Table 6 Clinical Outcomes in Patients Presenting With UA

Cardiac events	
During the first month	
Yes	*21 (2%)*
No	*806 (91%)*
Unknown	*58 (7%)*
Time from admission to event (days)	
Mean±SD	*9.7±7.9*
Details of events	
Death	*9*
MI	*6*
Urgent (re-) PCI	*4*
Urgent (re-) CABG	*2*
During the initial 6 months	
Yes	*78 (9%)*
No	*749 (85%)*
Unknown	*58 (7%)*
Time from admission to event (days)	
Mean±SD	*85.2±76.5*
Details of events	
Death	*22*
MI	*18*
Urgent (re-) PCI	*34*
Urgent (re-) CABG	*4*
Major bleeding	
During hospitalization	
Yes	*37 (4%)*
No	*848 (96%)*
Time from admission to event (days)	
Mean±SD	*6.9±7.6*
Details of bleeding	
Intracranial hemorrhage	*0*
Spontaneous or puncture site, etc	*8*
Need for blood transfusion	*23*
Hematoma with need for surgery	*1*
Other	*5*

PCI, percutaneous coronary intervention. Other abbreviations as in Table 2.

Table 7 Clinical Outcomes in Patients Presenting With AMI

Cardiac events	
During the first month	
Yes	*77 (8%)*
No	*807 (86%)*
Unknown	*53 (6%)*
Time from admission to event (days)	
Mean±SD	*8.9±8.6*
Details of events	
Death	*58*
Re-infarction	*2*
Post infarction angina	*8*
Urgent (re-) PCI	*7*
Urgent (re-) CABG	*2*
During the initial 6 months	
Yes	*132 (14%)*
No	*752 (80%)*
Unknown	*53 (6%)*
Time from admission to event (days)	
Mean±SD	*48.8±57.9*
Details of events	
Death	*77*
Re-infarction	*12*
Post infarction angina	*27*
Urgent (re-) PCI	*25*
Urgent (re-) CABG	*7*
Major Bleeding	
During hospitalization	
Yes	*81 (9%)*
No	*856 (91%)*
Time from admission to event (days)	
Mean±SD	*5.5±9.7*
Details of bleeding	
Intracranial	*3 (0.3%)*
Spontaneous or puncture site, etc	*33 (3.5%)*
Need for blood transfusion	*35 (3.7%)*
Hematoma with need for surgery	*5 (0.5%)*
Other	*15 (1.6%)*

Abbreviations as in Tables 2, 3, 6.

of revascularization, use of heparin, use of oral antiplatelet drugs, use of antianginal drugs (only for UA patients).

Outcome All-cause death, AMI, and urgent coronary revascularization during the first 6 months, as well as in-hospital major bleeding events.

In this study, information about medical treatment with nicorandil, ACE inhibitors, ARBs and statins, and information of device usage (thrombectomy or distal protection) was not included.

Prior to initiation, the protocol and conduct of the study were approved by the ethical committee or institutional review board of each participating site.

Results

Study 1: Questionnaire Survey

Of the 770 sites, 584 responded to the questionnaire (response rate of 76%).

Number of Patients No more than 25 patients with UA were hospitalized annually at 274 of the 582 sites (48%). The annual number of UA patients was 26–50 at 186 sites (32%), 51–100 at 90 sites (15%), and greater than 100 at 32 sites (5%) (Fig 1).

The annual number of AMI patients was no greater than 25 at 194 of the 580 sites (33%), 26–50 at 175 sites (30%), 51–100 at 146 sites (25%), and greater than 100 at 65 sites (12%). In general there were fewer UA patients than AMI patients at each site (Fig 2).

Fig 3 shows the percentage of non-ST-elevation patients among all those with AMI. Non-ST-elevation AMI accounted for not more than 20% of all cases of AMI at 409 of the 574 sites (71%).

To obtain a more accurate estimate of the number of UA patients relative to AMI patients, another questionnaire was sent to the 389 sites that reported treating more than 25 AMI patients per year. Of these, 217 (56.1%) responded to the additional questionnaire. The total annual number of UA and AMI patients at the 217 sites was 9,656 and 15,102, respectively, a ratio of 1:1.56. Among the 15,102 AMI patients, 2,535 (17%) were diagnosed as non-ST-elevation AMI (Fig 4).

Treatment Provided (1) Timing of coronary angiography–"after stabilization by drug treatment" was the most frequent response chosen by 341 of the 574 sites (59%). Patients underwent coronary angiography as soon as possible after arrival at 211 sites (37%) (Fig 5).

(2) Use of heparin–Heparin was administered immediately after arrival at hospital to all patients without contraindications at 411 of the 582 sites (70%). The next most frequent choice was "only refractory patients not responding to appropriate antianginal treatment or for severe cases", the management selected by 133 sites (23%) (Fig 6).

