Table 4. Combined Effects of CRP and LVMI as Predictors of CVD Events

LVH and CRP	Crude		Risk factor–adjusted model#		
	HR (95% CI)	*p*	HR (95% CI)	χ^2	*p*
Non-LVH/CRP <1 mg/L	1 (reference)		1 (reference)		
Non-LVH/CRP ≥1 mg/L	1.63 (0.77–3.68)	0.199	1.40 (0.65–3.18)	0.772	0.380
LVH/CRP <1 mg/L	2.42 (1.42–4.98)	<0.001	2.212 (1.29–4.57)	9.166	0.003
LVH/CRP ≥1 mg/L	3.37 (1.99–6.90)	<0.001	2.648 (1.55–5.46)	15.095	<0.001

#Risk factor–adjusted model adjusts for the effects of age, sex, diabetes, systolic blood pressure, and HDL-chol. CRP, C-reactive protein; HR, hazard ratios; CI, confidence intervals; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; HDL, high-density lipoprotein.

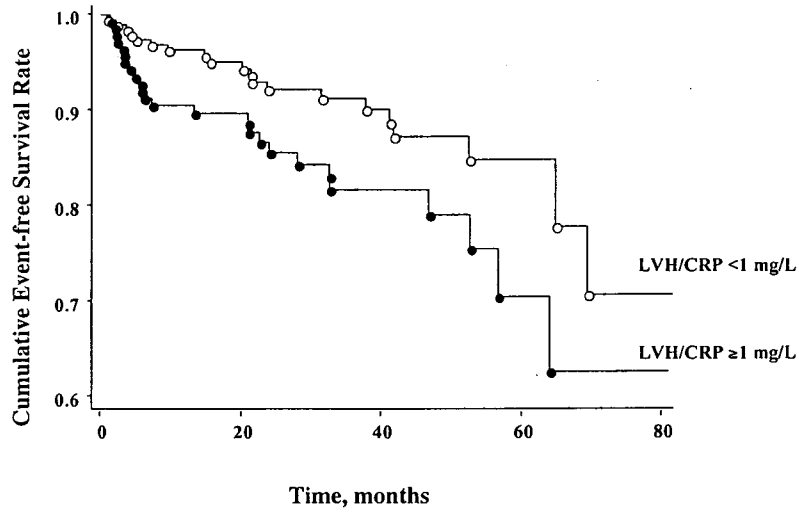


Fig. 3. *Kaplan-Meier survival curves for CVD events in the subgroup with LVH (n=362) (log-rank $\chi^2=5.13$, $p=0.024$).*

There was a linear increase in LVMI levels as the CRP categories increased; median LVMI levels for those with a CRP level of <1, 1 to 2, and >2 mg/L were 128.5, 133.9, and 139.7 in males, and 111.3, 125.1, and 121.8 g/m^2 in females, respectively (both, *p* for trend <0.01). Table 2 shows the crude mean levels and SEM ranges of echocardiographic parameters according to CRP category at enrollment. A similar linear increase in the levels of the S-D ratio and DcT, and decrease in the levels of the E-A ratio, were also seen as the levels of CRP category increased. Multivariate analysis including age, body mass index, diabetes, duration of hypertension, SBP and DBP, heart rate, total cholesterol, triglycerides, HDL-chol, and smoking status was performed, and indicated that the CRP category was independently associated with LVMI both in male (CRP [mg/L] <1: 127.2±2.9; 1–2: 138.7±4.1; >2: 141.8±3.5 g/m^2; $F=6.85$, $p=0.001$) and female subjects (CRP [mg/L] <1: 119.5±3.6; 1–2: 129.2±4.9; >2: 130.2±4.8 g/m^2; $F=4.23$, $p=0.031$). In addition, even after adjustment for taking antihyperlipidemia medication such as statins, fibrates, and niacin, and antihypertensive medication, increasing categories of CRP were still independent predictors of LVMI (male, $F=5.12$, $p=0.007$; female, $F=4.20$, $p=0.032$). To exclude the effect of drugs on CRP level, we further examined the association between CRP category and LVMI after excluding subjects receiving antihyperlipidemia medication (male, $n=233$; female, $n=209$). Even after excluding these subjects, increasing categories of CRP were significant predictors of LVMI in both male (CRP [mg/L] <1: 129.7±2.6; 1–2: 133.5±4.6; >2: 145.8±4.0 g/m^2 ($p<0.01$ *vs.* CRP<1 mg/L)) and female subjects (CRP [mg/L] <1: 116.2±2.8; 1–2: 124.9±5.5; >3: 127.8±5.8 g/m^2 ($p<0.01$ *vs.* CRP<1 mg/L)).

Predictive Value of CRP and LVMI for CVD

During the follow-up period, 52 patients (8.3%, 19 female) developed CVD. There were 27 subjects with CHF, 12 with stroke, 5 with myocardial infarction, and 2 with peripheral arterial occlusive disease, and 6 patients died of CVD causes. The CRP level and LVMI were significantly higher in patients who developed CVD during the follow-up period than in event-free subjects (CRP: 3.87±0.98 *vs.* 1.93±0.29 mg/L; LVMI: 156.4±4.7 *vs.* 125.2±1.4 g/m^2; $p<0.01$, respectively). The results of the life table analysis of CVD

events throughout the follow-up period according to the two groups on the basis of the CRP level (<1 or ≥1 mg/L) and the absence or presence of LVH are plotted in Figs. 1 and 2, respectively. These curves show significantly poorer event-free survival in the group with high CRP and that with LVH, respectively. A univariate Cox proportional-hazard model showed that high CRP (HR 1.51; 95% CI, 1.15–2.01; $p<0.01$) and LVH (HR 2.45; 95% CI, 1.66–3.96; $p<0.01$) were significant predictors of CVD events. Other variables in this study that significantly predicted CVD events included age (HR 1.04 for each 1 year increase; 95% CI: 1.01–1.07; $p<0.01$), sex (HR 1.40 for males; 95% CI: 1.06–1.88; $p<0.02$), diabetes (HR 1.61 for diabetes; 95% CI: 1.21–2.12; $p<0.01$), and SBP (HR 1.03 for each 1.0 mmHg increase; 95% CI: 1.01–1.04; $p<0.01$), and HDL-chol (HR 0.87 for each 10 mmol/L increase; 95% CI: 0.80–0.95; $p<0.01$).

Incidence of CVD Jointly with CRP and LVH

To assess the combined effects of CRP and LVH, we constructed survival curves after dividing the total subjects into four groups on the basis of CRP level (<1 or ≥1 mg/L) and the absence or presence of LVH: non-LVH/CRP <1, non-LVH/CRP ≥1, LVH/CRP <1, and LVH/CRP ≥1. The baseline clinical and biochemical characteristics of the study subjects are shown in Table 3. The group with LVH/CRP ≥1 showed a significantly higher prevalence of current smokers and diabetes, significantly lower HDL-chol and E-A ratio than that with LVH/ CRP <1. Kaplan-Meier curves in the four groups showed significantly poorer event-free survival in subjects with LVH/CRP ≥1 (log-rank $\chi^2=28.02$, $p<0.001$). In Cox regression analysis (Table 4), the risk for CVD was markedly increased in the group with LVH/CRP ≥1 (HR 3.37) compared with the non-LVH/CRP <1 group. In multivariate Cox regression analysis including age, sex, diabetes, SBP, and HDL-chol, the combination of LVH and CRP ≥1 mg/L was an independent predictor of CVD (HR 2.65).

