Hyperuricemia							
No	*14.4% (121/839)*	*0.0661*	*75*	*8*	*23*	*12*	*3*
Yes	*24.4% (11/45)*		*2*	*3*	*3*	*3*	*0*
Renal disease							
No	*14.0% (115/824)*	*0.0026*	*66*	*8*	*24*	*14*	*3*
Yes	*28.3% (17/60)*		*11*	*3*	*2*	*1*	*0*
Liver disease							
No	*15.1% (131/869)*	*0.3650*	*76*	*11*	*26*	*15*	*3*
Yes	*6.7% (1/15)*		*1*	*0*	*0*	*0*	*0*
Acute heart failure on admission							
No/Yes							
No	*9.2% (57/620)*	*0.0000*	*18*	*7*	*20*	*11*	*1*
Yes	*28.4% (74/261)*		*59*	*4*	*5*	*4*	*2*
Killip class							
1	*8.9% (41/463)*	*<0.0001*	*15*	*3*	*15*	*7*	*1*
2	*16.5% (15/91)*		*11*	*0*	*2*	*2*	*0*
3	*37.1% (13/35)*		*9*	*1*	*3*	*0*	*0*
4	*57.7% (41/71)*		*37*	*3*	*0*	*0*	*1*
Forrester class							
1	*9.0% (23/255)*	*<0.0001*	*9*	*2*	*8*	*4*	*0*
2	*19.3% (17/88)*		*11*	*1*	*1*	*3*	*1*
3	*18.9% (10/53)*		*6*	*1*	*3*	*0*	*0*
4	*43.3% (26/60)*		*22*	*1*	*2*	*0*	*1*
ECG abnormality on admission							
ST change							
No	*6.3% (2/32)*	*0.1290*	*0*	*1*	*0*	*1*	*0*
Elevation	*14.0% (103/736)*		*60*	*8*	*21*	*11*	*3*
Depression	*19.8% (19/96)*		*11*	*2*	*4*	*2*	*0*
CLBBB							
No	*14.5% (124/856)*	*0.0396*	*72*	*8*	*26*	*15*	*3*
Yes	*28.6% (8/28)*		*5*	*3*	*0*	*0*	*0*
Abnormal Q wave							
No	*14.0% (80/571)*	*0.2900*	*42*	*8*	*19*	*9*	*2*
Yes	*16.7% (52/312)*		*35*	*3*	*7*	*6*	*1*
CK, CK-MB							
CK max							
<3,000	*13.6% (74/544)*	*0.2792*	*32*	*9*	*21*	*11*	*1*
≥3,000	*16.3% (54/332)*		*42*	*2*	*5*	*4*	*1*
CK-MB max							
<250	*12.6% (57/452)*	*0.4479*	*22*	*9*	*19*	*5*	*2*
≥250	*14.5% (45/310)*		*36*	*0*	*3*	*6*	*0*

PIA, post infarction angina; CLBBB, complete left bundle branch block; CK, creatine kinase. Other abbreviations as in Tables 2,3,6,8.

the first month and in 78 patients (9.0%) during the initial 6 months. During hospitalization, 37 UA patients (4.0%) experienced severe hemorrhagic events. Both cardiac events and severe hemorrhagic events were less frequent in the UA patients than in the AMI patients (Tables 6,7).

Events Stratified by Clinical Profile and Treatment

Table 8 shows the 6-month incidence of cardiac events stratified by baseline characteristics of the UA patients. The incidence of cardiac events was significantly higher in patients with renal disease than in those without renal disease. Cardiac events were more frequent in women, patients with a history of myocardial infarction (MI), and patients with diabetes. The incidence of cardiac events was significantly higher in patients with ST segment changes on admission than in those without such changes. It was also higher, but not significantly so, in patients with T-wave inversion than in those without T-wave inversion. The incidence of cardiac events tended to increase with the severity of Braunwald classification.

Table 9 shows the 6-month incidence of cardiac events in UA patients stratified by treatment. With regard to antianginal therapy, the incidence of cardiac events was significantly lower in those treated with an oral calcium-channel blocker than in those not so treated. The incidence of cardiac events was also significantly lower in those undergoing coronary angiography after arrival at hospital than in those not undergoing it. Neither use of heparin nor revascularization was significantly associated with the incidence of cardiac events. Cardiac events did not occur in any of the patients without significant stenosis on initial coronary angiography. The outcome was worse in patients with significant stenosis persisting after revascularization than in those without.

Because oral calcium-channel blockers are suggested to reduce the risk of cardiac events in UA patients, the effects of the most commonly used drugs of this class (eg, diltiazem, amlodipine, and nifedipine) were evaluated. The incidence of cardiac events was lower in patients taking amlodipine than in those not taking it (Table 10).

The relationship of the timing of treatment with calcium-channel blockers to the risk of cardiac events was evaluated and the incidence of cardiac events was lower in patients who started treatment with a calcium blocker after admission than in those who were continuously treated before the onset of UA, although the difference was not significant (Table 11).

Tables 12 and 13 summarize the 6-month incidence of cardiac events in AMI patients stratified by clinical profile and by treatment, respectively. Clinical factors that were associated with a significantly higher incidence of cardiac events were female sex, age ≥65 years, a history of angina

Table 13 Stratified Analysis of Cardiac Events According to Treatment of AMI

	Cardiac events during initial 6 months (incidence)	χ^2 test p value	Details of events (cases)				
			Death	MI	PIA	u-PCI	u-CABG
Heparin							
No	20.1% (32/159)	0.0432	24	1	2	4	1
Yes	13.8% (100/724)		53	10	24	11	2
Max daily dosage (units)							
<12,000	15.7% (51/325)	0.1857	29	5	13	3	1
≥12,000	12.3% (49/399)		24	5	11	8	1
Duration of infusion (days)							
<5	11.1% (60/539)	0.0001	28	8	14	9	1
≥5	22.7% (40/176)		25	2	10	2	1
Antiplatelet							
No	62.5% (20/32)	<0.0001	17	0	0	2	1
Yes	13.1% (112/852)		60	11	26	13	2
Aspirin							
No	43.5% (27/62)	<0.0001	21	0	0	5	1
Yes	12.8% (105/822)		56	11	26	10	2
Ticlopidine							
No	21.1% (68/322)	<0.0001	45	4	8	10	1
Yes	11.4% (64/562)		32	7	18	5	2
Coronary angiography							
No	37.5% (6/16)	0.0106	4	0	1	1	0
Yes	14.5% (126/868)		73	11	25	14	3
Vessel (s) with significant stenosis							
0	40.0% (4/10)		1	2	1	0	0
1	7.9% (36/453)		16	4	10	6	0
2	13.3% (32/240)	<0.0001	15	2	7	7	1
3	32.0% (49/153)		38	3	5	1	2
LMT	36.4% (4/11)		3	0	1	0	0
Reperfusion therapy							
No	25.0% (18/72)	0.0124	9	2	6	1	0
Yes	14.0% (114/812)		68	9	20	14	3
Time from admission (h)							
<6	13.5% (91/675)	0.4474	57	9	13	9	3
≥6	16.1% (19/118)		8	0	6	5	0
<12	13.9% (98/705)	0.9461	60	9	15	11	3
≥12	13.6% (12/88)		5	0	4	3	0
PTCA							
No	20.9% (18/86)	0.0517	11	1	2	3	1
Yes	13.2% (96/726)		57	8	18	11	2
Stent							
No	13.7% (39/284)	0.8535	23	3	6	6	1
Yes	14.2% (75/528)		45	6	14	8	2
ICT							
No	14.7% (109/743)	0.0895	66	9	18	14	2
Yes	7.2% (5/69)		2	0	2	0	1
IVCT							
No	13.3% (100/752)	0.0313	61	9	15	12	3
Yes	23.3% (14/60)		7	0	5	2	0
CABG							
No	13.0% (101/778)	<0.0001	56	9	20	14	2
Yes	38.2% (13/34)		12	0	0	0	1
Stenosis (%) of culprit vessel before reperfusion therapy							
0	0.0% (0/0)		0	0	0	0	0
25	20.0% (1/5)		0	1	0	0	0
50	100.0% (2/2)		1	1	0	0	0
75	8.3% (1/12)	0.0012	0	0	0	1	0
90	20.4% (21/103)		9	1	6	5	0
99	9.4% (20/212)		12	3	5	0	0
100	14.2% (67/472)		44	5	8	7	3
Stenosis (%) of culprit vessel after reperfusion therapy							
0	11.5% (40/348)		21	4	7	8	0
25	12.9% (38/294)		20	3	10	3	2
50	19.0% (15/79)		9	1	3	2	0
75	7.1% (1/14)	0.3249	1	0	0	0	0
90	0.0% (0/5)		0	0	0	0	0
99	10.0% (1/10)		1	0	0	0	0
100	26.7% (4/15)		2	1	0	1	0
TIMI flow grade past the culprit lesion before reperfusion therapy							
0	13.6% (62/455)		40	5	7	7	3
1	7.2% (6/83)	0.0307	4	0	2	0	0
2	11.5% (15/130)		9	3	3	0	0
3	20.8% (27/130)		11	3	7	6	0

TIMI flow grade past the culprit lesion after reperfusion therapy							
0	*15.0% (3/20)*		*1*	*1*	*0*	*1*	*0*
1	*15.4% (2/13)*	*0.8950*	*2*	*0*	*0*	*0*	*0*
2	*9.3% (4/43)*		*3*	*0*	*1*	*0*	*0*
3	*12.0% (80/664)*		*46*	*8*	*13*	*11*	*2*

Abbreviations as in Tables 2,8,12.

pectoris, a history of MI, hypertension, renal disease, detection of acute heart failure on admission, and complete left bundle branch block on ECG.

