[1,2] Furthermore, their potential harm for cardiovascular patients, such as generation of reactive oxygen species with resultant endothelial dysfunction,[3] sympathetic nerve activation,[4] and increase in sensitivity to vasoconstrictors[5] has also been suggested. Despite these aspects, nitrates are often prescribed for long-term use in patients with heart failure, organic coronary artery disease and vasospastic angina (VSA), although their prognostic effects remain unclear.

Vasospastic angina is an important functional cardiac disorder characterized by transient myocardial ischaemia due to epicardial coronary artery spasm, and is basically synonymous with the terms 'Prinzmetal's angina' and 'variant angina'.[6] Calcium channel blockers (CCBs) are the established first-line therapy for VSA,[7] and nitrates are generally used as a concomitant therapy. Furthermore, the introduction of nicorandil, a hybrid of nitrate, and K_{ATP} channel agonist has expanded the range of choices of concomitant therapy for VSA.[8] In the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society, both long-acting nitrates and nicorandil are classified as Class IIa agents for the treatment of coronary spasm.[7] However, despite their widespread use, the contribution of chronic treatment with nitrates, including nicorandil, to long-term prognosis of VSA patients remains to be fully elucidated. At present, there is no algorithm available regarding the combinatorial approach of nitrates and/or nicorandil in addition to CCBs for patients with refractory VSA.

The Japanese Coronary Spasm Association has established several prognostic findings of VSA through the nationwide multicentre registry study.[9–12] In the present study, we thus aimed to examine the prognostic impact of chronic nitrate therapy in VSA patients in our registry.

Methods

The Japanese Coronary Spasm Association was founded in 2006 and currently consists of 81 institutes in Japan. The study protocol was approved by the institutional review boards and/or ethics committees of all participating institutes.

Study population

Vasospastic angina patients diagnosed between 1 April 2003 and 31 December 2008 were enrolled. The registration was made between 1 September 2007 and 31 December 2008. The data collection were conducted in a retrospective manner for patients seen before September 2007 and in a prospective manner for those seen after that date. The diagnosis of VSA was made based on the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society.[7]

Medical treatments

Selection of medical treatments for VSA was at the discretion of each attending physicians. Nitrates include nitroglycerin (GTN), isosorbide mononitrate (ISMN), and isosorbide dinitrate (ISDN), and they were categorized as conventional nitrates. Nicorandil was also included in nitrates. No information was available regarding the dose of nitrates.

Endpoints

The primary endpoint was defined as major adverse cardiac events (MACE), including cardiac death, non-fatal myocardial infarction, hospitalization due to unstable angina pectoris, and heart failure and appropriate ICD shocks. The secondary endpoint was all-cause mortality.

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. To reduce the effect of selection bias, we adjusted baseline characteristics of the study population using propensity score matching. To confirm the result of the propensity matching analysis, inverse probability of treatment weighting (IPTW) method based on the propensity score was also applied to assess the effect of chronic nitrate. To handle more than two treatment conditions, the multinomial propensity score method was used.[13] Survival free from MACE and death were analysed by the Kaplan–Meier method. Univariable and multivariable Cox proportional hazard models were applied to calculate hazard ratio (HR) and 95% confidence interval (CI) comparing the risk of MACE between patients with and those without nitrates. A value of $P < 0.05$ was considered to be statistically significant. Refer to Supplementary material online for further information.

Results

Patient characteristics and treatments

Among the 1528 patients registered from the 47 participating hospitals, 99 were excluded because they did not meet the inclusion criteria. Finally, 1429 VSA patients, including retrospective ($n = 1276$) and prospective populations ($n = 153$), were analysed in the present study. For the treatment of VSA, 695 patients (49%) received chronic nitrate therapy, whereas 734 (51%) did not. The demographic and angiographic characteristics and medical treatments of the two groups as an entire population are shown in *Table 1*. The patients with nitrates were characterized by older age and had higher proportion of ST-segment elevation during angina attacks, coronary spasm of the left anterior descending coronary artery, multivessel spasm, and antiplatelet use, whereas those without nitrates were characterized by higher prevalence of previous myocardial infarction and significant organic coronary stenosis. Calcium channel blockers were used in >90% of both groups.

After performing propensity score matching for the entire population, 413 matched pairs of patients were identified. For the logistic model to estimate propensity score, AUC of ROC curve was equal to 0.642 and the Hosmer–Lemeshow test provided $P = 0.873$, suggesting goodness of fit of the model. There were no significant differences in baseline variables for the propensity-matched population (*Table 1*).

Long-term outcomes

The primary and secondary outcomes of the unmatched and propensity-matched populations are shown in *Table 2* and *Figure 1*. During the median follow-up period of 32 months (IQR: 17–46 months), 85 patients (5.9%) in the unmatched population reached the primary endpoint, which was predominantly accounted for by unstable angina. All-cause death as the secondary endpoint occurred in

Table 1 Demographic, angiographic characteristics and treatments of vasospastic angina patients before and after propensity score matching