When the analysis was restricted to the subgroup with LVH ($n=362$), 45 CVD events occurred during the follow-up period. Even in these subjects, the CRP level was significantly higher in patients who developed CVD during the follow-up period than in event-free subjects (3.82±0.92 *vs.* 2.02±0.35 mg/L, $p<0.01$). The results of the life table analysis of CVD throughout the follow-up period according to the two groups on the basis of CRP level (<1 or ≥1 mg/L) are plotted in Fig. 3, and these curves show significantly poorer event-free survival in the group with CRP ≥1 mg/L. In addition, in Cox regression analysis, CRP ≥1 mg/L was associated with a 1.37-fold higher risk of CVD events in the subgroup with LVH (HR 1.37; 95% CI: 1.02–1.85; $p=0.025$).

Discussion

Our cross-sectional study revealed a linear relationship between categories of CRP and LVMI, and the relationship was evident even after adjustment for confounding factors by multivariate analysis. In a follow-up study, both high CRP and LVH were significant determinants of CVD events, and the combination of elevated CRP and LVH was a powerful predictor for CVD events. In addition, the present study also demonstrated that, in patients with LVH, CRP had additive predictive value for CVD risk.

The present observation of an independent association between categories of CRP level and LVMI is consistent with previous findings (*15*, *19*), and the present study extended these observations for CRP to essential hypertension. A raised baseline CRP value has been associated with inflammation, endothelial dysfunction (*14*), obesity (*14*), the metabolic syndrome (*30*, *31*), diabetes mellitus (*32*), insulin resistance (*13*), and severity of hypertension (*33*), and thus, various metabolic disorders may occur with increasing CRP level, and simultaneously promote an increase in LV mass. On the other hand, local CRP synthesis and secretion by smooth muscle cells, including those of the human coronary artery, have been suggested (*34*). It is possible to speculate that CRP may play a more direct role in promoting LVH, including 1) increasing phosphatidylinositol-3 kinase activity (*35*); 2) upregulating inducible nitric oxide synthase, certain cell signal transduction pathways including the mitogen-activated protein kinase pathway, and nuclear factor κ-B; 3) upregulating angiotensin II type 1 receptor in vascular smooth muscle cells, and directly quenching the production of nitric oxide by endothelial cells (*2*, *4*), resulting in increased production of endothelin-1 (*34*, *36*); and 4) elevation of von Willebrand factor (*37*), which is known to be associated with endothelial dysfunction. Thus, cardiac hypertrophy may be, at least in part, attributable to an increase in CRP itself, *via* activated transcriptional regulatory mechanisms, proinflammatory and proatherogenic effects, and stimulation of endothelial dysfunction.

Previous studies have demonstrated that CRP evaluation adds prognostic value to metabolic syndrome (*38*), higher fibrinogen (*39*), or higher BP (*3*) in terms of CVD risk. The present prospective cohort of initially asymptomatic essential hypertensive patients revealed the importance of measuring CRP in addition to LVMI by echocardiography, and also showed that the combined evaluation of both CRP and LVMI was superior as a method of risk detection compared to measurement of either biologic marker alone. In addition, the present findings suggest that, in the presence of LVH, CRP adds important and independent prognostic information in terms of CVD risk. This result may have been due to the fact that our subjects with higher LVMI and CRP had more severe dyslipidemia, as well as a higher prevalence of current-smoking and diabetes, which are established risk factors for CVD. On the other hand, several mechanisms have been proposed to account for the association between CRP and CVD, including: 1) induction of loss of vasoreactivity, expression of adhesion molecules and secretion of chemoattractants in the endothelium; 2) increases in tissue factor secretion, promo-

tion of monocyte chemotaxis and adhesion to endothelial cells, reactive oxygen species release, matrix metalloproteinase-1 induction, and promotion of oxidized low-density lipoprotein uptake, which leads to increased foam cell formation; 3) increased expression of angiotensin II type 1 receptor mRNA and protein expression as well as increased vascular smooth muscle cell proliferation and migration; 4) binding of CRP to enzymatically modified low density lipoprotein, with the resulting complex showing increased ability to convert C3 and activate its complement (*34*, *36*); and 5) attenuation of the production of nitric oxide and prostacyclin by endothelial cells (*2*, *4*). Furthermore, our results showed that more severe impairment of relaxation was observed in subjects with high LVMI and high CRP, and this "impaired relaxation" is known to be associated with increased risk of CVD (*40*). In addition, a significant association between the categories of CRP and the E-A ratio, DcT, and S-D ratio, markers of relaxation impairment, was observed in this study, and a high CRP level may contribute to the progression of LV dysfunction. Consequently, we propose that, in subjects with LVH, activation of the renin-angiotensin system, activation of proatherogenic and proinflammatory responses in cardiovascular cells, and more impaired relaxation may occur with increasing CRP level, and enhance the risk for CVD.

It is not possible to conclude whether CRP stimulates higher LVMI or whether CRP is increased before the development of LVH. Indeed, it is possible that both these effects work in tandem in CVD. In addition, this study had missing baseline data and information on other potentially important characteristics, such as alcohol intake and physical activity, which are also associated with a lower CRP level. Finally, we did not account for the duration of hypertension prior to treatment at our institution. Because our data were obtained in subjects with already-treated essential hypertension at the start of the study, these results could underestimate the involvement of BP itself in the development of LVH and CVD events.

In conclusion, in essential hypertensive subjects initially free of CVD, CRP showed a significant association with LVMI. In those with LVH, the baseline CRP level added clinically relevant prognostic information concerning CVD risk. In hypertensive as well as LVH subjects, assessment of CRP levels may help to refine CVD risk stratification.