The treatments associated with a significantly lower incidence of cardiac events were heparin, oral antiplatelet drugs (aspirin or ticlopidine), coronary angiography, and reperfusion therapy. Cardiac events even occurred in some AMI patients without significant stenosis on initial coronary angiography.

Discussion

Our questionnaire survey revealed that fewer patients are hospitalized with UA than with AMI in Japan. Among several overseas studies that simultaneously investigated the number of UA and AMI patients, a Spanish study of inpatients reported similar results, with an approximate ratio of 1:2 for UA patients vs AMI patients[8] Of 2 investigations of patients admitted to the ICU or CCU, 1 showed that the number of AMI patients was more than twice that of UA patients[9] and the other revealed that UA patients outnumbered AMI patients by a ratio of 1.5 to 1[10] The ratio of UA vs AMI patients obtained in the present study, which involved inpatients only, might be different if those treated as outpatients had been included. Because the largest percentage of UA patients in the case report investigation had Braunwald class III disease, those with Braunwald class I or II disease may have been treated on an outpatient basis. This finding should be taken into consideration when developing the recommendations for treatment of UA because inpatient care is standard management for suspected UA.

The results of both the questionnaire survey and the case report investigation indicate that non-ST-elevation AMI accounts for 15–20% of all AMI, a finding that is also consistent with overseas data[11] The present study showed that both ST-elevation and non-ST-elevation AMI are managed in Japan according to the principle of early invasive therapy as first-line treatment. Although the ACC/AHA and Japanese guidelines for the management of ACS recommend different treatment pathways for ST-elevation and non-ST-elevation AMI, it seems acceptable in practice to make no distinction between the 2 types of AMI in Japan. Compared with the USA and Europe, in Japan a larger proportion of institutions are capable of providing coronary intervention relative to the number of patients with ischemic heart disease.

The present study also showed a trend toward early invasive treatment of UA, especially those cases of Braunwald class III disease (median time from admission to conduct the invasive treatment of Braunwald classes I, II and III was 144, 79 and 34 h, respectively). However, UA patients received invasive treatment later than AMI patients and were usually given drug treatment immediately after arrival at hospital. Because the present study investigated the medical management of UA in 2000, these patients may now receive invasive treatment earlier because of subsequent improvements in the devices for coronary intervention and the skills of the interventionists. However, a GUSTO-IV substudy recently demonstrated that patients with non-ST-elevation ACS showing low levels of biomarkers have a very low 1-year mortality with medical management, and early invasive procedures appear to increase their overall risk of mortality[12] That study may be a warning against early invasive management in UA patients.

According to the present case report data, approximately 70% of patients received continuous infusion of heparin immediately after admission, which indicates that heparin is regarded as essential if medical treatment is used to stabilize the patient in the early hospital phase.

In UA patients, the incidence of cardiac events was 2% at 1 month and 9% at 6 months, which is lower than in AMI patients for both time intervals. Previous overseas studies of patients with non-ST-elevation ACS have revealed a higher incidence of cardiac events[13,14] suggesting that the prognosis of UA may be better in Japanese patients. Although many of the patients were treated with antithrombotic drugs, such as heparin, aspirin, and ticlopidine, only 4% of them experienced major bleeding events during hospitalization and none of them developed intracranial hemorrhage, which suggests that the use of antithrombotic drugs was appropriate, with adequate precautions taken to prevent bleeding complications.

The results of the stratified analyses of the 6-month outcomes in UA patients should be interpreted carefully because of the nonrandomized, retrospective design of this study. For example, our analysis in UA patients failed to detect any significant difference in the incidence of cardiac events between patients undergoing or not undergoing PCI and between those with or without heparin infusion. Patients who undergo PCI or who receive heparin usually have more severe disease than those not receiving these treatments and this difference in severity may have masked the beneficial effect of such treatments on the outcome.

On the other hand, the incidence of cardiac events in patients using any calcium-channel blocker was significantly lower than those in patients who had not received calcium-channel blocker and these 2 subgroups had similar clinical profiles (data not shown). This suggests that calcium-channel blocker therapy may be an independent determinant of the prognosis of UA. Because it has long been known that coronary vasospasm plays a greater role in the etiology of ischemic heart disease in Japanese than in Caucasians, the reduction of cardiac events observed in patients treated with calcium-channel blockers may reflect the ability of drugs in this class to suppress coronary vasospasm[15] However, a randomized clinical trial should be carried out to confirm the efficacy of calcium blockers in the treatment of ACS in Japanese patients.

There was no significant difference in the stratified analysis of cardiac events by infarct location (Table 12). Concerning the relationship between infarct location and long-term prognosis, there is not consensus. Kandzari et al reported that the long-term prognosis of anterior infarction was worse than for other infarction sites[16] whereas Karlson et al

reported that there was no significant difference in long-term prognosis by infarct location![7]

As shown in Table 13, there was no apparent difference in the incidence of cardiac events between patients obtaining Thrombolysis In Myocardial Infarction (TIMI) 3 flow after reperfusion therapy and patients who did not. It is well known that TIMI 0 to TIMI 2 flow is an independent predictor of prognosis[18,19] and the reason why our result was different from previous reports is unclear.

With the cooperation of many cardiovascular specialists, the present nationwide investigation has provided the first insight into the actual management of ACS (including UA) in Japan. It is of great importance to develop appropriate treatments for Japanese patients based on the specific characteristics of this population.

Therefore, more studies in patients with ACS and AMI should be performed in the future. In particular, it would be valuable to collect information about medical treatment with nicorandil, ACE inhibitors, ARBs and statins, and invasive treatments (drug-eluting stents, distal protection devices, thrombectomy, etc).

Acknowledgment

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Nifedipine retard prevents hospitalization for angina pectoris better than angiotensin-converting enzyme inhibitors in hypertensive Japanese patients with previous myocardial infarction (JMIC-B substudy)

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Objectives and background We previously reported that nifedipine retard showed comparable efficacy to angiotensin-converting enzyme (ACE) inhibitors for the prevention of cardiac events in hypertensive patients with coronary artery disease during the Japan Multicenter Investigation for Cardiovascular Diseases B study. In the nifedipine group, patients with a history of myocardial infarction (MI) showed a significant reduction in hospitalization for angina pectoris compared with the ACE inhibitor group. We investigated whether this difference was related to the progression of coronary arteriosclerosis.

Methods To evaluate coronary arteriosclerosis, we performed coronary angiography (CAG) and a quantitative analysis of coronary angiograms.

Results The cumulative incidence of hospitalization for angina was significantly lower in the nifedipine group (log-rank test $P = 0.013$). The etiology of angina requiring hospitalization was determined on the basis of CAG findings. Its incidence secondary to the development of new lesions or the progression of existing lesions was significantly lower in the nifedipine group than in the ACE inhibitor group (log-rank test $P = 0.042$ and $P = 0.028$, respectively). Using quantitative coronary analysis, changes in the coronary artery luminal diameter were compared between the nifedipine and ACE inhibitor groups. The minimum coronary lumen diameter did not show a significant change in the nifedipine group, whereas it decreased significantly in the ACE inhibitor group (paired *t*-test $P = 0.002$), and there was a significant difference between the two groups by analysis of covariance ($P = 0.047$).

Conclusion These results indicate that nifedipine more effectively prevented admission for angina pectoris by inhibiting the progression of coronary artery disease in patients with a history of MI. *J Hypertens* 25:2019–2026

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Keywords: angina pectoris, angiotensin-converting enzyme inhibitor, coronary angiography, myocardial infarction, nifedipine retard

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Introduction

According to Western and Japanese epidemiological data, the incidence of cardiac events is clearly higher in patients with a history of myocardial infarction (MI) than in those without [1–3].

Several large-scale clinical studies [4–6] have shown that angiotensin-converting enzyme (ACE) inhibitors are useful for improving the long-term prognosis of patients after MI, whereas calcium antagonists have no such beneficial effect [7–9]. Those studies were, however, conducted using short-acting calcium antagonists, so it remains unclear whether the results are also applicable to long-acting calcium antagonists.