After PCI, heparin was used in principle at 333 of the 521 sites (64%), but was not usually administered at 112 sites (21%) (Fig 7).

(3) Treatment of ST-elevation and non-ST-elevation

Table 8 Stratified Analysis of Cardiac Events According to Baseline Characteristics in UA

	Cardiac events during initial 6 months (incidence)	χ^2 test p value	Details of events (cases)			
			Death	MI	u-PCI	u-CABG
Sex, age						
M	8.4% (51/609)	0.0821	12	13	24	2
F	12.4% (27/218)		10	5	10	2
<65 years	7.7% (29/376)	0.1225	5	8	16	0
≥65 years	10.9% (49/451)		17	10	18	4
Previous disease						
MI						
No	8.3% (51/616)	0.0527	8	17	24	2
Yes	12.8% (27/211)		14	1	10	2
History of PTCA, stent, etc						
No	9.2% (59/638)	0.8758	18	16	22	3
Yes	9.6% (18/187)		3	2	12	1
History of CABG						
No	9.4% (74/787)	0.8588	20	18	32	4
Yes	10.3% (4/39)		2	0	2	0
Concomitant disease						
Any of below						
No	5.1% (5/98)	0.1183	1	1	3	0
Yes	10.0% (73/729)		21	17	31	4
Hypertension						
No	8.6% (29/339)	0.4720	11	5	12	1
Yes	10.0% (49/488)		11	13	22	3
Diabetes						
No	8.0% (42/524)	0.0668	12	8	18	4
Yes	11.9% (36/303)		10	10	16	0
Hyperlipidemia						
No	10.2% (48/469)	0.3659	16	8	24	0
Yes	8.4% (30/358)		6	10	10	4
Cerebrovascular disease						
No	9.0% (68/754)	0.1914	19	15	30	4
Yes	13.7% (10/73)		3	3	4	0
Renal disease						
No	7.7% (58/752)	<0.0001	12	15	28	3
Yes	26.7% (20/75)		10	3	6	1
Liver disease						
No	9.4% (76/806)	0.9883	21	17	34	4
Yes	9.5% (2/21)		1	1	0	0
ECG abnormality on admission						
ST change						
No	6.7% (24/356)	0.0331	3	8	12	1
Yes	11.1% (51/460)		18	10	20	3
T wave inversion						
No	7.6% (34/446)	0.0935	10	10	12	2
Yes	11.0% (41/372)		11	8	20	2
Braunwald class						
I/II/III						
I	6.2% (13/211)		2	5	4	2
II	8.7% (9/104)	0.1304	1	2	6	0
III	10.9% (56/512)		19	11	24	2
A/B/C						
A	13.9% (11/79)		6	0	5	0
B	8.7% (63/725)	0.1327	15	16	28	4
C	17.4% (4/23)		1	2	1	0

u-PCI, urgent PCI; u-CABG, urgent CABG. Other abbreviations as in Tables 2,6.

AMI–most of the sites (83%; 477/576) used invasive therapy as first-line treatment of AMI of both types (Fig 8).

Study 2: Case Report Investigation

The 20 randomly selected sites submitted case reports on 885 UA patients and 937 AMI patients.

Baseline characteristics of the UA patients were similar to those of the AMI patients with respect to sex, age, and concomitant disease. The median time from symptom onset to admission of the UA patients was 15.25 h, substantially longer than for the AMI patients. Among the UA patients, 62% were classified as Braunwald Class III. Among the AMI patients, 17% were diagnosed as non-ST-elevation AMI (Tables 2,3).

Among the UA patients, 92% underwent coronary angiography and 73% underwent coronary revascularization: percutaneous transluminal coronary angioplasty in 80%, coronary stenting in 63%, and CABG in 16%. The median time from admission to revascularization was 57 h for the UA patients, much longer than the 1.5 h for the AMI patients. A lower percentage of UA patients (68%) than AMI patients (82%) received continuous infusion of heparin (Tables 4,5).