References

1. Ross R: Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999; **340**: 115–126.
2. Verma S, Wang CH, Li SH, *et al*: A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation* 2002; **106**: 913–919.
3. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM: C-reactive protein and the risk of developing hypertension. *JAMA* 2003; **290**: 2945–2951.
4. Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I: Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. *Circulation* 2002; **106**: 1439–1441.
5. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; **336**: 973–979.
6. Koenig W, Sund M, Frohlich M, *et al*: C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999; **99**: 237–242.
7. Danesh J, Whincup P, Walker M, *et al*: Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000; **321**: 199–204.
8. Ridker PM, Stampfer MJ, Rifai N: Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 2001; **285**: 2481–2485.
9. Rost NS, Wolf PA, Kase CS, *et al*: Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. *Stroke* 2001; **32**: 2575–2579.
10. Tracy RP, Lemaitre RN, Psaty BM, *et al*: Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* 1997; **17**: 1121–1127.
11. 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**: 1011–1053.
12. Pearson TA, Mensah GA, Alexander RW, *et al*: Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; **107**: 499–511.
13. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000; **102**: 42–47.
14. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW: C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; **19**: 972–978.
15. Kim BS, Jeon DS, Shin MJ, *et al*: Persistent elevation of C-reactive protein may predict cardiac hypertrophy and dysfunction in patients maintained on hemodialysis. *Am J Nephrol* 2005; **25**: 189–195.
16. Olsen MH, Christensen MK, Hansen TW, *et al*: High-sensitivity C-reactive protein is only weakly related to cardiovascular damage after adjustment for traditional cardiovascular risk factors. *J Hypertens* 2006; **24**: 655–661.
17. Conen D, Zeller A, Pfisterer M, Martina B: Usefulness of B-type natriuretic peptide and C-reactive protein in predicting the presence or absence of left ventricular hypertrophy in patients with systemic hypertension. *Am J Cardiol* 2006;

97: 249–252.
18. Palmieri V, Tracy RP, Roman MJ, *et al*: Relation of left ventricular hypertrophy to inflammation and albuminuria in adults with type 2 diabetes: the strong heart study. *Diabetes Care* 2003; **26**: 2764–2769.
19. Yasunari K, Maeda K, Watanabe T, Nakamura M, Yoshikawa J, Asada A: Comparative effects of valsartan *versus* amlodipine on left ventricular mass and reactive oxygen species formation by monocytes in hypertensive patients with left ventricular hypertrophy. *J Am Coll Cardiol* 2004; **43**: 2116–2123.
20. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003; **26** (Suppl 1): S5–S20.
21. Iwashima Y, Horio T, Kamide K, Rakugi H, Ogihara T, Kawano Y: Uric acid, left ventricular mass index, and risk of cardiovascular disease in essential hypertension. *Hypertension* 2006; **47**: 195–202.
22. Iwashima Y, Horio T, Takami Y, *et al*: Effects of the creation of arteriovenous fistula for hemodialysis on cardiac function and natriuretic peptide levels in CRF. *Am J Kidney Dis* 2002; **40**: 974–982.
23. Schiller NB, Shah PM, Crawford M, *et al*: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; **2**: 358–367.
24. Cooper JW, Nanda NC, Philpot EF, Fan P: Evaluation of valvular regurgitation by color Doppler. *J Am Soc Echocardiogr* 1989; **2**: 56–66.
25. Devereux RB, Alonso DR, Lutas EM, *et al*: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**: 450–458.
26. Basnight MA, Gonzalez MS, Kershenovich SC, Appleton CP: Pulmonary venous flow velocity: relation to hemodynamics, mitral flow velocity and left atrial volume, and ejection fraction. *J Am Soc Echocardiogr* 1991; **4**: 547–558.
27. McKee PA, Castelli WP, McNamara PM, Kannel WB: The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971; **285**: 1441–1446.
28. Mosterd A, Deckers JW, Hoes AW, *et al*: Classification of heart failure in population based research: an assessment of six heart failure scores. *Eur J Epidemiol* 1997; **13**: 491–502.
29. Hammond IW, Devereux RB, Alderman MH, *et al*: The prevalence and correlates of echocardiographic left ventricular hypertrophy among employed patients with uncomplicated hypertension. *J Am Coll Cardiol* 1986; **7**: 639–650.
30. Saijo Y, Yoshioka E, Fukui T, Kawaharada M, Kishi R: Metabolic syndrome, C-reactive protein and increased arterial stiffness in Japanese subjects. *Hypertens Res* 2006; **29**: 589–596.
31. Frohlich M, Imhof A, Berg G, *et al*: Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care* 2000; **23**: 1835–1839.
32. Ford ES: Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care* 1999; **22**: 1971–1977.
33. Blake GJ, Rifai N, Buring JE, Ridker PM: Blood pressure, C-reactive protein, and risk of future cardiovascular events. *Circulation* 2003; **108**: 2993–2999.
34. Jialal I, Devaraj S, Venugopal SK: C-reactive protein: risk marker or mediator in atherothrombosis? *Hypertension* 2004; **44**: 6–11.
35. Zhong W, Zen Q, Tebo J, Schlottmann K, Coggeshall M, Mortensen RF: Effect of human C-reactive protein on chemokine and chemotactic factor–induced neutrophil chemotaxis and signaling. *J Immunol* 1998; **161**: 2533–2540.
36. Mazer SP, Rabbani LE: Evidence for C-reactive protein's role in (CRP) vascular disease: atherothrombosis, immunoregulation and CRP. *J Thromb Thrombolysis* 2004; **17**: 95–105.
37. Bisoendial RJ, Kastelein JJ, Levels JH, *et al*: Activation of inflammation and coagulation after infusion of C-reactive protein in humans. *Circ Res* 2005; **96**: 714–716.
38. Ridker PM, Wilson PW, Grundy SM: Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation* 2004; **109**: 2818–2825.
39. Lowe GD, Sweetnam PM, Yarnell JW, *et al*: C-reactive protein, fibrin D-dimer, and risk of ischemic heart disease: the Caerphilly and Speedwell studies. *Arterioscler Thromb Vasc Biol* 2004; **24**: 1957–1962.
40. Schillaci G, Pasqualini L, Verdecchia P, *et al*: Prognostic significance of left ventricular diastolic dysfunction in essential hypertension. *J Am Coll Cardiol* 2002; **39**: 2005–2011.

Enhanced cardiac production of matrix metalloproteinase-2 and -9 and its attenuation associated with pravastatin treatment in patients with acute myocardial infarction

Satoshi YASUDA, Shunichi MIYAZAKI, Hideyuki KINOSHITA, Noritoshi NAGAYA, Munetake KANDA, Yoichi GOTO and Hiroshi NONOGI

Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan

ABSTRACT

Previous experimental studies have demonstrated that MMPs (matrix metalloproteinases) contribute to LV (left ventricular) remodelling. We hypothesized that cardiac MMPs are activated in patients with AMI (acute myocardial infarction) and, if so, MMP production may be attenuated by statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) through their cardiovascular protective actions. We studied 30 patients, ten control patients with stable angina pectoris and 20 patients with AMI, in whom LV catheterization at the chronic stage was performed 22 ± 12 days (value is mean ± S.D.) after the onset of AMI. Blood samples were collected from the CS (coronary sinus) and a peripheral artery. In patients with AMI, the levels of MMP-2 and MMP-9 were significantly ($P < 0.05$) higher in the CS than the peripheral artery (MMP-2, 853 ± 199 compared with 716 ± 127 ng/ml; MMP-9, 165 ± 129 compared with 98 ± 82 ng/ml), whereas no significant differences were observed in the patients with angina pectoris. The CS–arterial concentration gradients of MMP-2 and MMP-9 correlated positively with BNP (brain natriuretic peptide) levels (MMP-2, $R = 0.68$, $P < 0.01$; MMP-9, $R = 0.59$, $P < 0.05$) and LV end-diastolic volume index (MMP-2, $R = 0.70$, $P < 0.01$; MMP-9, $R = 0.70$, $P < 0.01$). When patients with AMI treated with 10 mg of pravastatin or without ($n = 10$ in each group) were compared, this statin therapy significantly ($P < 0.05$) decreased the CS–arterial concentration gradients of MMP-2 (69 ± 43 compared with 213 ± 185 ng/ml) and MMP-9 (14 ± 27 compared with 119 ± 84 ng/ml). In conclusion, the enhanced production of cardiac MMP-2 and MMP-9 is associated with LV enlargement and elevated BNP levels in patients with AMI. A pleiotropic effect of statins appears to be associated with the modulation of cardiac MMP activation, which may be potentially beneficial in the attenuation of post-infarction LV remodelling.

