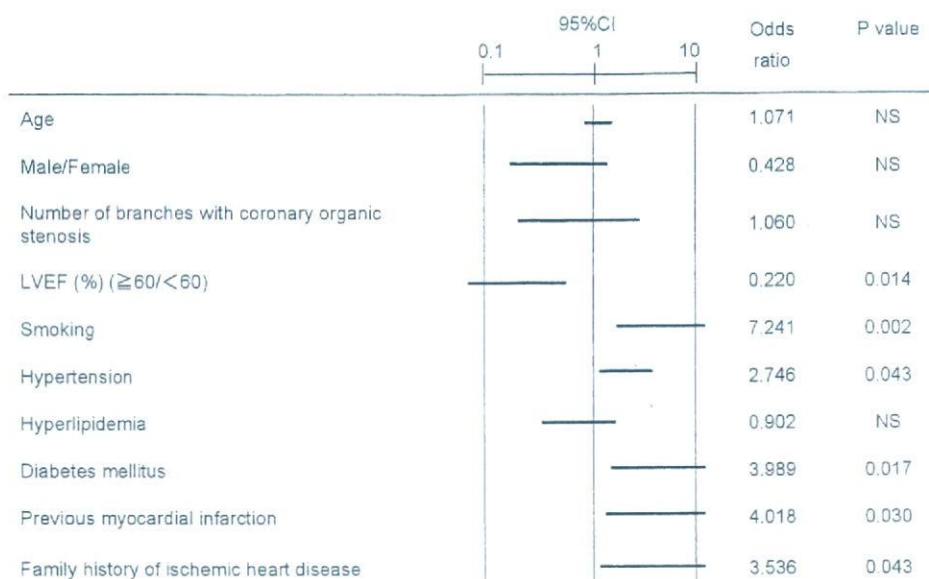


FIGURE 1. Prognostic effects of clinical characteristics in patients with vasospastic angina. Multivariate analysis demonstrated that left ventricular ejection fraction (LVEF), smoking, hypertension, and diabetes mellitus were the significant prognostic factors.



prognosis was better in patients treated with benidipine than in those with amlodipine or diltiazem. The follow-up period was longer in the diltiazem group as compared with the benidipine/amlodipine groups because diltiazem was launched before 1990 in Japan and some new VSA patients were already treated with diltiazem at the entry in 1990.

DISCUSSION

Calcium channel blockers are effective in patients with VSA and many drugs of this category have been launched and used in daily practice. Since some of the calcium channel blockers exert pleiotropic pharmacological effects other than simple vasodilation by inhibition of L-type calcium channels, it is highly possible that the cardiovascular effects of calcium channel blockers may substantially differ among them.⁴ However, few reports are available on what calcium channel blockers are more effective for the treatment of VSA. Thus, in the present study, we aimed to analyze the prognostic impact of the 3 calcium channel blockers (benidipine, diltiazem, and amlodipine) to clarify the difference in their prognostic effects

in our cohort study. We found that the prognostic effects of calcium channel blockers indeed varied and that benidipine was associated with a better prognosis as compared with other 2 drugs.

Difference Prognostic Effects of Calcium Channel Blockers

The present study demonstrated that benidipine improved the prognosis of VSA patients more effectively than diltiazem or amlodipine. Sakata et al⁸ reported that benidipine significantly prevented cardiovascular events compared with diltiazem in a small patient population. Ito et al⁹ also reported that the outcome of medical therapy in VSA patients was better in patients treated with benidipine than in those with other calcium channel blockers. Taken together, benidipine may be associated with a better prognosis of VSA patients as compared with diltiazem and amlodipine.

Benidipine may improve the prognosis of VSA patients through multiple mechanisms of action. First, benidipine exerts anti-atherosclerotic effects. Indeed, benidipine is more effective than other calcium channel blockers in terms of antioxidant

TABLE 2. Influence of Medical Treatment on the Incidence of Cardiovascular Events in Patients With Vasospastic Angina

Event	Benidipine (n = 148)		Diltiazem (n = 313)		Amlodipine (n = 111)		P Value
	n	(%)	n	(%)	n	(%)	
Cardiac deaths	0	(0)	9	(2.9)	1	(0.9)	0.067
Deaths from MI	1	(0.7)	2	(0.6)	1	(0.9)	>0.2
Deaths from stroke	1	(0.7)	4	(1.3)	1	(0.9)	>0.2
MI	3	(2.0)	11	(3.5)	4	(3.6)	>0.2
Heart failure	7	(4.7)	24	(7.7)	7	(6.3)	>0.2
Cerebral infarction	2	(1.4)	14	(4.5)	2	(1.8)	>0.133
Cerebral hemorrhage	2	(1.4)	3	(1.0)	1	(0.9)	>0.2
Aortic aneurysm	2	(1.4)	4	(1.3)	2	(1.8)	>0.2