Cardiac events occurred in 21 UA patients (2.0%) during

Table 9 Stratified Analysis of Cardiac Events According to Treatment of UA

	Cardiac events during initial 6 months (incidence)	χ^2 test p value	Details of events (cases)			
			Death	MI	u-PCI	u-CABG
Antianginal treatment						
Nitrates (po)						
No	9.3% (41/441)	0.8874	14	11	13	3
Yes	9.6% (37/386)		8	7	21	1
Nitrates (iv)						
No	8.6% (32/370)	0.4882	3	8	20	1
Yes	10.1% (46/457)		19	10	14	3
Nitrates (td)						
No	9.4% (64/678)	0.9869	18	16	27	3
Yes	9.4% (14/149)		4	2	7	1
Ca blocker (po)						
No	12.2% (52/425)	0.0046	19	11	21	1
Yes	6.5% (26/402)		3	7	13	3
Ca blocker (iv)						
No	9.6% (76/795)	0.5299	20	18	34	4
Yes	6.3% (2/32)		2	0	0	0
β-blocker						
No	9.1% (54/596)	0.5573	15	17	22	0
Yes	10.4% (24/231)		7	1	12	4
Heparin						
No	10.2% (26/255)	0.6155	6	6	14	0
Yes	9.1% (52/572)		16	12	20	4
Coronary angiography						
No	16.4% (11/67)	0.0413	6	1	2	2
Yes	8.8% (67/760)		16	17	32	2
Revascularization						
No	9.3% (19/204)	0.9470	9	4	3	3
Yes	9.5% (59/623)		13	14	31	1
PTCA						
No	9.4% (12/127)	0.9926	5	2	5	0
Yes	9.5% (47/496)		8	12	26	1
Stent						
No	10.0% (23/231)	0.7503	8	3	12	0
Yes	9.2% (36/392)		5	11	19	1
CABG						
No	9.7% (51/524)	0.6067	9	13	28	1
Yes	8.1% (8/99)		4	1	3	0
Time from admission (h)						
To coronary angiography						
<6	11.7% (23/196)	0.1032	7	4	12	0
≥6	7.9% (44/558)		9	13	20	2
To revascularization						
<6	11.1% (14/126)	0.4866	2	2	10	0
≥6	9.1% (44/485)		11	12	20	1
No. coronary vessels with significant stenosis						
0	0.0% (0/59)		0	0	0	0
1	7.8% (27/344)		3	9	14	1
2	11.1% (23/207)	0.0683	8	6	9	0
3	11.1% (18/162)		6	2	8	2
LMT	12.5% (2/16)		0	0	2	0
Stenosis (%) of culprit vessel before revascularization						
0	0.0% (0/41)		0	0	0	0
25	0.0% (0/4)		0	0	0	0
50	0.0% (0/6)		0	0	0	0
75	10.1% (7/69)	0.0244	2	1	4	0
90	7.6% (25/330)		5	6	14	0
99	8.9% (19/213)		5	7	6	1
100	18.1% (15/83)		4	3	7	1
Stenosis (%) of culprit vessel after revascularization						
0	4.8% (13/270)		2	5	5	1
25	11.9% (24/202)		4	7	13	0
50	23.3% (7/30)		1	0	6	0
75	0.0% (0/1)	<0.0001	0	0	0	0
90	50.0% (2/4)		1	0	1	0
99	50.0% (1/2)		1	0	0	0
100	60.0% (3/5)		0	0	3	0
TIMI flow grade past the culprit lesion before revascularization						
0	20.0% (14/70)		3	3	7	1
1	18.4% (7/38)	0.0002	1	2	4	0
2	8.4% (11/131)		3	4	3	1
3	6.1% (29/474)		6	8	15	0

TIMI flow grade past the culprit lesion after revascularization					
0	27.3% (3/11)	0.1856	0	3	0
1	0.0% (0/1)		0	0	0
2	0.0% (0/3)		0	0	0
3	8.8% (43/488)		13	22	1

Abbreviations as in Tables 2, 6, 8.

Table 10 Stratified Analysis of Cardiac Events by Treatment With Calcium-Channel Blockers in Patients With UA

	Incidence of cardiac events during initial 6 months		χ^2 test p value
	Treated	Not treated	
Diltiazem	8.44% (13/154)	9.66% (65/673)	0.6412
Amlodipine	5.88% (8/136)	10.13% (70/691)	0.1213
Nifedipine	8.11% (6/74)	9.56% (72/753)	0.6831

Abbreviation as in Table 2.

Table 11 Stratified Analysis of Cardiac Events by the Timing of Initial Calcium-Channel Blocker Treatment in Patients With UA

Incidence of cardiac events during initial 6 months		χ^2 test p value
Before onset of UA	After admission	
7.47% (13/174)	6.96% (11/157)	0.8706

Abbreviation as in Table 2.