Key words: acute myocardial infarction, angina pectoris, brain natriuretic peptide (BNP), metalloproteinase (MMP), remodelling, statin, tissue inhibitor of metalloproteinases (TIMP).

Abbreviations: ACE-I, angiotension-converting enzyme inhibitor; AMI, acute myocardial infarction; Ang II, angiotensin II; AP, angina pectoris; BNP, brain natriuretic peptide; CK, creatine kinase; CRP, C-reactive protein; CS, coronary sinus; LDL, low-density lipoprotein; LV, left ventricular; LVEDVI, LV end-diastolic volume index; LVEF, LV ejection fraction; MMP, matrix metalloproteinase; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinases; WBC, white blood cell.

Correspondence: Dr Satoshi Yasuda, at the present address: Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aobaku, Sendai, 980-8574, Japan (email syasuda@cardio.med.tohoku.ac.jp).

INTRODUCTION

The loss of myocytes as a consequence of AMI (acute myocardial infarction) results in progressive changes in ventricular architecture [1,2]. This process, defined as post-infarction ventricular remodelling, is associated with a higher mortality and a higher incidence of complications, such as the development of heart failure, aneurysm formation and ventricular rupture [3,4]. During the remodelling process, as well as intrinsic changes in cardiac myocytes, it has been recognized that important alterations also occur within the extracellular matrix of the myocardium [5,6].

MMPs (matrix metalloproteinases) belong to a family of zinc-containing endoproteinases responsible for extracellular protein degradation, and are inhibited by specific tissue inhibitors [TIMP (tissue inhibitor of metalloproteinases)] [5,6]. In experimental myocardial infarction, MMPs are up-regulated in myocardial tissues, and are the driving force in extracellular matrix remodelling and infarct expansion [7,8]. Among the MMPs, the importance of MMP-9 during the processes of infarct healing and LV (left ventricular) remodelling has been demonstrated in previous studies using genetically modified mice [9,10]. Infarcted mice with the targeted deletion of MMP-9 had a decreased incidence of early myocardial rupture [9] and progressive LV dilation [10]. However, in the clinical setting, there has been little evidence regarding the production of MMPs in the infarcted human heart.

Statins have various cardiovascular protective actions, including anti-inflammatory and anti-apoptotic actions, independent of their effects on cholesterol levels. A study using a mouse AMI model demonstrated that statin treatment attenuated LV remodelling [11], which was associated with decreased MMP activity [12].

In the present study, we hypothesized that cardiac MMP activation may be associated with the degree of LV enlargement and the level of BNP (brain natriuretic peptide), a biochemical marker of post-infarction remodelling [13,14]. If so, MMP production may be attenuated by statin treatment in patients with AMI.

MATERIALS AND METHODS

Patients

This study included 30 male patients. All of the patients gave their written informed consent prior to participation in the study. The Institutional Ethical Committee on Human Research approved the study protocol. Patients with the following disorders were excluded from the study: prior myocardial infarction, and liver (elevated activities of aminotransferases), kidney (elevated level of creatinine or urea) or lung dysfunction (restrictive or obstructive pattern in spirometry).

The control group consisted of ten patients with stable AP (angina pectoris), who complained of symptoms consistent with Canadian Cardiovascular Society Classification of angina level I, II or III, with evidence of myocardial ischaemia. All of the control patients had no evidence of a previous AMI, and had severe coronary artery stenosis and therefore underwent coronary angioplasty (with adjunctive stenting in five patients). The treated sites were the left anterior descending artery in four patients (40 %), the right or left circumflex artery in four patients (40 %), and both the left anterior descending and right coronary arteries in two patients (20 %).

We also studied 20 patients with AMI who fulfilled the following criteria: typical chest pain >30 min of duration, ST segment elevation > 0.1 mV in two or more ECG leads with the subsequent evolution of a typical infarct pattern, and increased serum CK (creatine kinase) level. A total of 14 patients underwent PTCA (percutaneous transluminal coronary angioplasty) of the infarct-related artery (with adjunctive stenting in nine patients), and the remaining six patients received an intravenous administration of a tissue-type plasminogen activator and/or heparin in the acute phase. In all the patients, coronary angiography immediately after treatment showed a TIMI 3 grade flow in the infarct-related artery. The elapsed time to reperfusion was 4.6 h on average. The infarct sites were in the anterior wall in ten patients (50 %), the inferior wall in seven patients (35 %) and the postero-lateral wall in three patients (15 %). In this study, all of the patients with AMI were treated with the ACE-I (angiotension-converting enzyme inhibitor) enalapril (5 mg) after their hospital admission. Among them, ten patients with hyperlipidaemia (total cholesterol level > 220 mg/dl) were treated with 10 mg of pravastatin; the remaining ten patients did not have hyperlipidaemia and thus did not receive pravastatin. A recent Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial [14a] has shown a similar decrease in coronary artery disease incidence following treatment with 10–20 mg of pravastatin used in Asia to that observed for 20–40 mg doses used in Europe and the United States.

Cardiac catheterization and analysis of LV function

In patients with AMI, chronic-stage cardiac catheterization was repeated approx. 3–4 weeks after the onset of AMI. A 5 French multipurpose catheter (Cathex) was introduced into the CS (coronary sinus) through the left subclavian vein under fluoroscopic guidance [14]. The position of the catheter tip was confirmed by the injection of contrast medium. Blood samples were collected from the CS before the intravenous administration of heparin. Following the collection of blood samples from the right brachial artery (as peripheral blood samples) through a 6 French sheath, heparin was administered and coronary

angiography and left ventriculography were performed, according to the conventional Judkins' technique. LV pressure was measured using a 2 French high-fidelity micromanometer catheter (Miller Instruments) advanced into the left ventricle via the lumen of a 6 French pig-tail catheter. The restenosis of a treated artery was defined as an arterial narrowing of > 75 %, as determined by coronary angiography.