It has been reported that vasospasm is closely related to the occurrence of MI in Japanese patients [10]. Therefore, long-acting calcium antagonists with a strong antispastic effect [11] and a mild antihypertensive effect may possibly be an appropriate treatment for patients after MI.

In the Japan Multicenter Investigation for Cardiovascular Diseases B (JMIC-B) study, we found that nifedipine had

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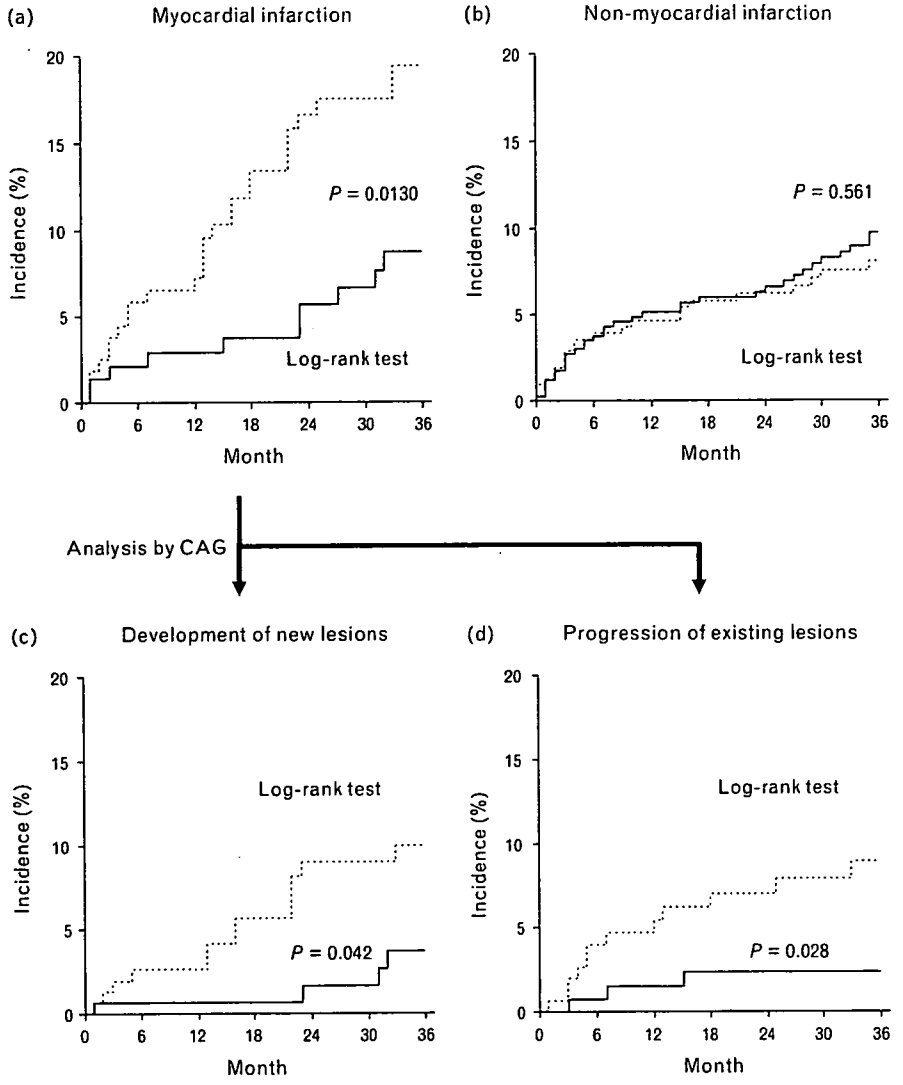
Fig. 1



Kaplan–Meier analysis of the incidence of angina pectoris requiring hospitalization in patients with or without a history of myocardial infarction. (a) and (b) The incidence of angina pectoris requiring hospitalization in patients with a history of myocardial infarction was significantly lower for the nifedipine group than for the angiotensin-converting enzyme (ACE) inhibitor group. (c) The incidences of angina pectoris requiring hospitalization as a result of the development of new lesions and (d) angina pectoris requiring hospitalization as a result of the progression of existing lesions were both significantly lower in the nifedipine group than in the ACE inhibitor group. CAG, Coronary angiography. (a, c and d) —— Nifedipine ($n = 148$); ------ ACE inhibitors ($n = 170$); (b) —— Nifedipine ($n = 418$); ------ ACE inhibitors ($n = 337$).

coronary intervention, the angiograms obtained immediately before percutaneous coronary intervention were used for evaluation.

The chi-squared test was employed to compare baseline clinical characteristics (Table 1) and concomitant drugs (Table 2). The unpaired *t*-test was used for the comparison of blood pressure and heart rate findings over time with the baseline data (Table 3). During the evaluation of QCA data, the paired *t*-test was used for comparison between the baseline and follow-up minimum lumen diameter (MLD; percentage diameter stenosis; %DS) in each treatment group (Table 5). Changes in the MLD and percentage stenosis (%DS) in the individual patients were compared between groups (Table 6) by analysis of covariance (ANCOVA). As covariates, baseline MLD, hyperlipidemia, smoker, concomitant use of α-blockers, achieved SBP, and achieved DBP were employed. Data are expressed as the mean ± standard deviation (SD). All statistical analyses were performed using SAS software (version 6.14; SAS Institute Inc., Cary, North Carolina, USA).

Table 4 Patients with primary or secondary endpoints in the previous myocardial infarction subgroup

	Nifedipine *n* (%)	ACE inhibitors *n* (%)	Relative risk (95% CI)	*P* value
Number	315	381		
All cardiac events	52 (16.5)	66 (17.3)	0.92 (0.63–1.33)	0.64
Cardiac death and sudden death	2 (0.63)	3 (0.79)	1.28 (0.17–9.98)	0.81
Myocardial infarction	9 (2.86)	10 (2.62)	1.15 (0.46–2.87)	0.76
Angina pectoris requiring hospitalization	13 (4.13)	34 (8.92)	0.42 (0.22–0.80)	0.01
Heart failure requiring hospitalization	5 (1.59)	6 (1.57)	0.58 (0.16–2.04)	0.39
Serious arrhythmia	2 (0.63)	2 (0.52)	0.43 (0.05–4.00)	0.46
Coronary intervention	35 (11.11)	49 (12.86)	0.82 (0.53–1.28)	0.39
Cerebrovascular accidents	9 (2.86)	8 (2.10)	1.52 (0.56–4.11)	0.41
Worsening of renal dysfunction	3 (0.95)	1 (0.26)	2.35 (0.22–24.6)	0.48
Total mortality	6 (1.90)	7 (1.84)	1.05 (0.32–3.53)	0.93

ACE, Angiotensin-converting enzyme; CI, confidence interval. The relative risk and *P* values were determined by using the Cox proportional hazard model with adjustment for history of hyperlipidemia, smoker, concomitant use of α-blocker, and achieved blood pressure. Coronary intervention: percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stenting.

In the MI group, the achieved blood pressure was $134 \pm 13/76 \pm 8$ mmHg in the nifedipine group and $136 \pm 16/78 \pm 8$ mmHg in the ACE inhibitor group. SBP tended to be lower in the nifedipine group than in the ACE inhibitor group ($P = 0.086$), whereas DBP was significantly lower in the former group ($P = 0.003$). Among non-MI patients, the achieved blood pressure was $138 \pm 14/77 \pm 8$ mmHg in the nifedipine group and $140 \pm 15/79 \pm 9$ mmHg in the ACE inhibitor group. Both SBP and DBP were significantly lower in the nifedipine group than in the ACE inhibitor group (unpaired *t*-test $P < 0.01$). No significant changes in heart rate were seen throughout treatment with any drug in the patients with or without MI.

Endpoints and previous myocardial infarction

Among the MI patients, comparison between the two treatment groups showed differences in the incidence of hyperlipidemia, smoker, concomitant use of α-blocker, achieved SBP, and achieved DBP. These parameters were therefore entered into the Cox proportional hazard model. Table 4 shows a comparison of the incidence of each event between treatment groups for the MI patients. The incidence of angina pectoris requiring hospitalization was significantly lower in the nifedipine group than in the ACE inhibitor group. Among the non-MI patients, there were no differences in the same endpoints between the two treatment groups.

Cumulative incidence of angina pectoris requiring hospitalization in relation to coronary angiography findings

The cumulative incidence of angina pectoris requiring hospitalization determined by the Kaplan–Meier method (Fig. 1a) was significantly lower in the nifedipine group (log-rank test $P = 0.013$).

Among the non-MI patients, there was no difference in the incidence of angina pectoris requiring hospitalization between the two treatment groups (Fig. 1b).