Table 12 Stratified Analysis of Cardiac Events According to Baseline Characteristics in AMI

	Cardiac events during initial 6 months (incidence)	χ^2 test p value	Details of events (cases)				
			Death	MI	PIA	u-PCI	u-CABG
Sex, age							
M	13.1% (90/688)	0.0038	50	7	18	13	2
F	21.4% (42/196)		27	4	8	2	1
<65 years	9.3% (41/442)	<0.0001	18	4	10	9	0
≥65 years	20.6% (91/441)		59	7	16	6	3
Infarct region							
Infarct region							
Anterior	16.7% (71/425)	0.6351	46	7	10	6	2
Inferior	13.2% (43/326)		21	3	11	7	1
Lateral	12.0% (9/75)		7	0	1	1	0
Posterior	16.7% (8/48)		2	1	4	1	0
Other	11.1% (1/9)		1	0	0	0	0
Time from onset to admission							
Time from onset to admission (h)							
<6	13.6% (89/655)	0.0545	52	8	21	7	1
≥6	18.9% (43/228)		25	3	5	8	2
<12	15.1% (117/773)	0.6799	64	10	25	15	3
≥12	13.6% (15/110)		13	1	1	0	0
Previous disease							
Angina							
No	11.6% (64/550)	0.0005	41	5	12	5	1
Yes	20.2% (67/332)		35	6	14	10	2
MI							
No	13.2% (98/740)	0.0019	55	8	22	11	2
Yes	23.4% (33/141)		21	3	4	4	1
History of PCI							
No	14.3% (113/791)	0.1628	67	9	23	11	3
Yes	19.8% (18/91)		9	2	3	4	0
History of CABG							
No	14.7% (126/858)	0.4612	72	10	26	15	3
Yes	20.0% (5/25)		4	1	0	0	0
Concomitant disease							
Any disease below							
No	8.4% (11/131)	0.0230	6	0	3	2	0
Yes	16.1% (121/753)		71	11	23	13	3
Hypertension							
No	12.2% (49/402)	0.0366	29	5	9	6	0
Yes	17.2% (83/482)		48	6	17	9	3
Diabetes							
No	13.3% (79/592)	0.0593	46	3	21	6	3
Yes	18.2% (53/292)		31	8	5	9	0
Hyperlipidemia							
No	16.3% (90/552)	0.1399	58	6	16	9	1
Yes	12.7% (42/332)		19	5	10	6	2
Cerebrovascular disease							
No	14.5% (119/820)	0.2099	65	10	26	15	3
Yes	20.3% (13/64)		12	1	0	0	0

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)*		*15*	*3*	*15*	*7*	*1*
2	*16.5% (15/91)*	*<0.0001*	*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)*		*9*	*2*	*8*	*4*	*0*
2	*19.3% (17/88)*	*<0.0001*	*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*	*1*	*0*	*1*	*0*
Elevation	*14.0% (103/736)*	*0.1290*	*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).

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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)

Yoshiki Yui[a], Eiji Shinoda[b], Kazuhisa Kodama[c], Atsushi Hirayama[d], Hiroshi Nonogi[e], Kazuo Haze[f], Tetsuya Sumiyoshi[g], Saichi Hosoda[g] and Chuichi Kawai[h], and the Japan Multicenter Investigation for Cardiovascular Diseases B (JMIC-B) Study Group

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

[a]Kyoto University Hospital, Kyoto, [b]Rakuyo Hospital, Kyoto, [c]Amagasaki Central Hospital, Amagasaki, [d]Nihon University School of Medicine, Tokyo, [e]National Cardiovascular Center, Osaka, [f]Osaka City General Hospital, Osaka, [g]The Sakakibara Heart Institute, Tokyo and [h]Takeda General Hospital, Kyoto, Japan

Correspondence to Yoshiki Yui, MD, Department of Cardiovascular Medicine, Kyoto University Hospital, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
E-mail: yoshiki@kuhp.kyoto-u.ac.jp

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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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an equivalent inhibitory effect on the occurrence of cardiac events to that of ACE inhibitors in patients with hypertension and coronary artery disease [12].

In the nifedipine group, patients with a history of MI showed a significant reduction in angina pectoris requiring hospitalization compared with the ACE inhibitor group.

In the present substudy of data from JMIC-B patient background factors, coronary angiography (CAG) findings, and the results of quantitative coronary analysis (QCA) were examined to assess differences in the inhibitory effect of nifedipine and ACE inhibitors on angina pectoris requiring hospitalization in patients with a history of MI.

Materials and methods

The JMIC-B study was performed to investigate whether treatment with nifedipine retard was associated with a significantly higher incidence of cardiac events than ACE inhibitor therapy in hypertensive Japanese patients with coronary artery disease [12]. The incidence of cardiac events and the mortality rate did not differ between the nifedipine and ACE inhibitor groups. The study employed a prospective, randomized, open design, and involved 3 years of treatment with either nifedipine retard (nifedipine) or any ACE inhibitor. Statistical analysis was performed on all patients who were assigned to therapy (analysis on an intention-to-treat basis) [13].