LV volume was evaluated angiographically by a cardiologist who was blinded to the results of the biochemical assays. Ventricular silhouettes in a 30° right anterior oblique projection were digitized using an ANCHOR ventriculography analysis system (Siemens-Elema). Using the area-length method, LV end-systolic volume index, LVEDVI (LV end-diastolic volume index) and LVEF (LV ejection fraction) were calculated.

Biochemical assessment

Blood samples were centrifuged and serum was stored at − 80 °C until assay. A sandwich enzyme immunoassay was performed to determine MMP-2 level (Fuji Chemical Industries) [15]. In addition, the level of MMP-9, another gelatinase-like MMP-2, and that of MMP-13, an interstitial collagenase, were analysed using MMP Biotrak enzyme-linked immunoadsorbent assay kits (Amersham Biosciences). The levels were back-calculated from the standard curve determined with the enzyme-linked immunoadsorbent assay kits using a 96-well microplate reader (Emax; Molecular Devices). These kits detect the pro-enzyme and the pro-enzyme complexed with TIMP. The detection limits were 0.5 ng/ml for MMP-2, 0.6 ng/ml for MMP-9 and 0.03 ng/ml for MMP-13.

We also measured levels of TIMP-1 (Fuji Chemical Industries) and TIMP-2 (Amersham Biosciences) using sandwich enzyme immunoassays [15]. The detection limits for TIMP-1 and TIMP-2 were 1.2 and 8.0 ng/ml respectively.

BNP was measured using specific immunoradiometric assay kits (Shionogi). The sensitivity of these kits was 2 pg/ml. Ang II (angiotensin II) and TGF-β (transforming growth factor-β) levels were also measured, as reported previously [16].

The serum CRP (C-reactive protein) level was measured by N Latex CRP II monoassay using a nephelometric analyser (BN II; Dade Behring). The lower detection limit of this test was 0.06 mg/dl. Total cholesterol, triacylglycerol (triglyceride) and HDL (high-density lipoprotein) cholesterol concentrations were determined by enzymatic methods using a Toshiba TBA 80M analyser. LDL (low-density lipoprotein) was calculated using Fredewald's formula. We also measured WBC (white blood cell) number.

Statistical analysis

The two groups were compared by Student's t test. Measurements from the CS and the peripheral artery were compared within a group by ANOVA. When a significant difference among groups was indicated by the initial analysis, individual paired comparisons were determined using the Student–Newman–Keuls method. A linear regression line was calculated by the least-square method to assess the correlation between two parameters. To investigate independent predictors, we used multivariate logistic regression analysis. In all cases, differences were considered significant at $P < 0.05$. Results are presented as means ± S.D., or medians.

Table 1 Clinical characteristics

*$P = 0.05$ and **$P < 0.01$ compared with control (patients with stable AP).

Characteristic	Patients with AMI ($n = 20$)	Patients with stable AP ($n = 10$)
Age (years)	66 ± 9	67 ± 6
Peak CK (units/l)	1986 (801–8574)	–
Cardiac function		
LVEF (%)	48 ± 7**	58 ± 7
LVEDVI (ml/m^2)	95 ± 18**	55 ± 21
Vessels > 75 % stenosed (n)	1.5 ± 0.7	1.6 ± 0.7
Risk factors (n)		
Hypertension	11 (55 %)	7 (70 %)
Diabetes mellitus	15 (75 %)	6 (60 %)
Hyperlipidaemia	10 (50 %)	6 (60 %)
Smoking	12 (60 %)	6 (60 %)
Biochemical parameters†		
Total cholesterol (mg/dl)	193 ± 27	198 ± 20
LDL (mg/dl)	120 ± 30	122 ± 31
WBC count (cells/μl)	6615 ± 1571	5600 ± 1063
CRP (mg/dl)	0.34 ± 0.33*	0.13 ± 0.06
Medication used (n)		
ACE-I	20 (100 %)	4 (40 %)
β-Blockers	11 (55 %)	6 (60 %)
Statins	10 (50 %)	6 (60 %)
Calcium antagonists	7 (35 %)	5 (50 %)
Nitrates	4 (20 %)	2 (20 %)
Aspirin	20 (100 %)	10 (100 %)

† Data obtained on the day when cardiac catheterization was performed.

RESULTS

The baseline clinical characteristics of the patients with AMI and the control patients with AP (without evidence of AMI) are summarized in Table 1. In the patients with AMI, cardiac function data were obtained at chronic-stage cardiac catheterization performed 22 ± 12 days after the onset of AMI. Coronary angiography revealed 90 % stenosis of the infarct-related artery in two patients and 100 % stenosis in three patients. These five patients with restenosis had received intravenous thrombolysis alone in the acute stage. In the remaining 15 patients, the treated

Table 2 Comparisons of BNP, MMP and TIMP levels in the CS and peripheral artery

*$P < 0.05$ compared with levels in artery; †$P < 0.05$ compared with control (patients with stable AP).

	Patients with AMI ($n = 20$)		Patients with stable AP ($n = 10$)	
Peptide	CS	Artery	CS	Artery
BNP (pg/ml)	400 ± 376*†	126 ± 176	54 ± 25	52 ± 25
MMP-2 (ng/ml)	853 ± 199*†	716 ± 127	631 ± 44	630 ± 46
MMP-9 (ng/ml)	165 ± 129*†	98 ± 82	68 ± 25	71 ± 24
MMP-13 (ng/ml)	0.05 ± 0.04	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.02
TIMP-1 (ng/ml)	155 ± 59	150 ± 53	130 ± 33	134 ± 32
TIMP-2 (ng/ml)	112 ± 18	108 ± 14	94 ± 11	97 ± 16

sites remained patent. With the exception of cardiac function (LVEF and LVEDVI) and the prevalence of ACE-I use, clinical characteristics were similar between patients with AMI and AP.

Enhancement of cardiac MMP production in patients with AMI

Table 2 shows the comparison of BNP, MMP and TIMP levels between blood samples from the CS and peripheral artery. In patients with AMI, levels of BNP, MMP-2 and MMP-9 were significantly ($P < 0.05$) higher in the CS than in the peripheral artery, whereas the levels of MMP-13, TIMP-1 and TIMP-2 were similar. In control patients with AP, no significant differences in the levels of BNP, MMPs and TIMPs were observed between the CS and peripheral artery. These findings indicate that the production of MMP-2 and MMP-9, as well as that of BNP, is enhanced in an infarcted heart.

Correlation of cardiac MMP production with post-infarction LV remodelling

In patients with AMI, the CS–arterial concentration gradients of MMP-2 and MMP-9 correlated positively with those of BNP and LVEDVI respectively (Figure 1), but not with LVEF, peak CK level and circulating WBC counts. These myocardial gradients were not different between patients with and without progression to restenosis (MMP-2, 87 ± 32 compared with 152 ± 173 ng/ml; MMP-9, 83 ± 86 compared with 61 ± 82 ng/ml).