When the aetiology of angina pectoris requiring hospitalization in the patients with previous MI was determined on the basis of CAG findings, the incidence of angina pectoris requiring hospitalization as a result of new lesions and that caused by the progression of existing lesions were both significantly lower in the nifedipine group than in the ACE inhibitor group (log-rank test $P = 0.042$ and $P = 0.028$, respectively; Fig. 1c,d).

Quantitative coronary analysis study

Eighty-seven patients with MI (nifedipine group 38, ACE inhibitor group 49) were subjected to QCA analysis. Table 5 shows the changes in coronary artery diameter (ΔMLD and Δ%DS) after treatment in these patients. There were no significant changes in MLD in any segment in the nifedipine group ($P = 0.810$), whereas a

Table 5 Changes in mean minimum lumen diameter and percentage diameter stenosis in myocardial infarction

Segments	Group	Baseline	Follow-up	Change	*P* value
All segments					
MLD mm, mean (SD)	Nifedipine ($n = 38$)	2.13 (0.49)	2.14 (0.44)	0.01 (0.28)	0.810
	ACE inhibitors ($n = 49$)	2.24 (0.47)	2.12 (0.43)	−0.11 (0.24)	0.002
DS (%) mean (SD)	Nifedipine ($n = 38$)	19.34 (5.59)	16.17 (4.46)	−3.17 (4.75)	0.001
	ACE inhibitors ($n = 49$)	16.76 (5.07)	17.62 (7.22)	0.86 (5.40)	0.270
Coronary lesion segments (%DS ≥ 21)					
MLD mm, mean (SD)	Nifedipine ($n = 38$)	1.63 (0.44)	1.76 (0.54)	0.12 (0.28)	0.011
	ACE inhibitors ($n = 44$)	1.68 (0.42)	1.69 (0.60)	0.00 (0.39)	0.953
DS (%) mean (SD)	Nifedipine ($n = 38$)	31.79 (5.38)	23.78 (10.34)	−8.01 (11.06)	0.001
	ACE inhibitors ($n = 44$)	31.70 (6.71)	27.83 (16.05)	−3.87 (15.79)	0.115

ACE, Angiotensin-converting enzyme; DS, diameter stenosis; MLD, minimum lumen diameter. *P* value (paired *t*-test). Changes: (ΔMLD and Δ%DS).

to the occurrence of coronary artery disease in Japanese patients. A joint Japanese/Italian study of patients immediately after acute MI [10] showed that the provocation of coronary vasospasm by acetylcholine was three times more frequent in Japanese patients than in Caucasian patients. Ozaki *et al.* [17] demonstrated by QCA that the progression of coronary stenosis occurs at sites of vasospasm, whereas stenosis improves when vasospasm is treated with calcium antagonists or nitrates.

Accordingly, it is possible that the antispastic effect of nifedipine [11] inhibited the progression of coronary artery lesions and thus reduced the onset of angina pectoris requiring hospitalization in our patients with a history of MI.

It was shown by ENCORE that nifedipine inhibits atherosclerosis by improving coronary endothelial function [18], whereas it inhibited the progression of coronary calcification and the increase in intima–media thickness [19,20] in the INSIGHT side arm study. Such anti-atherosclerotic effects of nifedipine would presumably be beneficial in patients with a history of MI.

This study adds to the growing body of evidence regarding the superior effectiveness of dihydropyridine calcium antagonists for preventing cardiovascular events in (hypertensive) patients with coronary artery disease compared with ACE inhibitors. In the PREVENT study, amlodipine had no demonstrable effect on the angiographic progression of coronary atherosclerosis or the risk of major cardiovascular events, but reduced the incidence of hospitalization for unstable angina and revascularization [21]. In the ALLHAT subanalysis, heart failure was the only secondary outcome for which ACE inhibitors showed superior efficacy compared with the calcium antagonist. In contrast, for stroke and several other 'minor' outcomes (peripheral arterial disease, hospitalized angina, gastrointestinal bleeding, and angioedema), the calcium antagonist was superior to ACE inhibitor therapy [22].

A limitation of this study is that JMIC-B had a prospective, randomized, open-blinded endpoint design. In addition, the present subanalysis is underpowered and randomization seems not to be secured, although the adjustment of covariates was done by Cox proportional hazard model and ANCOVA. Patients for CAG analysis by AHA criteria and QCA analysis were a portion of the total patients. Statistical correction of covariates does not give absolute safety. Less severe baseline characteristics (diabetes mellitus and smoking in Table 1) and greater blood pressure reduction (Table 3) in the nifedipine group might have shown a more marked anti-atherosclerotic effect.

Furthermore, the possibility cannot be ruled out that the effects of unknown factors other than those adjusted this time were confounded. The achieved blood pressure of MI patients was lower in the nifedipine group than in the ACE inhibitor group, but there was no significant difference of events other than angina pectoris requiring hospitalization (Table 4). This may have been partly ascribable to a fewer number of each events.

The subjects in the present study were in the stable phase at least 2 months after acute MI, and patients with cardiac dysfunction were excluded. Accordingly, if cardiac dysfunction is not present after MI, nifedipine seems to be useful for the management of blood pressure and improvement of ischaemic heart disease.

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There is no conflict of interests.

JMIC-B Substudy

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Validation of the Association Between the Gene Encoding Proteasome Subunit α Type 6 and Myocardial Infarction in a Japanese Population

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Background Recently, a large case-control study (2,851 cases and 2,592 controls) reported that a functional single nuclear polymorphism (SNP) in the proteasome subunit α type 6 gene (*PSMA6*) conferred a risk of myocardial infarction (MI) in a Japanese population. The SNP (exon 1, –8C/G) is located in the 5' untranslated region of exon 1, and the risk-conferring allele G appears to enhance the transcription of *PSMA6*, which may exaggerate inflammation through activation of nuclear factor-κ β protein. The frequency of the risk conferring genotype (GG) in cases was reported to be greater than that in controls (12.4% vs 8.9%). The purpose of the present study was to validate this observation in our study population.

Methods and Results Subjects with MI (n=433) were recruited from the outpatient clinic of the National Cardiovascular Center. Control subjects (n=2,186) were recruited from the Suita study. The frequencies of the GG genotype did not significantly differ between the control (9.8%) and MI groups (10.6%). Moreover, this genotype was not associated with C reactive protein levels in the Suita study. However, the GG genotype was significantly associated with greater intima-media thickness (n=2,051, p=0.015) after adjusting for blood pressure, sex, body mass index and age in the Suita study.

Conclusion The reported genotype in *PSMA6* appears not to contribute appreciably to MI, but may contribute slightly to atherosclerosis in the present study population. (*Circ J* 2007; **71:** 495–498)

Key Words: Genetic; Inflammation; Myocardial infarction; *PSMA6*

Myocardial infarction (MI) is a multifactorial disease caused by environmental and genetic factors. There are an increasing number of studies that identify genes that contribute to the incidence of MI; it is possible that these genes can be targeted for personalized prevention of MI.[1–3] Recently, a large case-control study (2,851 cases and 2,592 controls) showed that a functional single nuclear polymorphism (SNP) in the proteasome subunit α type 6 gene (*PSMA6*) conferred a risk for MI in a Japanese population.[4] The SNP (exon 1, –8C/G) is located in the 5' untranslated region of exon 1, and the risk-conferring allele G appears to enhance the transcription of *PSMA6*, which may increase inflammation through activation of nuclear factor-κ β (NF-κB) protein.[5,6] However, because the contribution of a common allele to the pathogenesis of MI appears to be small, validation is necessary in other study populations. The purpose of the present study was to validate the findings of Ozaki et al in a Japanese population and to evaluate the importance of *PSMA6* in the pathogenesis of MI.

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Methods

Study Population

The selection criteria and design of the Suita Study have been described previously.[7–9] Genotypes were determined in 2,500 subjects recruited from the Suita Study between April 2002 and February 2004. The MI group consisted of

Table 1 Characterization of Study Population

	Suita study	*MI subjects*	*p value*
Number	*2,186*	*433*	
Male (number)	*992 (45.38%)*	*370 (86.0%)*	*<0.0001*
Age (years)	*5.35±10.90*	*65.85±9.46*	*0.38*
BMI	*22.84±3.34*	*23.74±2.97*	*<0.0001*
HT (%)	*36.37*	*52.42*	*<0.0001*
DM (%)	*19.81*	*41.51*	*<0.0001*
HLP (%)	*62.44*	*73.31*	*0.0004*
TG (mg/dl)	*106.34±68.40*	*127.62±77.31*	*<0.0001*
TC (mg/dl)	*208.97±32.84*	*199.05±39.73*	*<0.0001*
HDL-C (mg/dl)	*60.05±15.41*	*43.91±13.09*	*<0.0001*
Smoking (%)	*15.74*	*57.60*	*<0.0001*
MI (number)	*34 (1.6%)*	*433 (100%)*	

Values are mean±standard deviation (SD).
MI, myocardial infarction; BMI, body mass index; HT, prevalence of hypertension; DM, prevalence of diabetes mellitus; HLP, prevalence of hyperlipidemia; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; Smoking, current smoking.