Patients in the nifedipine group received nifedipine retard (a long-acting nifedipine formulation that is administered at a dose of 10–20 mg twice a day in Japan) for 3 years, whereas patients in the ACE inhibitor group received an ACE inhibitor (enalapril at 5–10 mg, imidapril at 5–10 mg, or lisinopril at 10–20 mg once a day as recommended in Japan) for 3 years.

Assessment of endpoints was performed by the endpoint committee in a blinded manner (i.e. events were assessed without any knowledge of the treatment to which the patients had been assigned). The primary endpoint of the study was the overall incidence of cardiac events, which were defined as: (i) cardiac death or sudden death; (ii) MI (initial and recurrent; detected by symptoms combined with Q waves, ST-segment elevation, or both on the electrocardiogram, and elevated levels of cardiac enzymes); (iii) angina pectoris requiring hospitalization; (iv) heart failure requiring hospitalization [dyspnoea or fatigue at rest or on minimal exertion (New York Heart Association class III or IV) and a left ventricular ejection fraction of less than 30%]; (v) serious arrhythmia (ventricular tachycardia, ventricular fibrillation); and (vi) performance of coronary intervention (percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, or stenting). Angina pectoris requiring hospitalization was diagnosed according to the following criteria and ischaemic changes on the electrocardiogram.

The onset of any of the following three symptoms within the previous 3–4 weeks was required.

New effort angina

Effort angina occurring for the first time or the recurrence of effort angina after an asymptomatic period of at least 6 months.

Change in pattern

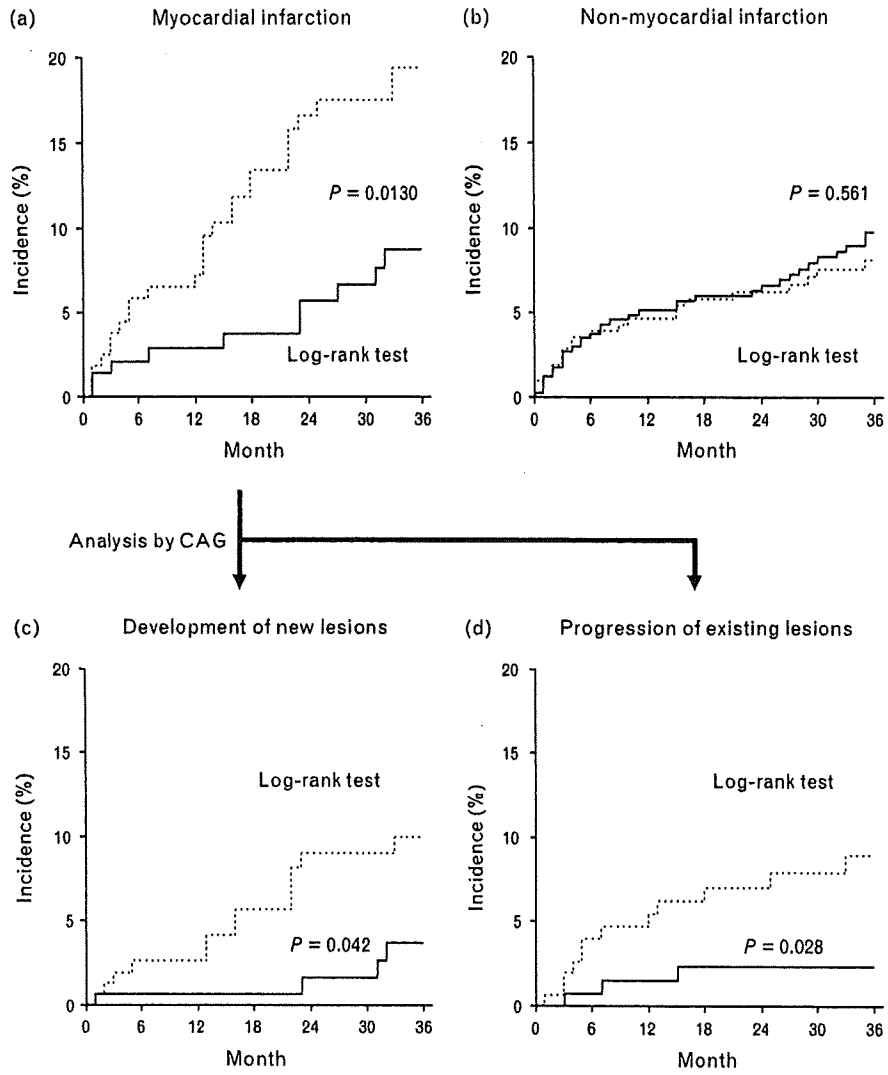
Stable effort angina that showed progression, resulting in an increased frequency of attacks, increased duration of attacks, or increased intensity of radiating pain. Moreover, angina was induced by less effort and nitroglycerin was not so effective.