Comparisons between pravastatin-treated patients with AMI and non-pravastatin-treated patients with AMI

We then compared levels of MMPs between ten patients treated with 10 mg of pravastatin and ten patients not treated with pravastatin (Table 3). Although the total cholesterol level before treatment was higher ($P < 0.05$) in the pravastatin-treated patients with AMI (223 ± 7 mg/dl in treated patients compared with 195 ± 17 mg/dl in

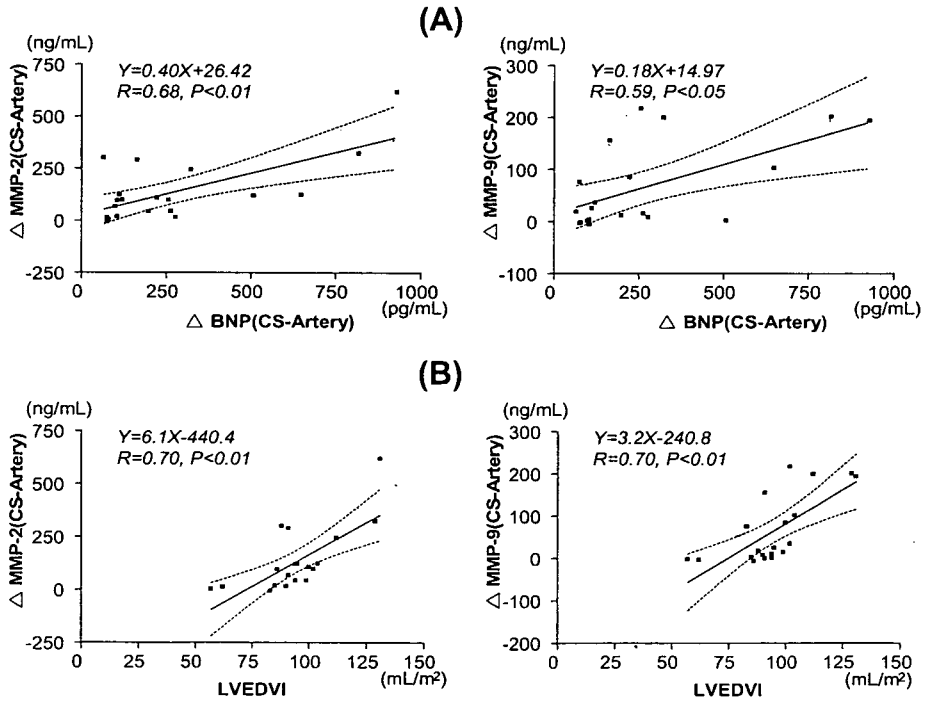


Figure 1 Correlations between CS–arterial concentration gradients of MMP-2 and -9 and BNP (A) and LVEDVI (B) in 20 patients with AMI

non-treated patients), no significant differences were observed after treatment between the two groups (183 ± 31 mg/dl in treated patients compared with 201 ± 20 mg/dl in non-treated patients). Levels of CRP (0.18 ± 0.13 mg/dl in treated patients compared with 0.50 ± 0.40 mg/dl in non-treated patients; $P = 0.03$) and the CS–arterial concentration gradients of MMP-2 and MMP-9 (Table 3) were significantly different between the two groups. However, the concentration gradients of TGF-β and Ang-II were similar between patients treated with pravastatin and those not treated (Ang-II, 19.5 ± 20.2 compared with 36.9 ± 32.4 pg/ml respectively; TGF-β, 1.2 ± 3.3 compared with 2.1 ± 4.7 pg/ml respectively).

We then performed multivariate analysis for the predictors of CS–arterial concentration gradients of MMP levels, including age, sex, coronary risk factors, peak CK, infarct site (anterior wall), CRP, TIMP, pravastatin treatment, LVEF and LVEDVI. The association between pravastatin treatment and cardiac MMP-2 production was modest, with an odds ratio of 0.074 (95 % confidence interval, 0.005–1.109; $P = 0.06$), and did not reach statistical significance.

DISCUSSION

The major findings of the present clinical study are that after AMI, the cardiac production of MMP-2 and MMP-9 is enhanced and associated with LV enlargement and BNP secretion, and that the pleiotropic effect of statins appears to be associated with the modulation of cardiac MMP activation.

Among the MMP species, MMP-2 and MMP-9 play an important role in LV remodelling, as these MMPs are activated in the myocardium and it has been reported that the targeted deletion of these MMPs prevents post-infarction cardiac dysfunction and rupture [9,10]. In the clinical setting, circulating MMP-2 and MMP-9 levels have been measured in previous studies of patients with AMI [17–19]; however, these results were conflicting. Squire et al. [17] reported that circulating MMP levels were inversely correlated with LV dilatation, whereas Matsunage et al. [18] and Nakaya et al. [19] found that serum MMP levels and activity were positively correlated with LV dilatation. In addition, circulating MMP levels could be affected at the acute stage following reperfusion therapy and by the clinically vulnerable state [20–23]. In the present study, we focused on cardiac production of MMP [14], and the measurement was performed at the clinically stable stage following AMI. As shown in Table 2, despite similar levels of TIMPs, significant differences in levels of BNP, MMP-2 and MMP-9 were observed between the CS and the peripheral artery in patients with AMI. To our knowledge, this is the first study demonstrating the enhanced production of MMP-2 and MMP-9 in a human infarcted heart. Moreover, as shown

Table 3 Comparisons of MMPs between pravastatin-treated and non-pravastatin-treated patients

*$P < 0.05$ compared with levels in artery; †$P < 0.05$ compared with levels in non-pravastatin-treated patients. CS–artery, CS–arterial concentration gradient.

	Patients with AMI						Patients with stable AP					
	Pravastatin-treated ($n = 10$)			Non-pravastatin-treated ($n = 10$)			Pravastatin-treated ($n = 6$)			Non-pravastatin-treated ($n = 4$)		
MMP (ng/ml)	CS	Artery	CS–artery	CS	Artery	CS–artery	CS	Artery	CS–artery	CS	Artery	CS–artery
MMP-2	808 ± 182	739 ± 158	69 ± 43†	897 ± 216*	684 ± 84	213 ± 185	631 ± 53	624 ± 51	7 ± 23	629 ± 32	639 ± 43	−9 ± 53
MMP-9	94 ± 61†	80 ± 59	14 ± 27†	236 ± 142*	117 ± 100	119 ± 84	68 ± 20	72 ± 16	−4 ± 4	68 ± 20	69 ± 29	0 ± 5
MMP-13	0.06 ± 0.06	0.03 ± 0.03	0.03 ± 0.06	0.03 ± 0.02	0.05 ± 0.03	−0.01 ± 0.03	0.03 ± 0.04	0.04 ± 0.02	−0.01 ± 0.01	0.04 ± 0.02	0.03 ± 0.02	0.01 ± 0.03

in Figure 1, the CS–arterial concentration gradients of MMP-2 and MMP-9 correlated positively with those of BNP and LVEDVI. Taking into account the delicate balance between MMPs and TIMPs in tissue remodelling, the present findings indicate that excessive cardiac production of MMPs may play an important pathological role in the progression of post-infarction LV dysfunction.