Table 2 Association Between MI and rs1048990

Genotype	Suita study*				MI				p value**	p value***
	CC	CG	GG	Total	CC	CG	GG	Total		
Number (%)	1,010 (46.93)	931 (43.3)	211 (9.8)	2,152 (100)	195 (44.3)	192 (45.0)	46 (10.6)	433 (100)	0.73	
Male (%)	44.9	45.5	40.8	44.7	84.6	85.4	89.1	85.5	<0.0001	0.45
Smoking (+) (%)	13.9	17.4	18.0	15.8	53.3	60.4	52.17	57.0	<0.0001	0.97
DM (+) (%)	22.0	17.7	17.1	19.7	38.5	43.2	39.1	40.6	<0.0001	0.089

*Subjects without cardiovascular disease.
**p values are for the comparison between the Suita study and MI subjects.
***p value are for the comparison among genotypes.
Abbreviations see in Table 1.

Table 3 Logistic Analysis of MI

MI	Chi-square	p value	Odds ratio	95%CI
Sex (F)	75.15	<0.0001	0.23	0.16–0.32
Age (years)	7.97	0.0048	3.13	1.42–6.94
Smoking (+)	103.2	<0.0001	3.99	3.06–5.21
Diabetes and/or hyperglycemia (+)	42.77	<0.0001	3.18	2.27–4.56
PSMA6 (GG)	0.02	0.88	0.97	0.63–1.44

Diabetes and/or hyperglycemia (+), subjects diagnosed as having diabetes and/or hyperlipidemia.
CI, confidence interval; PSMA6, proteasome subunit α type 6. Other abbreviation see in Table 1.

Table 4 Association Between *PSMA6* Polymorphism and Intima-Media Thickness

	CC	GC	GG	p value*	p value**
Number	938	884	195		
IMT-mean (mm)	0.79±0.14	0.78±0.13	0.81±0.13	0.025	0.024
Residual IMT-mean	-0.007±0.11	0.005±0.12	0.014±0.11	0.015	0.0073
IMT-max (mm)	1.26±0.53	1.30±0.66	1.24±0.48	0.32	0.38
Residual IMT-max	-0.014±0.469	0.026±0.606	-0.052±0.412	0.099	0.28

Values are mean±SD.
IMT, intima-media thickness. Other abbreviation see in Tables 1,3.
Residuals of IMT were calculated by adjusting for age, systolic blood pressure, sex and BMI.
*p values are for the comparison among CC, CG and GG genotypes.
**p value are for the comparison between CC and GC+GG genotypes.

Table 5 Association Between *PSMA6* Polymorphism and hCRP

	CC	GC	GG	p value*	p value**
Number	1,009	931	210		
hCRP (mg/dl)	0.15±0.47	0.15±0.43	0.11±0.18	0.43	0.69
Log transferred hCRP	-2.79±1.15	-2.76±1.15	-2.80±1.02	0.86	0.71

Values are mean±SD.
hCRP, high sensitivity C related peptide. Other abbreviation see in Table 3.
*p values are for the comparison among CC, CG and GG genotypes.
**p value are for the comparison between CC and GC+GG genotypes.

433 randomly selected inpatients and outpatients with documented MI (370 men, 63 women) who were enrolled in the Division of Cardiology at the National Cardiovascular Center between May 2001 and April 2003[10,11] All subjects enrolled in the present study provided written informed consent. The present study was approved by the Ethics Committee of the National Cardiovascular Center and by the Committee on Genetic Analysis and Gene Therapy of the National Cardiovascular Center.

Subjects with a systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or taking antihypertensive medication were categorized as having hypertension[3] Subjects with a fasting blood glucose ≥126 mg/dl, hemoglobin (Hb) A1c ≥6.5% and/or undergoing treatment for diabetes mellitus (DM) were categorized as having DM[3] Subjects with total cholesterol ≥220 mg/dl, triglycerides ≥150 mg/dl and/or taking antihyperlipidemic medication were categorized as having hyperlipidemia[3] The intima-media thickness (IMT), a well-known indicator of coronary atherosclerosis, was measured on a longitudinal scan of the common carotid artery at a point 10 mm proximal from the beginning of the dilation of the bulb[7]

DNA Study

Ozaki et al determined 8 polymorphisms in *PSMA6* genes, and found the most significant association with MI at the polymorphism rs1048990[4] In the present study, we determined the rs1048990 polymorphism using the TaqMan

methods. The following polymerase chain reaction primer and probe set was used: C_11599359_10 (Applied Biosystems, Foster City, USA).

Statistical Analysis

The values are expressed as mean±standard deviation. All statistical analyses were performed with the JMP statistical package (SAS Institute Inc, Cary, NC, USA). Simple correlation analyses and logistic analyses were performed to determine the association between laboratory data and MI cases. Multiple logistic analyses were performed to obtain predictors for MI. Odds ratio and 95% confidence intervals (CI) were also calculated. The continuous phenotypic variables and genotype were compared using one way analysis of variance, adjusting for appropriate confounding factors. Residuals of IMT were calculated by adjusting for age, SBP, sex and body mass index (BMI)? C reactive protein (CRP) levels were logarithmically transformed to attain normal distribution.

Results

The characteristics of the present study population are shown in Table 1. In the present study population, the frequencies of the GG genotype in the MI and the control group were 10.6% and 9.8%, respectively (Table 2). No significant difference was observed in the genotype frequency between the 2 groups. The GG genotype was not associated with smoking habits or the prevalence of DM (Table 2). The odds ratio of the GG genotype of *PSMA6* over the CC+CG genotype for MI was 0.97 (95%CI, 0.63–1.44) (Table 3). However, because it was possible that the sample size of the MI group (n=433) was too small to detect the small effects of the risk-conferring alleles, we observed the effects of this genotype on carotid IMT, an excellent non-invasive marker of atherosclerosis. The GG genotype was associated with mean IMT (p=0.025) and greater residuals of mean IMT (p=0.015) after adjusting for age, BMI, sex and SBP (Table 4).

No significant effects from this genotype on CRP levels were observed in the Suita population (Table 5).

Discussion

The purpose of the present study was to validate in our study population the association between *PSMA6* variants and MI that has been reported in a Japanese population. Because the genetic contribution of a single gene to common disease susceptibility appears to be low, as observed in the insertion/deletion polymorphism of the angiotensin converting enzyme gene in cardiovascular disease, validation studies in other study populations are important![12,13]

PSMA6 encodes the proteasome subunit α type 6, a component of the 20S proteasome![14] The 20S proteasome is composed of 7 α and 10 β subunits, and is the core particle for the 26S ubiquitin-proteasome system, which is important in the regulation of the abundance of proteins involved in various cellular functions, including inflammation![15–17] Of note, this system is involved in the degradation of the IκB protein, which inhibits the activation of NF-κB, a central transcriptional factor that regulates the expression of genes related to inflammation? Now vascular inflammation is considered a key player for atherogenesis, and CRP levels are a well-known predictor for subsequent MI![18–21]

The reported odds ratio of the GG genotype of *PSMA6* over the CC+CG genotype for MI was just 1.36 (95%CI, 1.12–1.65)[4] Thus, we were unable to detect the association of the GG genotype with MI, probably due to our small sample size. However, we did detect an influence of this genotype on IMT, a well-known index of atherosclerosis of coronary arteries![22–25] This may indicate that the influence of this gene may be directed to the pathogenesis of atherosclerosis.

The influence of the *PSMA6* genotype on the residuals of IMT-mean was significant but slight (r^2=0.0042, p=0.014). The IMT-maximum values may be considered to be more influenced by local micro environmental factors and may be difficult to predict using classical risk factors. Indeed, the r^2 values for IMT-maximum by confounding factors (age, gender, SBP and HbA1c) was 0.181, which is smaller than the r^2 values for IMT-mean (r^2=0.237) by confounding factors (age, gender, BMI, SBP and HbA1c). Therefore, a slight influence of the *PSMA6* genotype may not be detected in the IMT-maximum.

Ozaki et al reported that the frequencies of the genotype GG in the MI and the control groups were 12.4% and 8.9%, respectively[4] However, in the present study population, the frequencies of the GG genotype in the MI and the control group were 10.6% and 9.7%, respectively, with no significant differences between groups. Ozaki et al speculated that the effects of *PMSA6* might be due to potentiation of inflammation[4] CRP levels are known to be a good indicator of future MI![20] However, in the present study, the GG genotype was not associated with the CRP levels. The precise mechanism of how the GG genotype might accelerate atherosclerosis or infarction awaits further investigation.