New resting angina

New angina at rest that persisted for at least 15 min and was unresponsive to nitroglycerin, with ST-segment changes (elevation or depression) or inverted T waves being observed during an attack.

The relative risk and the 95% confidence interval were calculated using the Cox proportional hazard model, with the covariates of hyperlipidemia, smoker, concomitant use of α-blocker, achieved systolic blood pressure (SBP), and achieved diastolic blood pressure (DBP; Table 4). The Kaplan–Meier method was used to estimate the cumulative incidence of angina pectoris requiring hospitalization, the development of new coronary lesions, and the progression of existing lesions. The log-rank test was used for comparisons between the two treatment groups (Fig. 1). For the evaluation of coronary lesions, if organic stenosis of 75% or greater [American Heart Association (AHA) criteria] was revealed by CAG after the start of treatment, the endpoint committee classified this as the development of a new lesion or progression of an existing lesion based on comparison with the CAG findings before treatment. As shown in Table 1 and Fig. 1, in the MI group, 148 of 315 patients in the nifedipine group, and 170 of 381 patients in the ACE inhibitor group underwent CAG before the start of the study and 36 months after the start of treatment. These patients comprise all of those undergoing CAG. QCA was also performed using angiograms obtained before treatment and after 36 months of treatment. The QCA method has already been described in detail [14]. Table 5 and Table 6 show the results of QCA analysis recalculated using Shinoda *et al.* [14]. These patients were derived from patients for CAG analysis by AHA criteria. These were classified according to MI versus no MI and nifedipine versus ACE inhibitors, and were corrected by the background characteristics. If a cardiac event occurred during treatment that required percutaneous

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 1 Baseline clinical characteristics

		MI			Non-MI		
		Nifedipine 315 patients no. of patients (%)	ACE inhibitors 381 patients no. of patients (%)	*P* value	Nifedipine 513 patients no. of patients (%)	ACE inhibitors 441 patients no. of patients (%)	*P* value
Sex	Male/female	239 (75.8)/76 (24.2)	303 (79.5)/78 (20.5)	0.248	323 (63.0)/190 (37.0)	273 (61.9)/168 (38.1)	0.751
Age (years)		64 ± 9	64 ± 9	0.932	65 ± 8	65 ± 9	0.490
Risk factors	Hyperlipidemia	92 (29.2)	81 (21.3)	0.016	120 (23.4)	92 (20.9)	0.349
	Angina pectoris	148 (47.0)	170 (44.6)	0.533	418 (81.5)	337 (76.4)	0.055
	Diabetes mellitus	71 (22.5)	103 (27.0)	0.173	128 (25.0)	70 (15.9)	0.001
	Smoker	109 (34.6)	156 (40.9)	0.086	168 (32.8)	130 (29.5)	0.278
Number of diseased vessels (AHA ≥75%)	1-vessel	135 (42.9)	144 (37.8)	0.175	156 (30.4)	139 (31.5)	0.712
	2-vessel	66 (21.0)	86 (22.6)	0.607	94 (18.3)	57 (12.9)	0.023
	3-vessel	27 (8.6)	38 (10.0)	0.527	18 (3.5)	18 (4.1)	0.643
	Left main trunk	1 (0.3)	5 (1.3)	0.158	1 (0.2)	2 (0.5)	0.477
Body mass index (kg/m^2)		23.9 ± 2.9	24.1 ± 2.9	0.515	24.1 ± 3.0	24 ± 2.9	0.495

ACE, Angiotensin-converting enzyme; AHA, American Heart Association; MI, myocardial infarction. Chi-squared test.

Table 2 Concomitant drugs during the treatment period

	MI			Non-MI		
	Nifedipine 315 patients no. of patients (%)	ACE inhibitors 381 patients no. of patients (%)	*P* value	Nifedipine 513 patients no. of patients (%)	ACE inhibitors 441 patients no. of patients (%)	*P* value
Nitrates	261 (82.9)	304 (79.8)	0.303	326 (63.6)	263 (59.6)	0.215
α-Blocker	11 (3.5)	34 (8.9)	0.004	41 (8.0)	54 (12.2)	0.029
β-Blocker	80 (25.4)	96 (25.2)	0.952	125 (24.4)	96 (21.8)	0.343
Antiplatelet agents	244 (77.5)	303 (79.5)	0.509	282 (55.0)	240 (54.4)	0.865
Antihyperlipidemic agents	133 (42.2)	134 (35.2)	0.057	182 (35.5)	135 (30.6)	0.112
Diuretics	28 (8.9)	42 (11.0)	0.351	37 (7.2)	35 (7.9)	0.673

ACE, Angiotensin-converting enzyme; MI, myocardial infarction. Chi-squared test.