A previous experimental study of an AMI model using BNP-transgenic mice demonstrated a potential interaction of BNP with inflammation [24]. The overexpression of BNP leads to neutrophil infiltration and MMP-9 expression in the infarct region and increases the incidence of cardiac rupture. These findings suggest the significance of inflammatory reaction in the heart accompanied by changes in LV function. 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors, such as statins, exert various cardiovascular protective effects beyond their lipid-level lowering actions [12,25]. These pleiotropic effects include the inhibition of inflammatory responses. In the present study, we have shown that the CS–arterial concentration gradients of MMP-2 and MMP-9 were smaller in the pravastatin-treated group than in the non-pravastatin-treated group, which was accompanied by a decrease in CRP level. These findings indicate that pravastatin may modulate cardiac MMP production in patients with AMI, probably via its anti-inflammatory effects. Similar observations of decreased circulating MMP-2 levels in patients with AMI treated with 10 mg of paravastain have been reported previously [19].

There are several potential limitations of the present study. First, this study was not randomized. Pravastatin was administered to a small number of patients with AMI with hyperlipidaemia. In such a pro-inflammatory state, tissue MMPs might have been activated before treatment [26], which could affect the results. Therefore prospective studies will be required to determine if pravastatin has a causal role in reducing cardiac MMP production in patients with AMI. Secondly, the present study was carried out over the short term, whereas ventricular remodelling is known to progress over months or years. Thirdly, previous studies have shown that the renin–angiotensin system is also involved in the induction of post-infarction ventricular remodelling [27] and can be inhibited by statins [28,29]. However, we have shown that the CS–arterial concentration gradients of Ang II were similar between pravastatin-treated patients and non-pravastatin-treated patients. This may be related, in part, to the fact that all our patients with AMI had been treated with 5 mg of enalapril.

In conclusion, the present study demonstrates the enhancement of MMP production in an infarcted heart. Pleiotropic effects of statins may be associated with the modulation of cardiac MMP activation, which is potentially beneficial in the attenuation of post-infarction LV remodelling.

REFERENCES

1 Sutton, M. G. and Sharpe, N. (2000) Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 101, 2981–2988
2 Yousef, Z. R., Redwood, S. R. and Marber, M. S. (2000) Postinfarction left ventricular remodelling: where are the theories and trials leading us? Heart 83, 76–80
3 White, H. D., Norris, R. M., Brown, M. A., Brandt, P. W., Whitlock, R. M. and Wild, C. J. (1987) Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 76, 44–51
4 Weisman, H. F. and Healy, B. (1987) Myocardial infarct expansion, infarct extension, and reinfarction: pathophysiologic concepts. Prog. Cardiovasc. Dis. 30, 73–110
5 Creemers, E. E., Cleutjens, J. P., Smits, J. F. and Daemen, M. J. (2001) Matrix metalloproteinase inhibition after myocardial infarction: a new approach to prevent heart failure? Circ. Res. 89, 201–210
6 Spinale, F. G. (2002) Matrix metalloproteinases: regulation and dysregulation in the failing heart. Circ. Res. 90, 520–530
7 Cleutjens, J. P., Kandala, J. C., Guarda, E., Guntaka, R. V. and Weber, K. T. (1995) Regulation of collagen degradation in the rat myocardium after infarction. J. Mol. Cell. Cardiol. 27, 1281–1292
8 Rohde, L. E., Ducharme, A., Arroyo, L. H. et al. (1999) Matrix metalloproteinase inhibition attenuates early left ventricular enlargement after experimental myocardial infarction in mice. Circulation 99, 3063–3070
9 Heymans, S., Luttun, A., Nuyens, D. et al. (1999) Inhibition of plasminogen activators or matrix metalloproteinases prevents cardiac rupture but impairs therapeutic angiogenesis and causes cardiac failure. Nat. Med. 5, 1135–1142
10 Ducharme, A., Frantz, S., Aikawa, M. et al. (2000) Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction. J. Clin. Invest. 106, 55–62
11 Nahrendorf, M., Hu, K., Hiller, K. H. et al. (2002) Impact of hydroxymethylglutaryl coenzyme a reductase inhibition on left ventricular remodeling after myocardial infarction: an experimental serial cardiac magnetic resonance imaging study. J. Am. Coll. Cardiol. 40, 1695–1700
12 Hayashidani, S., Tsutsui, H., Shiomi, T. et al. (2002) Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. Circulation 105, 868–873
13 Nagaya, N., Nishikimi, T., Goto, Y. et al. (1998) Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. Am. Heart J. 135, 21–28
14 Yasuda, S., Goto, Y., Baba, T. et al. (2000) Enhanced secretion of cardiac hepatocyte growth factor from an infarct region is associated with less severe ventricular enlargement and improved cardiac function. J. Am. Coll. Cardiol. 36, 115–121
14a Nakamura, H., Arakawa, K., Itakura, H. et al. (2006) Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA study): a prospective randomised control trial. Lancet 368, 1155–1163
15 Fujimoto, N. and Iwata, K. (2001) Use of EIA to measure MMPs and TIMPs. Methods Mol. Biol. 151, 347–358
16 Yasuda, S., Goto, Y., Sumida, H. et al. (1999) Angiotensin-converting enzyme inhibition restores hepatocyte growth factor production in patients with congestive heart failure. Hypertension 33, 1374–1378
17 Squire, I. B., Evans, J., Ng, L. L., Loftus, I. M. and Thompson, M. M. (2004) Plasma MMP-9 and MMP-2 following acute myocardial infarction in man: correlation with echocardiographic and neurohumoral parameters of left ventricular dysfunction. J. Card. Failure 10, 328–333