Drug	Events	95%CI			Odds ratio	P value
		0.1	1	10		
Benidipine	total events	[0.1, 1, 10]			0.656	NS
	cardiovascular events	[0.1, 1, 10]			0.323	NS
	cerebral infarction	[0.1, 1, 10]			0.287	NS
	vascular infarction events	[0.1, 1, 10]			0.303	0.015
Diltiazem	total events	[0.1, 1, 10]			1.879	0.039
	cardiovascular events	[0.1, 1, 10]			1.651	NS
	cerebral infarction	[0.1, 1, 10]			5.777	0.022
	vascular infarction events	[0.1, 1, 10]			2.358	0.017
Amlodipine	total events	[0.1, 1, 10]			0.837	NS
	cardiovascular events	[0.1, 1, 10]			0.646	NS
	cerebral infarction	[0.1, 1, 10]			0.649	NS
	vascular infarction events	[0.1, 1, 10]			0.670	NS

FIGURE 2. Prognostic effects of calcium channel blockers in patients with vasospastic angina. Benidipine showed beneficial prognostic effects in general, whereas diltiazem showed worse prognostic effects. The effects of amlodipine were neutral.

Cardiovascular events: cardiovascular death and non-fatal myocardial infarction
Vascular infarction events: cardiovascular events and incidence of cerebral infarction.

effects¹⁰ and anti-inflammatory effects.¹¹ The antiarteriosclerotic effect of benidipine has also been reported in a clinical study with hypertensive patients.¹² Second, benidipine is known to ameliorate endothelial function.¹³ Endothelial dysfunction with reduced nitric oxide (NO) production causes reduced endothelial vasodilator function and enhanced vascular smooth muscle contraction.^{1,14,15} Benidipine enhances NO production in animal models of vascular remodeling^{16,17} as well as in patients with VSA.¹⁸ Third, benidipine may have greater coronary vasodilator effects than other calcium channel blockers. Indeed, it has been shown that benidipine acts more selectively on the coronary artery than other calcium channel blockers,^{19,20} has a potent antispastic effects,²¹ and is useful to treat patients with VSA resistant to diltiazem.¹⁸ These multiple effects may be involved in the beneficial prognostic effects of benidipine observed in the present study.

By contrast, the present study unexpectedly showed the unfavorable prognostic effects of diltiazem, particularly in terms of cerebrovascular events. Although the exact mechanism(s) for this observation is unclear, it is probably due, at least in part, to the facts that diltiazem causes less NO-mediated coronary dilation compared with dihydropyridine calcium channel blockers²² and that diltiazem does not exert any antioxidant effects.¹⁰

Incidence of Vascular Infarction Events

In the present study, vascular infarction events, defined as the combined risk of cardiovascular death, myocardial infarction, and cerebral infarction, was added to the endpoint. Cerebral infarction and myocardial infarction are caused by atherothrombotic occlusion of the cerebral and coronary artery, respectively. Thus, this combined endpoint can be regarded as

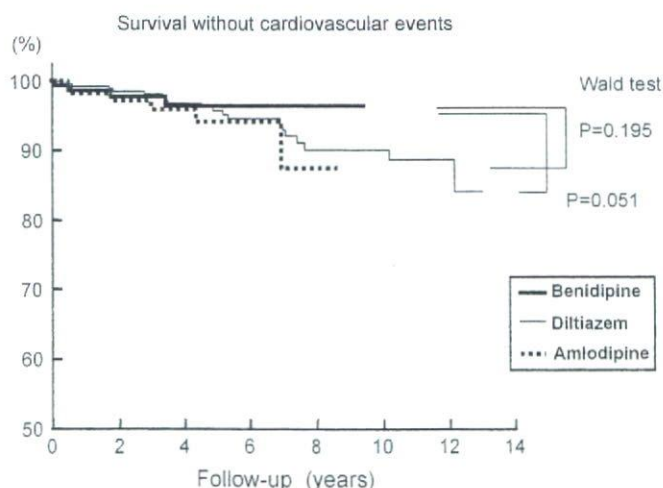


FIGURE 3. Effects of calcium channel blockers on survival without cardiovascular events in patients with vasospastic angina. Among the 3 calcium channel blockers, benidipine tended to be associated with a better prognosis of survival without cardiovascular events than diltiazem or amlodipine.