Results

Background factors

Of the 1650 patients enrolled in the JMIC-B study, 696 patients suffered from MI (nifedipine group 315, ACE inhibitor group 381) and 954 patients did not (nifedipine group 513, ACE inhibitor group 441). Table 1 shows the background factors of the MI and non-MI patients receiving each treatment. There was a difference between the two treatment groups with respect to the incidence of hyperlipidemia in MI patients, and there was also a difference between the two treatment groups with respect to the incidence of diabetes mellitus and the number of subjects with two-vessel disease among the patients without MI.

During the treatment period, the frequency of the concomitant use of α-blockers was significantly lower in the MI and non-MI patients from the nifedipine group, whereas no differences were seen with respect to the use of nitrates, β-blockers, antiplatelet agents, antihyperlipidemic agents, or diuretics (Table 2).

Blood pressure and heart rate

As shown in Table 3, the blood pressure at the start of the study showed no difference between the two treatment groups regardless of the history of MI.

Table 3 Blood pressure and heart rate

	Nifedipine	ACE inhibitors	*P* value
With previous MI			
Systolic blood pressure (mmHg)			
Baseline	142 (17)	140 (19)	0.108
Achieved	134 (13)	136 (16)	0.086
Change	−8	−4	0.002
Diastolic blood pressure (mmHg)			
Baseline	80 (11)	80 (12)	0.820
Achieved	76 (8)	78 (8)	0.003
Change	−4	−2	0.032
Heart rate (bpm)			
Baseline	72 (10)	71 (9)	0.138
Achieved	73 (11)	72 (10)	0.441
Change	+1	+1	0.642
Without previous MI			
Systolic blood pressure (mmHg)			
Baseline	150 (19)	150 (20)	0.960
Achieved	138 (14)	140 (15)	0.003
Change	−12	−10	0.034
Diastolic blood pressure (mmHg)			
Baseline	83 (12)	84 (12)	0.282
Achieved	77 (8)	79 (9)	<0.01
Change	−6	−5	0.138
Heart rate (bpm)			
Baseline	72 (10)	72 (10)	0.848
Achieved	72 (11)	70 (9)	0.045
Change	0	−2	0.015

ACE, Angiotensin-converting enzyme; MI, myocardial infarction. Achieved: mean blood pressure and heart rate during 6–36 months. Change: blood pressure and heart rate difference (achieved – baseline).

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).

Table 6 Changes in mean minimum lumen diameter and percentage diameter stenosis in myocardial infarction

Segments	Group	Baseline Mean (SD)	Follow-up LS-mean (SE)	Difference (Nifedipine-ACE inhibitors) Point estimate [95% CI]	P value
All segments					
MLD mm	Nifedipine ($n=38$)	2.13 (0.49)	2.19 (0.04)	0.10 [0.00, 0.20]	0.047
	ACE inhibitors ($n=49$)	2.24 (0.47)	2.09 (0.03)		
DS (%)	Nifedipine ($n=38$)	19.34 (5.59)	15.14 (0.82)	−3.28 [−5.49, −1.08]	0.004
	ACE inhibitors ($n=49$)	16.76 (5.07)	18.42 (0.72)		
Coronary lesion segments (%DS ≥ 21)					
MLD mm	Nifedipine ($n=38$)	1.63 (0.44)	2.08 (0.07)	0.18 [−0.06, 0.42]	0.139
	ACE inhibitors ($n=44$)	1.68 (0.42)	1.90 (0.09)		
DS (%)	Nifedipine ($n=38$)	31.79 (5.38)	18.73 (1.33)	−5.38 [−9.73, −1.02]	0.018
	ACE inhibitors ($n=44$)	31.70 (6.71)	24.11 (1.58)		

ACE, Angiotensin-converting enzyme; CI, confidence interval; DS, diameter stenosis; LS, least square; MLD, minimum lumen diameter. Comparison between two treatment groups by analysis of covariance using baseline MLD and concomitant use of α-blocker as covariates. Changes: (ΔMLD and Δ%DS).

significant decrease ($P=0.002$) was seen in some segments in the ACE inhibitor group. There was a significant difference of %DS ($P=0.001$) in the nifedipine group, but no change was seen in the ACE inhibitor group. A significant increase ($P=0.011$) in MLD and decrease in %DS at the coronary artery lesions (%DS ≥ 21%) occurred in the nifedipine group, but no such changes were seen in the ACE inhibitor group. As covariates for ANCOVA, baseline MLD, hyperlipidemia, smoker, concomitant use of α-blocker, achieved SBP, and achieved DBP were used. Among these, baseline MLD and concomitant α-blocker therapy were found to be significant. A significant difference in ΔMLD ($P=0.047$) was seen between the two treatment groups. A significant difference in Δ%DS ($P=0.004$) between the two groups was also noted for all segments (Table 6).