In conclusion, the reported genotype in *PSMA6* appears not to contribute appreciably to MI, but may contribute slightly to atherosclerosis in the present study population.

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Phenotypic Heterogeneity of Marfan-Like Connective Tissue Disorders Associated With Mutations in the Transforming Growth Factor-β Receptor Genes

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Background Mutations in the genes for transforming growth factor-β receptor (TGFBR) have been identified in patients with Marfan syndrome (MFS) and Marfan-like connective tissue disorders. There are several syndromes associated with mutations in TGFBR genes, including Loeys-Dietz syndrome (LDS), MFS2, Furlong syndrome, and Shprintzen-Goldberg syndrome. However, with the exception of the first report by Loeys et al, the phenotypic features of patients with TGFBR gene mutations have not been precisely reported.

Methods and Results A total of 18 patients suspected of having MFS were recruited and 7 were diagnosed with MFS and mutations in *FBN1*. Among the remaining 11 patients, 1 patient had mutations in *TGFBR1*, 2 had mutations in *TGFBR2*, and 1 had mutations in *COL3A1*. The clinical manifestations of the 3 patients with TGFBR gene mutations were examined according to the list of 36 clinical features described in the first report by Loeys et al. The clinical manifestations of these 3 patients differed from those previously observed in patients with MFS2, Furlong syndrome, and Shprintzen-Goldberg syndrome. Thus, the most probable diagnosis of these 3 patients was LDS, despite the fact that they presented with only a fraction of the 36 clinical features associated with LDS.

Conclusions Although the number of the patients was limited, the findings support the notion that mutations in the TGFBR gene may be associated with greater phenotypic heterogeneity than previously reported. (*Circ J* 2007; **71**: 1305–1309)

Key Words: Loeys-Dietz syndrome; Marfan-like connective tissue disorder; Marfan syndrome; Transforming growth factor-β receptor genes

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder associated with acute aortic dissection (AAD) and annulo-aortic ectasia (AAE). The diagnosis of MFS depends on manifestations in multiple organ systems, primarily the skeletal, ocular, and cardiovascular systems, and on family history. However, many patients with young-onset AAD or AAE fail to meet the diagnostic criteria for MFS and are not characterized by a mutation of the fibrillin-1 gene (*FBN1*). These cases have therefore been classified as Marfan-like connective tissue disorders.

Recently, mutations in the genes for transforming growth factor-β receptor (TGFBR) have been found in patients with MFS or Marfan-like connective tissue disorders[1,2] and several distinct syndromes have been proposed that are associated with such mutations, including MFS type 2 (MFS2)[1] Loeys-Dietz syndrome (LDS)[2,3] Shprintzen-Goldberg syndrome[4] and Furlong syndrome[5] With the exception of the first report by Loeys et al[2] however, none of these reports present precise clinical characteristics of each patient.

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We describe here the clinical features of 3 patients with Marfan-like connective tissue disorders associated with TGFBR gene mutations in accordance with the 36 clinical features proposed by Loeys et al[2]

Methods

Patients

Between March 2004 and February 2006, a total of 21 patients with suspected MFS were referred to us. Patients were suspected of MFS because of presentation of young-onset AAD (<40 years) (n=8), AAE (n=5), and patient background (n=8); that is, family history, physical findings, and the presence of mitral valve prolapse. Among the 21 patients, 3 were excluded because they had relatives in the study group. The current study thus included 18 patients.

All 18 patients underwent genetic analysis as well as careful assessment including physical examination, computed tomography scanning, magnetic resonance imaging, echocardiography, and slit-lamp examination. These assessments covered all the diagnostic criteria for MFS[6] as well as the 36 clinical features of LDS[2] (Table 1).

The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of the National Cardiovascular Center (Osaka, Japan). All patients gave written informed consent to participate in this study.

Table 1 Clinical Characteristics of the Patients With Mutations in the TGFBR Gene

	Patient 1	Patient 2	Patient 3	Loeys et al	Singh et al
Individual					
Age (years)	44	35	33		
Gene mutation	TGFBR2	TGFBR2	TGFBR1		
Craniofacial					
*Hypertelorism**	+	–	–	36/40 (90%)	1/7 (14%)
Cleft palate or abnormal uvula,††*	+	–	–	36/40 (90%)	1/7 (14%)
Malar hypoplasia	+	–	–	24/40 (60%)	5/7 (71%)
Rentrognathia	–	–	–	20/40 (50%)	
Craniosynostosis	–	–	–	19/40 (48%)	0/9 (0%)
Exotropia	–	+	–	7/13 (54%)	
Proptosis	–	–	–	6/13 (46%)	
Blue sclerae	–	–	–	16/40 (40%)	1/7 (14%)
Ectopia lentis†	–	–	–	0/40 (0%)	0/9 (0%)
Cardiovascular					
*Aortic root aneurysm**	+	+	+	39/40 (98%)	10/11 (91%)
Patent ductus arteriosus	–	–	–	14/40 (35%)	0/7 (0%)
*Arterial tortuosity**	–	+	–	21/25 (84%)	0/2 (0%)
Bicuspid aortic valve	–	–	–	2/12 (17%)	
Bicuspid pulmonary valve	–	–	–	1/9 (11%)	
Mitral valve prolapse	–	–	–	4/14 (29%)	
Pulmonary artery aneurysm	–	–	–	9/13 (69%)	
Descending aortic aneurysm	+	+	–	3/9 (33%)	
Ductal aneurysm	–	–	–	3/12 (25%)	
Subclavian artery anerurysm	–	–	–	2/7 (29%)	
Superior mesenteric artery aneurysm	–	–	+	1/8 (13%)	
Cerebral aneurysm	–	NE	NE	2/9 (22%)	
Atrial sptal defect	–	–	–	9/40 (22%)	0/7 (0%)
Aneurysm of other vessels,†*	–	–	+	21/40 (52%)	1/9 (11%)
Skeletal					
Dolichostenomelia	–	–	–	7/40 (18%)	7/9 (78%)
Arachnotactyly	–	–	–	28/40 (70%)	6/8 (75%)
Pectus deformity	–	+	+	27/40 (68%)	7/9 (78%)
Camptodactyly	–	–	–	6/14 (43%)	
Scoliosis	–	–	–	20/40 (50%)	6/9 (67%)
Postaxial polydactyly	–	–	–	2/14 (14%)	
Talipes equinovarus	–	–	–	18/40 (45%)	
Camptodactytly	–	–	–	15/40 (38%)	2/9 (22%)
Joint laxity	–	–	–	27/40 (68%)	6/9 (67%)
Cervical spine instability†	–	–	–	7/40 (18%)	
Cutaneous					
Velvety skin	–	–	–	11/40 (28%)	
Translucent skin	–	–	–	13/40 (32%)	
Nervous system					
Chiari malformation	–	–	–	2/10 (20%)	
Hydrocephalus	–	–	–	2/13 (15%)	0/11 (0%)
Developmental delay	–	–	–	3/14 (21%)	0/11 (0%)
Dural ectasia	–	–	–	1/2 (50%)	

**Defined as typical by Loeys et al (2006).*
TGFBR, transforming growth factor-β receptor; NE, not examined.
†Ectopia lentis, aneurysm of other vessels, and cervical spine instability were not listed in the first report by Loeys et al[2] of the 36 clinical features of Loeys-Dietz syndrome.
††Cleft palate and abnormal uvula were listed as separate 2 items in the first report by Loeys et al.[2]

Genetic Analysis

Genetic analysis was performed to screen for mutations in the *FBN1* and TGFBR genes. Genomic DNA was isolated from the peripheral blood leukocytes of patients by an NA-3000 Nucleic Acid Isolation System (Kurabo Industries Ltd, Osaka, Japan) and amplified by polymerase chain reaction (PCR). Primers and conditions for PCR were as described previously[1,2,7] Genetic variants were screened with a denaturing high-performance liquid chromatography method in which the PCR products were analyzed with a WAVE DNA Fragment Analysis System (Transgenomic Inc, Omaha, NB, USA) according to the manufacturer's protocol. All detected variations were further confirmed by direct sequencing with an ABI 3700 Autosequencing System (Applied Biosystems, Foster City, CA, USA).

Results

Genetic Analysis

The median age of the patients at the time of blood sampling for genetic analysis was 33 years (range: 9–58). Among the 18 patients with suspected MFS, 7 fulfilled the diagnostic criteria of MFS, including 2 patients with AAD and 3 with AAE. Each of these 7 patients had mutations in *FBN1*. Eleven of the 18 patients were not diagnosed with MFS according to the criteria, and these patients were instead classified as having a Marfan-like connective tissue disorder. Among the latter, 1 patient had mutations in type I TGFBR gene (*TGFBR1*), 2 had mutations in type II TGFBR gene (*TGFBR2*), 1 had mutations in *COL3A1* and 7 did not have any mutations in the *FBN1* and TGFBR genes.