	Entire population				Matched population			
	With nitrate	Without nitrate	*P*-value	SD	With nitrate	Without nitrate	*P*-value	SD
Demographic characteristics								
No. of patients, *n* (%)	695 (49)	734 (51)	0.3		413 (50)	413 (50)	1	
Age, median (IQR) (year)	67 (59, 73)	65 (58, 72)	0.011	0.14	66 (58, 73)	66 (59, 73)	0.3	−0.04
Male, *n* (%)	518 (75)	572 (78)	0.13	−0.08	299 (72)	319 (77)	0.12	−0.11
Coronary risk factors, *n* (%)								
Hypertension	339 (49)	327 (45)	0.11	0.08	206 (50)	182 (44)	0.11	0.12
Dyslipidaemia	309 (44)	338 (46)	0.55	−0.03	195 (47)	211 (51)	0.29	−0.08
Diabetes mellitus	112 (16)	121 (16)	0.85	−0.010	66 (16)	76 (18)	0.41	−0.06
Smoking	416 (60)	432 (59)	0.7	0.02	237 (57)	252 (61)	0.31	−0.07
Family history of ischaemic heart disease	101 (15)	67 (9)	0.002	0.17	42 (10)	46 (11)	0.74	−0.03
Previous myocardial infarction, *n* (%)	32 (5)	59 (8)	0.008	−0.14	19 (5)	23 (6)	0.63	−0.04
Circadian pattern of angina attack, *n* (%)[a]								
Night to morning	278 (84)	262 (80)	0.2	0.10	164 (85)	158 (84)	0.41	0.04
Daytime	87 (26)	91 (28)	0.66	−0.03	46 (24)	46 (24)	0.59	−0.012
ST-segment changes during angina attack, *n* (%)[b]								
ST elevation	157 (25)	115 (17)	<0.001	0.21	52 (13)	50 (12)	0.92	0.015
ST depression	58 (9)	63 (9)	0.93	0.005	43 (10)	31 (8)	0.16	0.10
Arrhythmic events during angina attack, *n* (%)								
PVC	9 (1)	5 (1)	0.24	0.06	5 (1)	2 (0.5)	0.45	0.08
VT/VF	22 (3)	21 (3)	0.74	0.018	14 (3)	11 (3)	0.68	0.04
AV block	15 (2)	6 (1)	0.035	0.11	4 (1)	4 (1)	1	0
Bradycardia/sinus pause	15 (2)	13 (2)	0.6	0.03	8 (2)	11 (3)	0.65	−0.05
Out-of-hospital cardiac arrest	19 (3)	16 (2)	0.5	0.04	15 (4)	8 (2)	0.19	0.10
Angiographic characteristics								
Organic coronary stenosis, *n* (%)								
Without stenosis	437 (63)	441 (60)	0.15	0.012	266 (64)	257 (62)	0.69	0.005
Non-significant stenosis	173 (25)	177 (24)			98 (24)	109 (26)		
Significant stenosis	85 (12)	116 (16)			49 (12)	47 (11)		
Spasm-positive arteries induced by provocation test, *n* (%)[c]								
LAD	340 (61)	326 (52)	0.003	0.17	256 (62)	251 (61)	0.72	0.02
LCx	155 (28)	162 (26)	0.51	0.04	119 (29)	132 (32)	0.36	−0.07
RCA	331 (59)	362 (58)	0.7	0.02	230 (56)	229 (55)	1	0.005
Multivessel	202 (36)	172 (28)	0.002	0.18	146 (35)	152 (37)	0.67	−0.03
Medical treatments								
CCB, *n* (%)	639 (92)	692 (94)	0.08	−0.09	411 (99)	406 (98)	0.18	0.12
Antiplatelet, *n* (%)	355 (51)	314 (43)	0.002	0.17	187 (45)	187 (45)	1	0
Statin, *n* (%)	216 (31)	256 (35)	0.13	−0.08	131 (32)	141 (34)	0.51	−0.05
ACEI/ARB, *n* (%)	172 (25)	168 (23)	0.41	0.04	95 (23)	82 (20)	0.33	0.08
β-Blocker, *n* (%)	18 (3)	43 (6)	0.002	−0.16	12 (3)	12 (3)	1	0

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; CCB, calcium channel blocker; IQR, interquartile range; LAD, left anterior descending artery; LCx, left circumflex coronary artery; PVC, premature ventricular contraction; RCA, right coronary artery; SD, standardized difference; VF, ventricular fibrillation; VSA, vasospastic angina; VT, ventricular tachycardia.

[a]Data of circadian pattern were available for 658 patients among the entire population and 380 patients among the matched population.

[b]Data of ST-segment changes were available for 1317 patients among the entire population.

[c]The spasm provocation test was performed on 1244 patients among the entire population, and the data of spasm-positive artery were available for 1184 patients.

Table 2 Primary and secondary outcomes in vasospastic angina patients with and those without nitrates

	Entire population				Matched population				IPTW	
	With nitrate (*n* = 695)	Without nitrate (*n* = 734)	HR (95% CI)	*P*-value	With nitrate (*n* = 413)	Without nitrate (*n* = 413)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
MACE, *n* (%)	49 (7)	36 (5)	1.35 (0.88–2.07)	0.17	26 (6)	21 (5)	1.28 (0.72–2.28)	0.40	1.54 (0.90–2.64)	0.12
Cardiac death	3 (0.4)	3 (0.4)			0 (0)	1 (0.2)				
Non-fatal MI	4 (1)	5 (1)			1 (0.2)	2 (0.5)				
Unstable angina	40 (6)	28 (4)			24 (6)	18 (4)				
Heart failure	3 (0.4)	1 (0.1)			0 (0)	0 (0)				
Appropriate ICD shock	1 (0.1)	1 (0.1)			1 (0.2)	1 (0.2)				
All-cause death, *n* (%)	9 (1)	10 (1)	0.88 (0.36–2.17)	0.78	5 (1)	4 (1)	1.27 (0.34–4.74)	0.72	1.15 (0.39–3.40)	0.80

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ICD, implantable cardioverter defibrillator; MACE, major adverse cardiac events; MI, myocardial infarction.

19 patients (1.3%). Kaplan–Meier curve and Cox proportional hazard model demonstrated that the patients with nitrates tended to have a higher incidence of MACE compared with those without nitrates (10 vs. 8% at 5 years, $P = 0.17$) (*Figure 1A*).