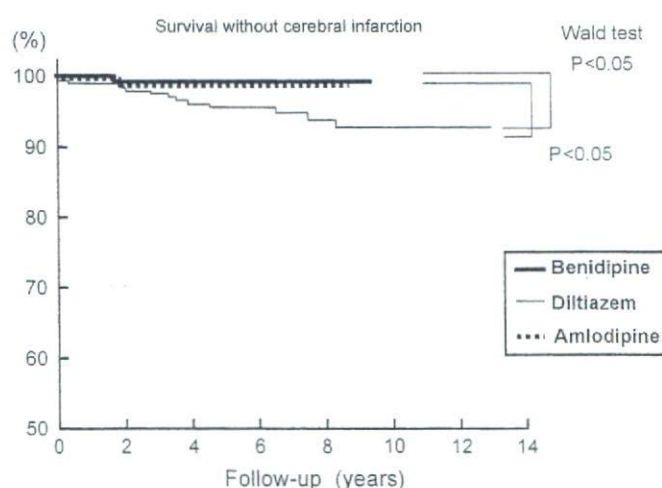


FIGURE 4. Effects of calcium channel blockers on survival without cerebral infarction in patients with vasospastic angina. Among the 3 calcium channel blockers, benidipine and amlodipine were associated with a significantly better prognosis of survival without cerebral infarction than diltiazem.

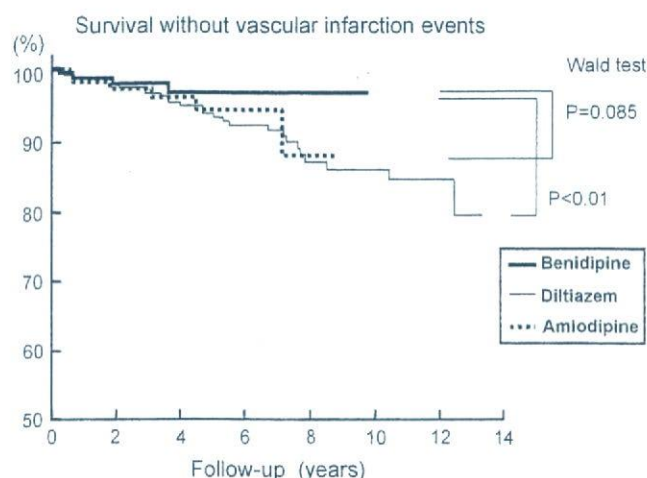


FIGURE 5. Effects of calcium channel blockers on survival without vascular infarction events in patients with vasospastic angina. Among the 3 calcium channel blockers, benidipine was associated with a significantly better prognosis of vascular infarction events than diltiazem or amlodipine.

an indicator of atherosclerosis and indeed it has been used in the large-scale clinical studies.^{23,24} In Japan, the incidence of atherosclerotic vascular disease, such as myocardial infarction and cerebral infarction, is now increasing due to the westernization of lifestyle (eg, diet) and the aging of the population, accounting for one-third of all-cause death in Japan.²⁵ Thus, it is important to note that in the present study, benidipine significantly reduced the incidence of vascular infarction events as compared with other calcium channel blockers.

Limitations of the Study

Several limitations should be mentioned for the present study. First, the present study was a retrospective and observational study. Thus, a prospective and randomized study is needed to confirm the present results, although placebo-controlled study is not feasible in VSA patients from ethical point of view. In addition, since the present study was based on the data obtained from more than 500 VSA patients, we believe that the present results should provide important information for the treatment of VSA. Second, in the present study, we only examined the prognostic effects of 3 calcium channel blockers and the effects of other calcium channel blockers remain to be examined. Third, the present study reports a single center experience. Thus, multi-center study is needed to confirm the present results. We have recently established the Coronary Spasm Association in Japan, in which 56 cardiovascular institutes have participated nationwide. It is expected that the present results will be reevaluated in a large number of VSA patients registered through those participating institutes in the future.

In conclusion, the present study suggests that benidipine has beneficial prognostic effects in patients with VSA as compared with diltiazem and amlodipine.

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