These 7 patients showed only reported polymorphisms in *FBN1*, *FBN2*, *TGFBR1*, and *TGFBR2*. Details of the 3 patients with TGFBR gene mutations are described below.

Clinical Course of the Patients With TGFBR Gene Mutations

Patient 1 Patient 1 was a 44-year-old woman (height, 157 cm; weight, 43 kg). She suffered the first episode of AAD (DeBakey IIIb) at the age of 29 years. Her identical twin sister also developed AAD at the same age. Surgical replacement of the proximal descending aorta for expansion of a false lumen was performed when the patient was 31 years of age. At 33 years of age, she suffered a recurrence of the AAD (IIIb), which was associated with expansion of the false lumen in the distal descending aorta to the abdominal aorta. At the age of 35 years, she suffered a third episode of AAD (II), for which emergency surgery, including total arch replacement, aortic root remodeling, and reconstruction of the right coronary artery, was performed. At 43 years of age she underwent surgical replacement of the thoracoabdominal aorta to correct expansion of the distal descending to abdominal aortic aneurysm and she also underwent the Bentall procedure for AAE with aortic regurgitation at 44 years of age. She did not show any of the following phenotypic manifestations of MFS: wrist sign, thumb sign, pectus carinatum, pectus excavatum, ectopia lentis, pneumothorax, mitral valve prolapse, striae distensae, or dural ectasia. The arm span to height ratio was <1.05. The clinical manifestations did not fulfill the diagnostic criteria for MFS, and Marfan-like connective tissue disorder was thus diagnosed. Although the patient had hypertelorism, bifid uvula, and aneurysm of aortic root, she had neither aneurysms of other vessels nor a tortuous aorta, which are typical clinical features of LDS? Mutations were not detected within the *FBN1*. However, we did detect a mutation in exon 7 of *TGFBR2*, leading to an Arg-to-Cys substitution at residue 537.

Patient 2 Patient 2 was a 35-year-old man (height, 179 cm; weight, 69 kg). His mother had died from AAD and his first episode of AAD (DeBakey IIIb) occurred at 34 years of age. Replacement of the descending aorta was performed when he was 35 years of age. Although he had moderate-grade pectus excavatum, he did not show any of the following phenotypic manifestations of MFS: wrist sign, thumb sign, pectus carinatum, ectopia lentis, pneumothorax, mitral valve prolapse, striae distensae, or dural ectasia. The arm span to height ratio was <1.05. The clinical manifestations did not fulfill the diagnostic criteria for MFS, and therefore he was classified as having a Marfan-like connective tissue disorder. Although the patient had aortic root aneurysm and a tortuous aorta, he did not have hypertelorism, cleft palate, abnormal uvula, or aneurysms of other vessels, which are typical clinical features of LDS. In addition, he had exotropia. Genetic analysis detected a nonsense mutation in exon 6 of *TGFBR2* that caused a stop codon instead of an Arg at amino acid position 495. We did not detect mutations in *FBN1* responsible for MFS.

Patient 3 Patient 3 was a 33-year-old man (height, 181 cm; weight, 56 kg). He did not have a family history suggestive of heritable connective tissue disorders or aortic disease. At 16 years of age, he developed AAD (DeBakey II) and underwent a modified Bentall procedure. At 27 years of age, he underwent surgeries to repair right pneumothorax and then left pneumothorax. Also at age 27 years, he had a second episode of AAD (DeBakey II) originating from the

Table 2 Clinical Characteristics of the 8 Patients Without Mutations in *FBN1* or TGFBR Genes

Age (years)	*Sex*	*Height (cm)*	*Skeletal involvement*	*Cardiovascular involvement*	*Ocular involvement*	*Family history related to cardiovascular events*	*Reasons for genetic analysis*	*Clinical diagnosis at the time of genetic analysis*
33	M	168	–	–	–	AAA: brother (21 yo), SAH: sister (19 yo), TAA: father (42 yo)	Family history	Ehlers-Danlos syndrome (COL3A1 mutation)
32	M	176	–	AAE, MVP	–	–	AAE	Post Bentall for AAE and AR (bicuspid aortic valve)
58	F	160	Pes planus	AD (IIIb, 58 yo)	–	AD: brother (54 yo)	Family history	Acute AD
28	M	168	–	–	NE	AD: father (30 yo), brother (25 yo)	Family history	NP
55	F	161	–	AD (I, 54 yo)	–	–	AD	Chronic AD, post TAR
31	F	174	Thumb sign, scoliosis, pectus excavatum	MVP	–	–	Physical examination	MR
20	F	156	–	MVP	–	–	MVP	MR, AR
44	F	159	–	AAE	NE	–	AAE	Post Bentall for AAE and AR

FBN1, fibrillin-1 gene; AAA, abdominal aortic aneurysm; yo, years old; SAH, subarachnoid hemorrhage; TAA, thoracic aortic aneurysm; AAE, annulo-aortic ectasia; MVP, mitral valve prolapse; AR, aortic regurgitation; AD, aortic dissection; NP, nothing particular; TAR, total arch replacement. Other abbreviations see in Table 1.

distal portion of the previously replaced ascending aorta, and replacement of the aortic arch was performed by the elephant trunk method. At 33 years of age, he presented with ectasia of the ostias of both coronary arteries, as well as an aneurysm of the superior mesenteric artery. He underwent another Bentall procedure and reconstruction of the left coronary artery. Although he had moderate grade pectus excavatum and a history of pneumothorax, he did not show any of the following phenotypic manifestations of MFS: wrist sign, thumb sign, pectus carinatum, ectopia lentis, mitral valve prolapse, striae distensae, or dural ectasia. The arm span to height ratio was <1.05. The clinical features did not fulfill the diagnostic criteria for MFS, and therefore a diagnosis of a Marfan-like connective tissue disorder was made. Although some features characteristic of LDS, including aortic root aneurysm and superior mesenteric artery aneurysm, were observed, other features such as hypertelorism, cleft palate, abnormal uvula, and tortuous aorta were absent. Genetic analysis detected a mutation in exon 9 of *TGFBR1*, resulting in an Arg487Gln substitution. Mutations of *FBN1* associated with MFS were not detected.

Comparison of the Present Clinical Features With Those in Previous Reports

The clinical features of these 3 patients are summarized and compared with those described by Loeys et al[2,3] and Singh et al[8] (Table 1). Loeys et al proposed 36 clinical features of LDS, of which the median number of features examined in each patient was 31, with a median number of positive features of 13, and a median positive ratio of 46%. In the present study, the number of these 36 features examined was 36 in patient 1, 35 in patient 2, and 35 in patient 3. The number of positive features in these 3 patients was 5 in patient 1, 5 in patient 2, and 3 in patient 3, with a positive ratio therefore of 14% (5/36), 14% (5/35), and 9% (3/35), respectively, which is much less than the ratio reported by Loeys et al.

Clinical Features of Patients Without FBN1 or TGFBR Gene Mutations

The clinical features of the 8 patients without *FBN1* or TGFBR gene mutations are shown in Table 2. Among them, 1 patient had mutations of *COL3A1* and was diagnosed as having Ehlers-Danlos syndrome. The remaining 7 patients showed reported polymorphisms only in *FBN1*, *FBN2*, *TGFBR1*, and *TGFBR2*. They were associated with several phenotypes of MFS such as pes planus, thumb sign, scoliosis, pectus excavatum, mitral valve prolapse, aortic dissection, and annuloaortic ectasia, but did not fulfill the criteria for MFS (Table 2).

Discussion

The diagnostic criteria for MFS were first established in 1986[9] and were based solely upon phenotypic abnormalities of the skeletal, ocular, and cardiovascular systems. The observation that mutations in *FBN1* were linked to this syndrome required that these classic criteria be revised to include genetic factors.[6] However, mutations in *FBN1* have been detected in only 66–91% of MFS patients![10,11] Some patients who present with Marfan-like skeletal and cardiovascular phenotypes, but who lack or exhibit only mild ocular involvement and who do not exhibit mutations in the *FBN1* locus have been classified as MFS2![12] Chromosome 3p25–p24.2 has been identified as a second locus for MFS[13] in lineages in which MFS2 was shown. This locus is also known as TAAD2 and is thought to be responsible for familial TAA and AAD![14] Subsequent studies by Mizuguchi et al[1] identified mutations in *TGFBR2* as a cause of MFS2. More recently, Loeys et al reported that mutations in *TGFBR1* or *TGFBR2* are responsible for the development of a Marfan-like connective tissue disorder in certain patients, and proposed a new disease entity, named LDS.[2] LDS is characterized by widely spaced eyes (hypertelorism), bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection. Although the phenotype overlaps somewhat with that of MFS, LDS does not fulfill the diagnostic criteria for MFS.