After performing the propensity score matching, 47 primary (5.6%) and 9 secondary (1.1%) events were noted during the median follow-up period of 30 months (IQR: 16 to 46 months). A slightly higher incidence of MACE was still noted in patients with nitrates, although the matching procedure reduced the trend for statistical difference between the two groups (11 vs. 8% at 5 years, $P = 0.40$) (*Figure 1B*). Based on the propensity score, the IPTW method also provided a similar result that the patients with nitrates had higher but not significant risk of MACE ($P = 0.12$) (*Table 2*).

Subgroup analysis

To elucidate whether chronic nitrate therapy benefited any specific conditions, univariable Cox model for MACE was applied to clinical subgroups identified by patient characteristics and medical treatments in the entire population (*Figure 2*). Rather than indicating the beneficial effect of nitrates on VSA patients, the Cox model consistently demonstrated that the patients with nitrates tended to have a worse outcome (*Figure 2*).

Types, forms, and number of nitrates

Among the 695 patients with chronic nitrate therapy, 551 (79%) were treated with conventional nitrates (GTN in 88, ISMN in 288, and ISDN in 193). Of those, baseline characteristics of the 515 patients with a single conventional nitrate are summarized in Supplementary material online, *Table S1* and the cumulative incidence of MACE for each conventional nitrate is shown in Supplementary material online, *Figure S1*. Nicorandil was used in 306 patients (44%), and 163 of them were also concomitantly treated with conventional nitrates. The relationship among the types, forms, and number of nitrates and patient outcomes was also assessed by univariate and multivariable Cox models in the entire population (*Table 3*). Importantly, while no statistical correlation was found in the univariable analysis, the multivariable Cox model, where variables were adjusted for seven established prognostic factors of VSA,[9,11] revealed the significant correlation between the multiple nitrate therapy, as typified by the combination of conventional nitrates and nicorandil, and MACE (*Table 3* and *Figure 3*). The similar result was obtained by the IPTW method based on the weights given by the multinomial propensity scores (*Table 3*).[13] Furthermore, when limited for the patients with combined therapy of a conventional nitrate and nicorandil, the concomitant use of GTN was significantly associated with a higher incidence of MACE (*Table 4*). In contrast, nicorandil itself had a neutral effect on patient prognosis (*Figure 4*), and we also found no difference in the prognostic impacts among GTN, ISMN, and ISDN, when used as a single nitrate therapy (*Table 4*).

Discussion

The major findings of the present study were that (i) >90% of the VSA patients were treated with CCBs, where chronic nitrate therapy did not further improve their long-term prognosis; (ii) the use of multiple nitrates was rather significantly correlated with MACE; and (ii) nicorandil itself had a neutral prognostic effect on

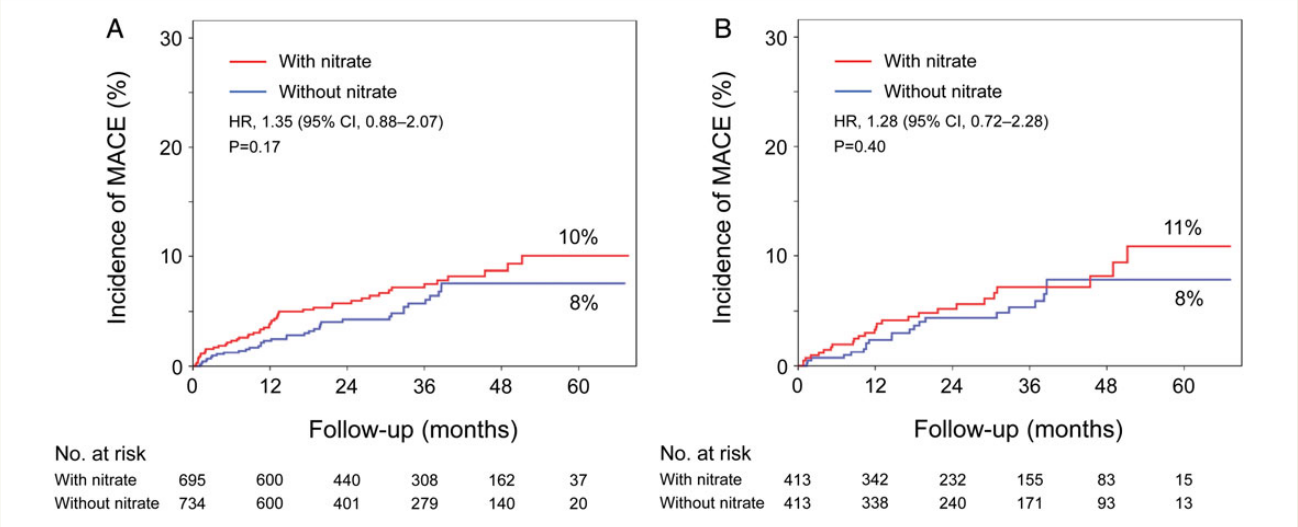

Figure 1 Cumulative incidence of major adverse cardiac event in vasospastic angina patients with and those without nitrates. (*A*) Kaplan–Meier curve in the entire population. (*B*) Kaplan–Meier curve in the propensity-matched population. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; VSA, vasospastic angina.

VSA patients. To the best of our knowledge, this is the first multicentre study with the largest patient population that demonstrates the prognostic impact of chronic nitrate therapy in VSA patients.