Among the non-MI patients, there were no differences in ΔMLD and Δ%DS for any of the segments or coronary lesions between the two treatment groups.

Discussion

The incidence of cardiac events was compared between nifedipine gastrointestinal system (GITS; once a day) and diuretics in patients with a history of MI by a subanalysis of the INSIGHT study [15]. It was found that the prophylactic effect of nifedipine GITS on cardiovascular events was similar to that of diuretics, suggesting that nifedipine was unlikely to worsen the prognosis of patients with a history of MI. In the present study, the overall incidence of cardiac events was also equal between the nifedipine group and the ACE inhibitor group, irrespective of the history of MI. The incidence of angina pectoris requiring hospitalization was, however, significantly lower in the nifedipine group than in the ACE inhibitor group for patients with a history of MI, suggesting that nifedipine may be more useful than ACE inhibitors for preventing angina pectoris requiring hospitalization in Japanese patients with MI.

This finding was considered to be possibly related to a differential effect on coronary atherosclerosis. Accordingly, the present substudy investigated whether the difference was ascribable to an antihypertensive effect or to other effects of the drugs.

The VALUE study [16] compared the influence of amlodipine and valsartan on the long-term prognosis of patients with hypertension, and found that the risk of cardiac events was equal for the two drugs, but amlodipine had a stronger antihypertensive effect and thus showed a stronger inhibitory effect on the onset of MI and angina pectoris requiring hospitalization. It was concluded that good control of hypertension was the most important factor for inhibiting the progression of ischaemic heart disease.

In the present study, the achieved SBP and achieved DBP were lower in the nifedipine group than in the ACE inhibitor group. Among the patients with previous MI, the incidence of angina pectoris requiring hospitalization was lower in the nifedipine group than in the ACE inhibitor group. This difference was presumably ascribable to differences in an antihypertensive effective or other effects of the drugs. The influence of achieved SBP and achieved DBP on the incidence of angina pectoris requiring hospitalization was not significant in the MI patients ($P=0.0541$ and 0.8547, respectively) according to the Cox proportional hazard model. There was also no significant influence of achieved SBP ($P=0.5365$) and achieved DBP ($P=0.3739$) when these were used as covariates for ANCOVA at the time of QCA analysis. Therefore, the present study suggested that differences between the two treatment groups were related to the influence of each therapy on coronary atherosclerosis. In the non-MI patients, the achieved SBP and achieved DBP were significantly lower in the nifedipine group, but there were no differences in the incidence of angina pectoris requiring hospitalization or the results of QCA analysis.

Nifedipine may have prevented angina pectoris requiring hospitalization better than ACE inhibitors in our patients with a history of MI because vasospasm is closely related

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 antiatherosclerotic 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

Steering committee: Kawai C. (Chairman), Yui Y., Hosoda S., Iimura O. (Hokkaido JR Sapporo Hospital), Ishii M. (Yokohama Seamen's Hospital), Saruta T. (Keio University Hospital), Arakawa K. (Fukuoka University Hospital), Shibata J. (Asahikawa City Hospital), Kanmatsuse K. (Nihon University School of Medicine), Motomiya T. (Ohmori Red Cross Hospital), Yabe Y., deceased (late of Toho University School of Medicine), Takatsu F. (Anjo Kosei Hospital), Haze K., Minamino T. (Sakurabashi Watanabe Hospital), and Satoh H. (Hiroshima Park Hill Hospital).

Endpoint committee: Kodama K., Hirayama A., Nonogi H., and Sumiyoshi T.

Quantitative coronary analysis committee: Shinoda E. and Yui Y.

Biostatistician: Origasa H. (University of Toyama School of Medicine).

Safety committee: Kato K. (the Cardiovascular Institute), Nakashima M. (Hamamatsu Institute of Clinical Pharmacology and Therapeutics).

Study secretaries: Hattori R. (Kinki University School of Medicine Nara Hospital) and Morishita H. (Morishita Cardiovascular Clinic).

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

Naoyuki Takashima, MD*; Keisuke Shioji, MD*; Yoshihiro Kokubo, MD**; Akira Okayama, MD**; Yoichi Goto, MD†; Hiroshi Nonogi, MD†; Naoharu Iwai, MD*,†

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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**Department of Epidemiology, **Department of Preventive Cardiology and †The Division of Cardiology, National Cardiovascular Center, Suita, Japan*

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Mailing address: Naoyuki Takashima, MD, Department of Epidemiology, Research Institute, National Cardiovascular Center, Suita 565-8565 Japan. E-mail: ntaka@ri.ncvc.go.jp

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)[9] 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[5] 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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