There is clear evidence in the literature for the existence of at least 4 syndromes associated with mutations in *TGFBR1* or *TGFBR2*; that is, LDS,[2] MFS2,[1] Shprintzen-Goldberg syndrome,[4] and Furlong syndrome.[5] LDS has been subdivided into types 1 and 2.[3] LDS type 1 is associated with craniofacial involvement consisting of cleft palate, craniosynostosis, or hypertelorism, whereas type 2 is associated with Ehlers-Danlos syndrome. Shprintzen-Goldberg syndrome is characterized by craniosynostosis and mental retardation, and Furlong syndrome is characterized by only craniosynostosis.

We report 3 cases of young-onset AAD associated with mutations in *TGFBR1* and *TGFBR2*. Diagnoses of MFS and MFS2 were excluded because the patients did not fulfill the diagnostic criteria for MFS. In addition, because the patients exhibited neither craniosynostosis nor mental retardation, diagnoses of Shprintzen-Goldberg or Furlong syndromes were excluded. We also did not observe characteristics associated with Ehlers-Danlos syndrome, such as skin hyperextensibility, fragile and soft skin, delayed wound healing with formation of atrophic scars, and generalized joint hypermobility. Thus, LDS type 2 was also ruled out. Consequently, the most probable diagnosis of these 3 patients was LDS type 1. However, these 3 patients presented only a fraction of the features associated with LDS type 1;[2] only 9–14% of the 36 reported clinical features of LDS, which is far less than that reported by Loeys et al (median 46% of the 36 features). It should be also pointed out that patient 3 had repetitive pneumothorax, which is not listed in the features of LDS. These observations support the notion that TGFBR gene mutations may give rise to greater phenotypic heterogeneity than previously reported.

Finally, as described above, several syndromes have been linked to TGFBR gene mutations. Although the phenotypic manifestations of these syndromes overlap, the extent of this remains to be determined more precisely, mainly because the precise clinical features have not been evaluated and/or reported in most patients with TGFBR gene mutations. In fact, to our knowledge, the study performed by Loeys et al[3] is the only one in which as many as 36 clinical features associated with TGFBR gene mutations have been evaluated, although there are some published reports of mutations of TGFBR genes![15–19] Given the current incomplete understanding of the clinical features associated with TGFBR gene mutations, more detailed clinical studies should be performed in patients who present with these mutations.

Conclusions

We described 3 cases of Marfan-like connective tissue disorder associated with TGFBR gene mutations. The clini-

cal features differed from those of previously reported cases of Marfan-like connective tissue disorder associated with TGFBR gene mutations. Although the number of patients was limited, our findings support the notion that these mutations may give rise to greater phenotypic heterogeneity than previously reported.

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座談会

虚血性心疾患にともなう致死性不整脈の緊急治療

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（順不同・敬称略／2007年2月23日収録）

野々木　近年、急性心筋梗塞（AMI）の院内救命率は冠疾患集中治療室（CCU）の整備や血行再建・不整脈治療の進歩などにより向上し、予後は極めて良好となっています。しかし、AMI全体の死亡率は依然として高く、その多くは院外での死亡であり、致死的な不整脈が未だ重要な問題です。

本日は、虚血性心疾患、特にAMIに伴う致死性不整脈に焦点を当て、第一線でご活躍の3名の先生方に対策の1つである薬物による緊急治療についてお話を伺っていきたいと思います。

急性心筋梗塞の現状

■院内の治療成績は向上

野々木　まず、各施設でのAMIの現状とその取り組みについて、白井先生からお話しいただけますか。

白井　小倉記念病院は人口200万人の診療圏にあり、当院でのAMIは年間350～400例で、ST上昇型AMIを始め、ほとんどで急性期に血行再建を施行しています。心肺停止（CPA）例に対しては、最近は明らかにAMIが疑われれば、経皮的人工心肺装置（PCPS）などを挿入して緊急カテーテル、その後に脳低温療法を施行するという取り組みを行っています。AMI死亡率は約8％ですが、AMIでショックに陥った場合の死亡率は50％にも跳ね上がります。ショックやCPAをきたさなければ、予後は非常に向上しています。

田原　横浜市立大学附属の市民総合医療センターには、私が所属する高度救命救急センターと心臓血管センターがあります。疾患により入院するセンターが異なるのですが、病院到着時には両センターが協力して患者さんに対応します。AMIは年間150例前後、院内死亡率は約5％です。

当院の特徴は、現場から12誘導心電図を伝送できるシステムがあることです。横浜市は人口360万人の都市で救急隊が62隊あり、すべての救急隊に院外12誘導心電図伝送装置が備えられています。このシステムにより救急車内でAMIの判別が可能になりました。救急隊が一番近い病院に搬送し、AMIと診断され、そこから緊急治療が可能な病院に転院していた頃に比べ、治療開始までの時間を約60分間短縮できるようになりました。

安田　東北大学では10月から救命センターが開設され、急性期の患者さんが増えました。基本的には、一般の病院では対応が難しい腎不全や悪性腫瘍といった併存疾患の多い患者さんを受け入れています。最近は、院外CPA例にも院内ガイドラインを作成し、さまざまな取り組みを行っています。

野々木　ありがとうございます。あまり地域差もなく、どの施設も治療成績が向上したことは間違いないようですね。私の所属する国立循環器病センターは人口約170万人の診療圏を有し、AMIは年間200例です。死亡率は5％以下で、心原性ショックと心破裂が未だに

野々木宏氏

起こっているためゼロにはならない状況ですが、以前に比べるとかなり改善されました。ただ問題は、AMIによる入院前死亡が多いために地域全体での死亡率が30%もあることで、現在取り組みを行っています。

▫救急隊や他病院との連携に工夫

野々木　横浜市には院外12誘導心電図伝送システムが構築されていますが、小倉記念病院がある北九州市でもそうした連携システムはあるのでしょうか。

白井　「北九州市方式」という機能別救急システムがあり、「胸が痛い」という患者さんは多くの場合当院に運ばれてくるシステムになっており、周辺の病院でもAMIと診断がついた時点で当院へ搬送してもらっています。ただ、「胸が痛い」といってもAMIではない場合も当然あり、いわゆるチェストペインセンターも兼ねているようなところがあります。

野々木　救急室に搬入されST上昇型AMIという診断がついてから経皮的冠動脈形成術（PTCA）まで、どれくらいの時間を要しますか。

白井　door-to-balloon timeは、早ければ30分です。当院では当直医が2名、メインベル当番医というPTCAのオペレーターが1名待機し、カテーテル室のナース1名と放射線技師1名が当直、心電図技師1名が待機しています。

野々木　素晴らしいですね。東北大学では、何か連携での工夫はありますか。

安田　現在は二次救急指定の地域医療支援病院がAMIのほとんどを受け入れ、当院では併存疾患の多い重症例や全身管理が必要な院外CPA例が多く運ばれてくる傾向にあります。

野々木　東北大学としては、救命救急病院として地域の病院と連携するという形ですね。

急性心筋梗塞に伴う致死性不整脈の実態

▫循環器医がfirst touchに関与していない

野々木　院外CPA例は三次救急施設（救命救急センター）に搬入されることが多く、救急医が救命しようと努力されているのが現状です。小倉記念病院では、院外CPA例は搬送されてきますか。

白井　搬送はされてきますが、数的には他の施設ほどではないと思います。多くの場合、一番近い救命救急センターに搬送され、そこで心拍再開の後にAMIの診断にて当院に搬送されてくることがほとんどです。

野々木　田原先生のところは救命救急センターですが、院外CPA例の搬送は多いのでしょうか。

田原　院外CPA例は、年間350例前後です（**表1**）。そのうち約60%は、虚血性心疾患がCPAの原因に関与しています。

野々木　かなり多いですね。AMI入院例の予後が向上してきたことは事実ですが、一方で院外CPA例を受け入れている三次救急施設などでAMIの死亡例がかなり存在することを循環器医は認識し、これから取り組んでいく必要があると思います。

▫日本でも多い発症直後の心室細動

野々木　田原先生、院外CPA例の約60%が虚血性心疾患だとすると、その多くは心室細動（VF）を起こしていたと考えていいのでしょうか。

田原　日本救急医学会関東地方会院外心停止多施設共同研究（SOS-KANTO）の長尾 建先生の論文によると、院外CPA例のうち、現状では救急隊が現場でVFを確認できるのは16.2%ですが、患者さんが倒れてから救急隊が心電図を装着するまでの時間とVFの頻度をグラフにすると、院外CPA例の62.7%はVFではないかと推定されています[1]。

野々木　確かに欧米同様に日本でもAMIの発症直後にはVFが高率に起こっており、時間の経過とともに心静止や無脈性電気活動（PEA）に移行して病院に到着しているのだろうと思います。こうした致死的な心室性不整脈に対し、院外で少しでも早く対応するにはどうすればいいでしょうか。

田原　やはり、bystander CPR（心肺蘇生）が重要だ