Chronic nitrate therapy for vasospastic angina

When Prinzmetal *et al.* first reported VSA as a 'variant angina' in 1959,[14] the patients with this disorder were treated with conventional anti-ischaemic agents such as nitrates and β-blockers.[15] However, these agents alone were often ineffective against VSA, leading to the development of CCBs for the disorder. The previous studies performed in 1970s demonstrated that nifedipine reduced the frequency of angina attack in VSA patients who were refractory to ISDN with a good tolerability.[16] Subsequently, several randomized trials with a large number of patients confirmed the superiority of CCBs (nifedipine and diltiazem) over ISDN.[17] These lines of evidence have established CCBs as the first-line therapy for VSA, and nitrates are currently used mainly as a concomitant therapy.[7] Although nitrate therapy acutely improves vasospastic symptoms,[17] its prognostic effects have been controversial. While some studies showed the neutral effects of nitrates,[18] other studies showed the aggravating effects of nitrates on long-term prognosis of patients with organic coronary disease[19] and those with VSA.[20] The possible aggravating mechanisms include the rapid development of tolerance,[1,2] the generation of reactive oxygen species with resultant endothelial dysfunction,[3] sympathetic nerve activation,[4] and increase in sensitivity to vasoconstrictors.[5] In the present study, chronic nitrate therapy did not improve the outcomes of VSA patients. Since the patients were sufficiently treated with CCBs, this result may indicate no additive beneficial effects of nitrates on the top of CCBs therapy in VSA patients. Rather, the patients with nitrates tended to have a higher incidence of MACE in the present study. In addition, multivariable Cox model, where variables were adjusted for the established prognostic factors,[9,11] revealed that the multiple nitrate therapy was significantly correlated with worse outcomes. In the present study, the patients with concomitant use of a conventional nitrate and nicorandil accounted for the majority with multiple nitrate therapy. Since previous papers suggested that conventional nitrates could be different with each other,[1] we examined the relationship between the use of conventional nitrates and MACE in the patients with nicorandil. Indeed, a significant correlation was noted between the concomitant use of GTN (a high-potency agent) and nicorandil and the occurrence of MACE, whereas the concomitant use of ISMN or ISDN (low-potency agents) with nicorandil was not associated with poor prognosis (*Table 4*; Supplementary material online, *Table S2*). Increased sensitivity to vasoconstrictors in response to chronic GTN therapy has been demonstrated,[5] which may be involved in worsening of VSA in patients with concomitant use with GTN and nicorandil. It still could be possible that nitrates are required for patients with more serious conditions and that the present propensity score matching and multivariable analysis failed to adjust for unmeasured variables reflecting such serious conditions. However, the present results do not advocate the aggressive use of nitrates, especially in case of multiple use, for long-term prognosis of VSA patients.

Nicorandil for vasospastic angina patients

In the clinical setting, we sometimes experience VSA cases refractory to CCBs therapy. To control angina symptom, ~60% of VSA patients require additional medications in addition to initial treatment.[21] The angina symptoms refractory to two or more CCBs therapy was found in 14% of VSA patients in a research report from the Ministry of Health, Labour, and Welfare in Japan. There also is a concern

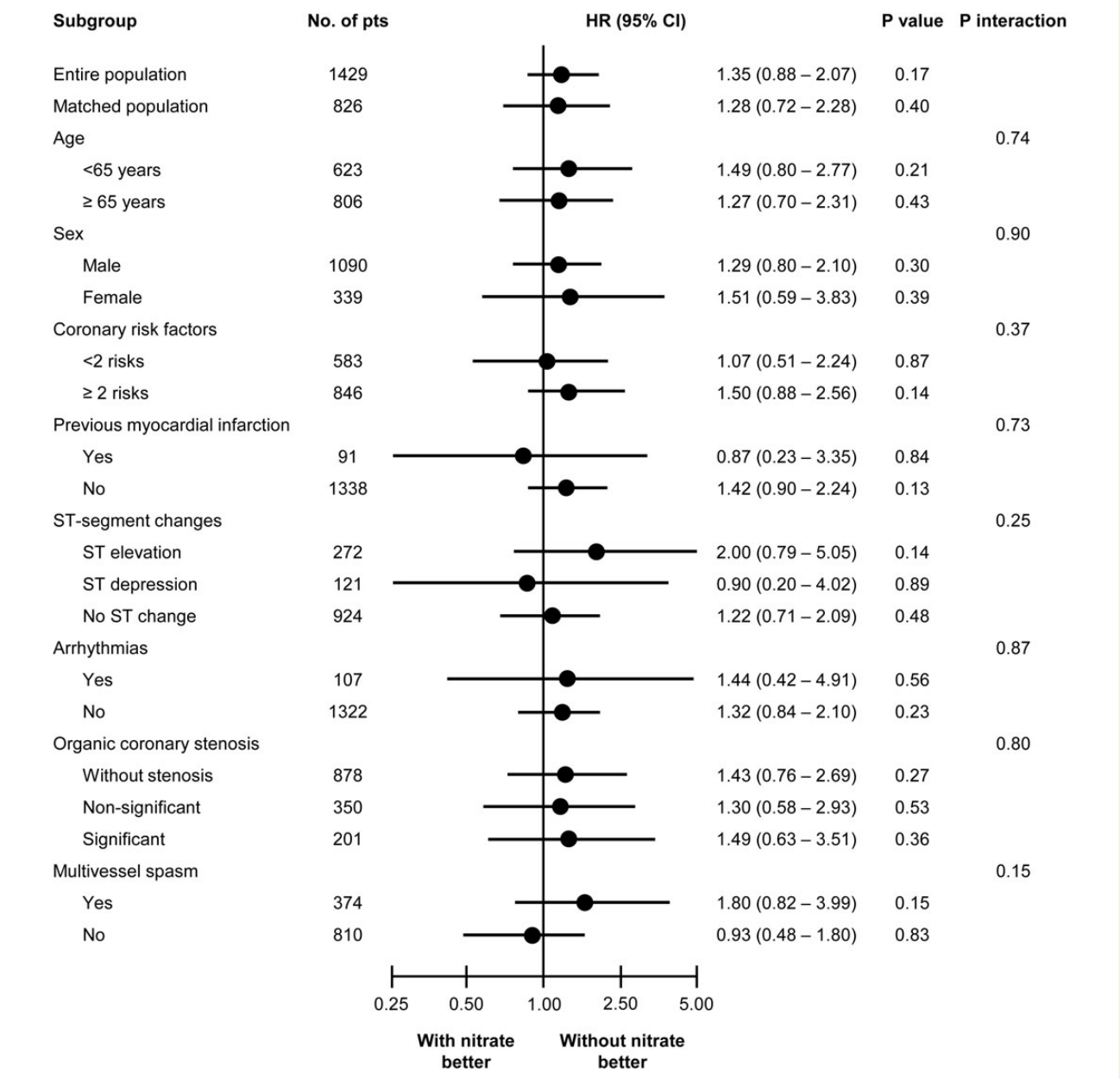

Figure 2 Hazard ratios for major adverse cardiac event according to clinical subgroups. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; pts, patients.

regarding the tolerability of multiple or high-dose CCB therapy in the refractory cases, including the excessive decrease in blood pressure and peripheral oedema.[22] Nicorandil has been expected to be a useful therapeutic agent for such VSA patients refractory to CCBs.[8] Nicorandil has the dual properties of nitrate and K_{ATP} channel agonist, showing the cardiovascular protective effects without tolerance development.[23] In fact, nicorandil could cause vascular relaxation without intracellular cGMP accumulation through opening potassium channels in the plasma membrane with resultant hyperpolarization of vascular smooth muscle cells. Importantly, a functional role for K_{ATP} channels in response to nicorandil becomes more apparent when cyclic GMP formation is suppressed as in the case of nitrate tolerance.[24] However, little information was available on its prognostic impact on VSA. The present study provides the novel finding that nicorandil itself has a neutral prognostic effect on VSA patients when treated with CCBs, suggesting its acceptability for concomitant use. In contrast, the combination of nicorandil and conventional nitrates showed a significant correlation with MACE. Thus, it is recommended for clinicians to avoid concomitant use of nicorandil and GTN, although there is no harmful effect of

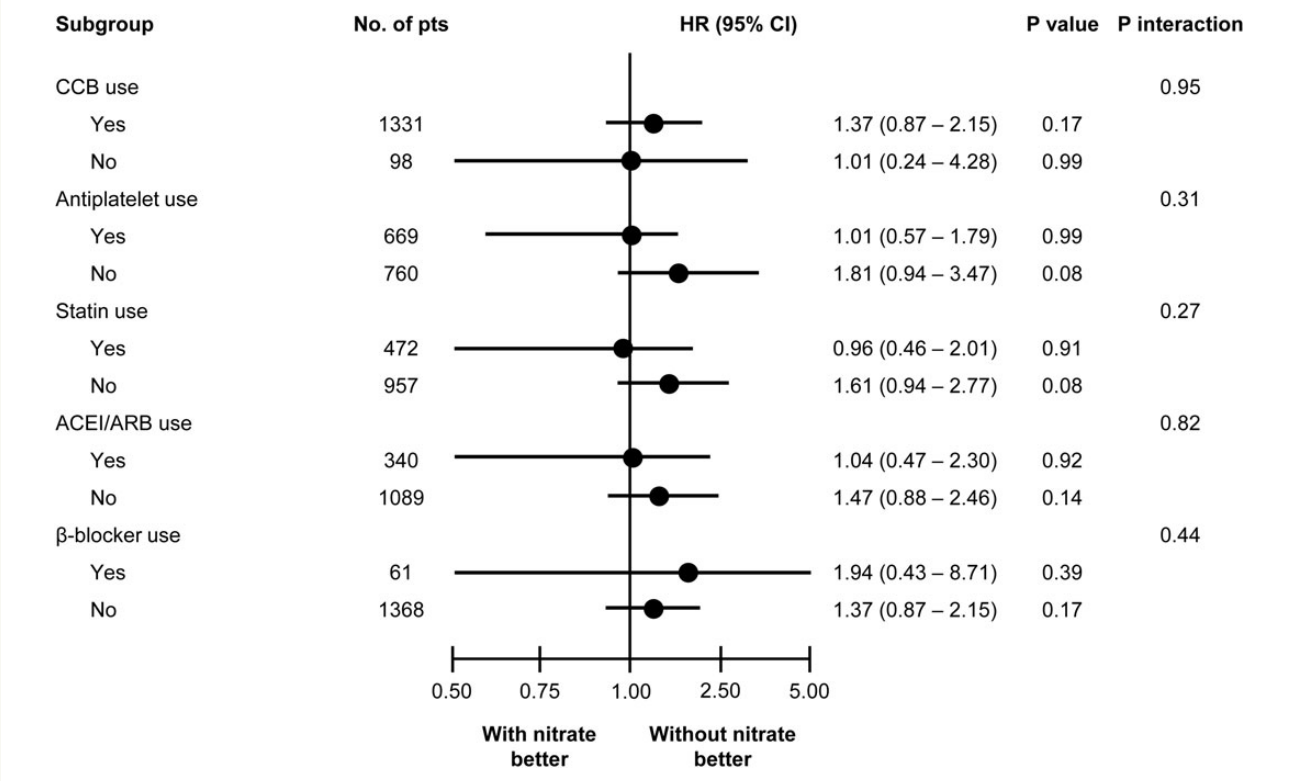

Figure 2 Continued

Table 3 Relationships among types, forms, and number of nitrates and major adverse cardiac event

	No. of patients (%)[a]	Unadjusted		Adjusted[b]		IPTW by multinomial propensity score	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Types of nitrates							
Without nitrate (reference)	734 (51)	1		1		1	
Conventional nitrate	388 (27)	1.37 (0.83–2.24)	0.22	1.39 (0.77–2.52)	0.28	1.32 (0.91–1.92)	0.15
Nicorandil	143 (10)	1.13 (0.53–2.44)	0.75	0.80 (0.28–2.27)	0.67	0.83 (0.54–1.28)	0.40
Combination	163 (11)	1.49 (0.79–2.81)	0.22	2.14 (1.02–4.47)	0.044	2.34 (1.65–3.31)	<0.001
Forms of nitrates							
Without nitrate (reference)	734 (51)	1		1		1	
Oral	462 (32)	1.23 (0.76–2.00)	0.4	1.11 (0.61–2.02)	0.72	1.32 (0.91–1.92)	0.15
Skin patch	129 (9)	1.32 (0.64–2.74)	0.46	1.47 (0.60–3.62)	0.4	1.69 (1.17–2.45)	0.005
Combination	93 (7)	1.68 (0.78–3.61)	0.19	2.80 (1.24–6.35)	0.013	2.18 (1.52–3.11)	<0.001
Number of nitrates							
Without nitrate (reference)	734 (51)	1		1		1	
Single	517 (36)	1.26 (0.79–2.02)	0.33	1.15 (0.65–2.04)	0.63	1.22 (0.83–1.78)	0.316
Dual or more	177 (12)	1.60 (0.88–2.92)	0.13	2.30 (1.15–4.60)	0.019	2.70 (1.92–3.78)	<0.001

[a]Eleven patients with unknown type of nitrate were excluded from the analysis when appropriate.
[b]Adjusted for smoking, previous myocardial infarction, history of out-of-hospital cardiac arrest, ST elevation during angina attack, significant organic coronary stenosis, multivessel spasm, and β-blocker use. IPTW, inverse probability of treatment weighting.

single use of conventional nitrates or nicorandil in VSA patients. Although the precise mechanisms of the worse prognosis with nicorandil and nitrates remain to be elucidated, the use of multiple vasodilators may lead to the deleterious reactions, such as neurohormonal impairment including an increased sensitivity to vasoconstrictors[5] and sympathetic nerve activation.[4] In the future, a new

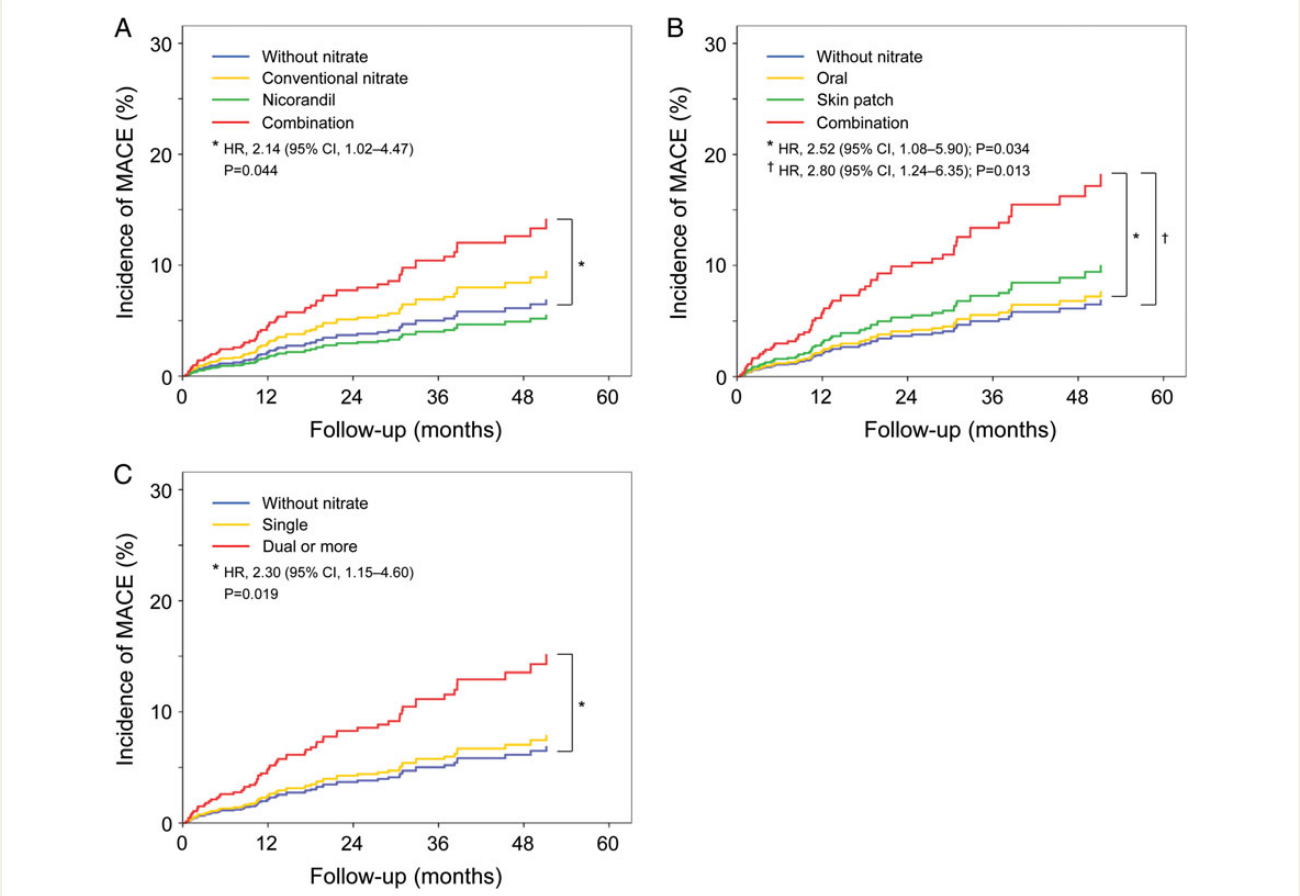

Figure 3 Cumulative incidence of major adverse cardiac event after adjusting for established prognostic factors according to types, forms, and number of nitrates. (*A*) Types of nitrates. (*B*) Forms of nitrates. (*C*) Number of nitrates. Prognostic factors include smoking, previous myocardial infarction, history of out-of-hospital cardiac arrest, ST elevation during angina attack, significant organic coronary stenosis, multivessel spasm, and β-blocker use. MACE, major adverse cardiac events; CI, confidence interval; HR, hazard ratio.

Table 4 Relationships between conventional nitrates and major adverse cardiac event depend on the presence or absence of concomitant use of nicorandil

	No. of patients (%)	Unadjusted		Adjusted[a]	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Cohort 1					
Without nitrate (reference)	734 (83)	1		1	
GTN	32 (4)	2.02 (0.72–5.69)	0.18	4.47 (1.47–13.6)	0.008
ISMN	65 (7)	1.10 (0.39–3.09)	0.86	1.28 (0.30–5.53)	0.74
ISDN	49 (6)	1.64 (0.58–4.61)	0.35	2.19 (0.65–7.43)	0.21
Cohort 2					
Without nitrate (reference)	734 (67)	1		1	
GTN	46 (4)	1.69 (0.60–4.76)	0.32	1.85 (0.65–5.26)	0.25
ISMN	198 (18)	1.33 (0.72–2.47)	0.37	1.34 (0.71–2.52)	0.36
ISDN	125 (11)	1.03 (0.46–2.32)	0.94	1.11 (0.49–2.50)	0.81

Cohort 1 includes the patients without nitrates and the patients with a combination therapy of a conventional nitrate and nicorandil.
Cohort 2 includes the patients without nitrates and the patients with a conventional nitrate alone.
GTN, nitroglycerin; ISMN, isosorbide mononitrate; ISDN, isosorbide dinitrate.
[a]Adjusted for smoking, previous myocardial infarction, history of out-of-hospital cardiac arrest, ST elevation during angina attack, significant organic coronary stenosis, multivessel spasm, and *β*-blocker use.

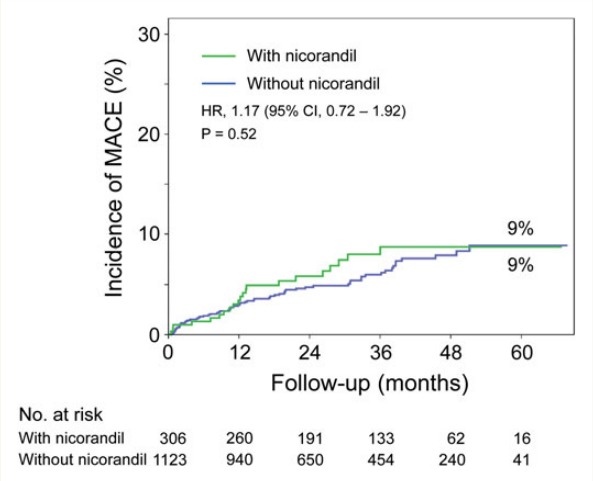

Figure 4 Cumulative incidence of major adverse cardiac event in vasospastic angina patients treated with nicorandil. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; VSA, vasospastic angina.

approach should be developed for patients with refractory coronary spasm to the present CCBs-based multi-agent regimen. Among them, fasudil, a Rho-kinase inhibitor, could be a promising drug for refractory VSA,[25] when its oral form becomes available.

Study limitations

Several limitations should be mentioned for the present study. First, the present study was conducted as an observational design. The management decisions were left to the discretion of each attending physician, and the prescription for nitrates was not randomized. Although we performed propensity score-matched analysis and multivariable Cox model to adjust for potential confounders, it still remains possible that the present analyses failed to correct for unmeasured variables that could have affected the present results. In addition, the present study was of retrospective and prospective designs, and the retrospective population accounted for the majority of the patients. These issues may prevent us from establishing the cause–result relationship between nitrates use and patient outcomes. Indeed, we were unable to clarify whether chronic use of nitrates itself causes adverse events in VSA patients or whether patients who take nitrates have increased disease activity of VSA with resultant occurrence of MACE. Thus, the prospective randomized study is needed regarding the adjuvant nitrates therapy for VSA patients refractory to CCBs. Second, the follow-up period varied in individual patients, and the composite primary endpoint was used. Third, the information about medical treatments was not sufficient. Since the present analysis was performed based on the prescriptions at the beginning of follow-up, the relationship between the compliance or changes in medications during the follow-up period and the patient outcomes was not evaluated. Furthermore, there was no information available regarding the dose of nitrates that could linked to the development of nitrate tolerance.[3,26] Fourth, in the present study, the information on efficacy of nitrates or CCBs in controlling angina and the extent of resultant improvement in symptoms (e.g. frequency of angina attack) after nitrates or CCBs was not available. Thus, we were unable to assess the relationship between short-term clinical efficacy of nitrates and the long-term prognosis of VSA patients. However, despite these limitations, the present findings should merit emphasis for better understanding of the medical treatment and prognosis of VSA patients.

Conclusions

The present multicentre study by the Japanese Coronary Spasm Association demonstrates the prognostic impact of chronic nitrate therapy in VSA patients. The present results indicated that chronic nitrate therapy did not improve the long-term prognosis of VSA patients when combined with CCBs. The chronic use of multiple nitrates could be rather correlated with a poor outcome, while nicorandil itself may be acceptable in the adjuvant setting. These findings may have an important implication for the management of VSA patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Munzel T, Daiber A, Gori T. More answers to the still unresolved question of nitrate tolerance. *Eur Heart J* 2013;**34**:2666–2673.
2. Daiber A, Wenzel P, Oelze M, Munzel T. New insights into bioactivation of organic nitrates, nitrate tolerance and cross-tolerance. *Clin Res Cardiol* 2008;**97**:12–20.
3. Thomas GR, DiFabio JM, Gori T, Parker JD. Once daily therapy with isosorbide-5-mononitrate causes endothelial dysfunction in humans: evidence of a free-radical-mediated mechanism. *J Am Coll Cardiol* 2007;**49**:1289–1295.
4. Gori T, Floras JS, Parker JD. Effects of nitroglycerin treatment on baroreflex sensitivity and short-term heart rate variability in humans. *J Am Coll Cardiol* 2002;**40**:2000–2005.
5. Heitzer T, Just H, Brockhoff C, Meinertz T, Olschewski M, Munzel T. Long-term nitroglycerin treatment is associated with supersensitivity to vasoconstrictors in men with stable coronary artery disease: prevention by concomitant treatment with captopril. *J Am Coll Cardiol* 1998;**31**:83–88.
6. Maseri A, Beltrame JF, Shimokawa H. Role of coronary vasoconstriction in ischemic heart disease and search for novel therapeutic targets. *Circ J* 2009;**73**:394–403.
7. JCS joint working group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008). *Circ J* 2010;**74**:1745–1762.
8. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, Nakamura S, Umemura T, Yoshida M. Usefulness of massive oral nicorandil in a patient with variant angina refractory to conventional treatment. *Intern Med* 2003;**42**:163–167.
9. Takagi Y, Yasuda S, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H. Clinical characteristics and long-term prognosis of vasospastic angina patients who survived out-of-hospital cardiac arrest: multicenter registry study of the Japanese coronary spasm association. *Circ Arrhythm Electrophysiol* 2011;**4**:295–302.
10. Takagi Y, Yasuda S, Takahashi J, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura SI, Ogawa H, Shimokawa H. Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications, and prognostic impact: multicentre

registry study of the Japanese coronary spasm association. *Eur Heart J* 2013;**34**: 258–267.
11. Takagi Y, Takahashi J, Yasuda S, Miyata S, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura SI, Ogawa H, Shimokawa H. Prognostic stratification of patients with vasospastic angina: a comprehensive clinical risk score developed by the Japanese coronary spasm association. *J Am Coll Cardiol* 2013;**62**:1144–1153.
12. Kawana A, Takahashi J, Takagi Y, Yasuda S, Sakata Y, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Kubo N, Momomura S, Ogawa H, Shimokawa H, Japanese Coronary Spasm A. Gender differences in the clinical characteristics and outcomes of patients with vasospastic angina – a report from the Japanese coronary spasm association. *Circ J* 2013;**77**:1267–1274.
13. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med* 2013;**32**:3388–3414.
14. Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. A variant form of angina pectoris: preliminary report. *Am J Med* 1959;**27**:375–388.
15. Guazzi M, Magrini F, Fiorentini C, Polese A. Clinical, electrocardiographic, and haemodynamic effects of long-term use of propranolol in prinzmetal's variant angina pectoris. *Br Heart J* 1971;**33**:889–894.
16. Antman E, Muller J, Goldberg S, MacAlpin R, Rubenfire M, Tabatznik B, Liang CS, Heupler F, Achuff S, Reichek N, Geltman E, Kerin NZ, Neff RK, Braunwald E. Nifedipine therapy for coronary-artery spasm. Experience in 127 patients. *N Engl J Med* 1980;**302**:1269–1273.
17. Rizzon P, Scrutinio D, Mangini SG, Lagioia R, de Toma L. Randomized placebo-controlled comparative study of nifedipine, verapamil and isosorbide dinitrate in the treatment of angina at rest. *Eur Heart J* 1986;**7**:67–76.
18. Kojima S, Matsui K, Sakamoto T, Ishihara M, Kimura K, Miyazaki S, Yamagishi M, Tei C, Hiraoka H, Sonoda M, Tsuchihashi K, Shimoyama N, Honda T, Ogata Y, Ogawa H. Long-term nitrate therapy after acute myocardial infarction does not improve or aggravate prognosis. *Circ J* 2007;**71**:301–307.
19. Nakamura Y, Moss AJ, Brown MW, Kinoshita M, Kawai C. Long-term nitrate use may be deleterious in ischemic heart disease: A study using the databases from two large-scale postinfarction studies. Multicenter myocardial ischemia research group. *Am Heart J* 1999;**138**:577–585.
20. Kosugi M, Nakagomi A, Shibui T, Kato K, Kusama Y, Atarashi H, Mizuno K. Effect of long-term nitrate treatment on cardiac events in patients with vasospastic angina. *Circ J* 2011;**75**:2196–2205.
21. Sueda S, Kohno H, Fukuda H, Watanabe K, Ochi N, Kawada H, Uraoka T. Limitations of medical therapy in patients with pure coronary spastic angina. *Chest* 2003;**123**: 380–386.
22. Ogawa T, Komukai K, Ogawa K, Kosuga T, Nagoshi T, Minai K, Sakamoto H, Hashimoto K, Yoshida S, Taniguchi I, Mochizuki S, Yoshimura M. High incidence of repeat anginal attacks despite treatment with calcium-channel blockers in patients with coronary spastic angina. *Circ J* 2009;**73**:512–515.
23. Horinaka S. Use of nicorandil in cardiovascular disease and its optimization. *Drugs* 2011;**71**:1105–1119.
24. O'Rourke ST. Katp channel activation mediates nicorandil-induced relaxation of nitrate-tolerant coronary arteries. *J Cardiovasc Pharmacol* 1996;**27**:831–837.
25. Inokuchi K, Ito A, Fukumoto Y, Matoba T, Shiose A, Nishida T, Masuda M, Morita S, Shimokawa H. Usefulness of fasudil, a rho-kinase inhibitor, to treat intractable severe coronary spasm after coronary artery bypass surgery. *J Cardiovasc Pharmacol* 2004; **44**:275–277.
26. Uxa A, Thomas GR, Gori T, Parker JD. Standard versus low-dose transdermal nitroglycerin: differential effects on the development of tolerance and abnormalities of endothelial function. *J Cardiovasc Pharmacol* 2010;**56**:354–359.