18 Matsunaga, T., Abe, N., Kameda, K. et al. (2005) Circulating level of gelatinase activity predicts ventricular remodeling in patients with acute myocardial infarction. Int. J. Cardiol. **105**, 203–208
19 Nakaya, R., Uzui, H., Shimizu, H. et al. (2005) Pravastatin suppresses the increase in matrix metalloproteinase-2 levels after acute myocardial infarction. Int. J. Cardiol. **105**, 67–73
20 Wagner, D. R., Delagardelle, C., Ernens, I., Rouy, D., Vaillant, M. and Beissel, J. (2006) Matrix metalloproteinase-9 is a marker of heart failure after acute myocardial infarction. J. Card. Failure **12**, 66–72
21 Higo, S., Uematsu, M., Yamagishi, M. et al. (2005) Elevation of plasma matrix metalloproteinase-9 in the culprit coronary artery in patients with acute myocardial infarction: clinical evidence from distal protection. Circ. J. **69**, 1180–1185
22 Kai, H., Ikeda, H., Yasukawa, H. et al. (1998) Peripheral blood levels of matrix metalloproteases-2 and -9 are elevated in patients with acute coronary syndromes. J. Am. Coll. Cardiol. **32**, 368–372
23 Fukuda, D., Shimada, K., Tanaka, A. et al. (2006) Comparison of levels of serum matrix metalloproteinase-9 in patients with acute myocardial infarction versus unstable angina pectoris versus stable angina pectoris. Am. J. Cardiol. **97**, 175–180
24 Kawakami, R., Saito, Y., Kishimoto, I. et al. (2004) Overexpression of brain natriuretic peptide facilitates neutrophil infiltration and cardiac matrix metalloproteinase-9 expression after acute myocardial infarction. Circulation **110**, 3306–3312
25 Davignon, J. (2004) Beneficial cardiovascular pleiotropic effects of statins. Circulation **109**, III39–III43
26 El Messal, M., Beaudeux, J. L., Drissi, A. et al. (2005) Elevated serum levels of proinflammatory cytokines and biomarkers of matrix remodeling in never-treated patients with familial hypercholesterolemia. Clin. Chim. Acta **366**, 185–189
27 Bader, M. (2002) Role of the local renin-angiotensin system in cardiac damage: a minireview focusing on transgenic animal models. J. Mol. Cell. Cardiol. **34**, 1455–1462
28 Dechend, R., Fiebler, A., Lindschau, C. et al. (2001) Modulating angiotensin II-induced inflammation by HMG Co-A reductase inhibition. Am. J. Hypertens. **14**, 55S–61S
29 Luo, J. D., Zhang, W. W., Zhang, G. P., Guan, J. X. and Chen, X. (1999) Simvastatin inhibits cardiac hypertrophy and angiotensin-converting enzyme activity in rats with aortic stenosis. Clin. Exp. Pharmacol. Physiol. **26**, 903–908

Received 10 May 2006/24 August 2006; accepted 29 August 2006
Published as Immediate Publication 29 August 2006, doi: 10.1042/CS20060110

Circ J 2007; **71**: 1335–1347

Unstable Angina and Non-ST Elevation Acute Coronary Syndrome

— Epidemiology and Current Management in Japan (Japan Multicenter Investigation for Cardiovascular Disease-D (JMIC-D) Committee) —

Yoshiki Yui, MD; Atsushi Hirayama, MD*; Hiroshi Nonogi, MD**; Kazuo Kimura, MD†; Kazuhisa Kodama, MD††; Saichi Hosoda, MD§; Chuichi Kawai, MD§§

Background A multicenter study was conducted to assess the current medical management of unstable angina (UA) and non-ST-elevation acute coronary syndrome in Japan.

Methods and Results This study presents the results of a nationwide questionnaire survey of 770 sites and a case report investigation performed at 20 sites. The questionnaire survey revealed that the number of acute myocardial infarction (AMI) patients treated annually was 1.56-fold greater than the number of UA patients. Non-ST-elevation AMI accounted for 17% of all patients with AMI. Analysis of case reports for 885 UA patients showed extensive use of invasive treatment. In the UA patients, the cumulative incidence of a composite endpoint (all-cause mortality, AMI, and urgent coronary revascularization) was 2% at 1 month and 9% at 6 months. Stratified analysis with respect to the composite endpoint through 6 months showed a significantly lower incidence in patients treated with a calcium-channel blocker than in patients not treated with a calcium-channel blocker.

Conclusions In Japan, fewer patients are hospitalized annually for treatment of UA than for AMI. The largest percentage of UA patients had Braunwald class III disease. Non-ST-elevation AMI is managed in Japan according to the principle of early invasive treatment, resembling the treatment for ST-elevation AMI. The outcome of treatment is better for Japanese UA patients than for Japanese AMI patients. (*Circ J* 2007; **71**: 1335–1347)

Key Words: Acute coronary syndromes; Epidemiology; Non-ST elevation; Unstable angina

According to the Population and Vital Statistics of Japan for 2003, heart disease is the second leading cause of death, and ischemic heart disease, including acute myocardial infarction (AMI), is the most frequent cause of cardiac death[1] If the aging of society continues, mortality from ischemic heart disease will increase further, so more effort should be made to improve treatment.

In 2002, the Japanese Circulation Society established guidelines for the diagnosis and treatment of acute coronary syndrome (ACS), but most of the clinical data used as the basis for the guidelines was gathered overseas[2] Because of differences in the pathophysiology of ACS between Japanese and Caucasians[3] the Japanese ACS guideline should be based on data obtained from Japanese patients.

Several multicenter studies on the treatment of AMI have already been conducted in Japan[4] but there have been few studies of unstable angina (UA). According to recent recommendations for treatment of ACS made by the Japanese Circulation Society, as well as the relevant American and European societies, the treatment of individual patients should not be based on diagnoses such as AMI or UA, but on whether ST changes are found on admission[2,5] In Japan, none of the multicenter studies has compared baseline characteristics, treatment, and outcomes in patients with ST-elevation and non-ST-elevation ACS, except for a few single-center studies[6,7]

Accordingly, we launched the Japan Multicenter Investigation for Cardiovascular Disease-D (JMIC-D) to investigate the number of patients with UA and non-ST-elevation ACS and the current management practices for both disease manifestations in Japan, with the aim of using the results to optimize specific therapeutic recommendations.

Methods

This study comprised a questionnaire survey (study 1) and a case report investigation (study 2). The questionnaire survey was designed to investigate the number of hospitalized patients with UA or AMI, and the treatment policies for these conditions at the participating sites. The case report investigation was designed to obtain detailed treatment and outcome data for individual patients. All statistical tests were 2-sided with an α=0.05 significance level. Between-group comparisons were tested using chi-square tests or Fisher's exact test where appropriate. In this study,

(Received November 30, 2006; revised manuscript received May 1, 2007; accepted May 23, 2007)

*Department of Cardiovascular Medicine, Kyoto University Hospital, Kyoto, *Nihon University Hospital, Tokyo, **National Cardiovascular Center, Suita, †Yokohama City University Medical Center, Yokohama, ††Amagasaki Central Hospital, Amagasaki, §The Sakakibara Heart Institute, Tokyo and §§Takeda General Hospital, Kyoto, Japan*

Mailing address: Yoshiki Yui, MD, Department of Cardiovascular Medicine, Kyoto University Hospital, 54 Kawahara-cho, Shougoin, Sakyou-ku, Kyoto 606-8397, Japan. E-mail: yoshiki@kuhp.kyoto-u.ac.jp

Table 1 Clinical Sites and Principal Investigators

1. Asahikawa City Hospital	*Kunihiko Hirasawa*
2. Sendai Cardiovascular Center	*Shunsuke Tanino (Moved to Tanino Naika Junkannki Clinic)*
3. Jichi Medical School Omiya Medical Center	*Muneyasu Saito (Changes to Saitama kinen Hosipital)*
4. Sekishinkai Sayama Hospital	*Masami Sakurada (Moved to Tokorozawa Heart Clinic)*
5. Nippon Medical School Hospital	*Teruo Takano, Keiji Tanaka*
6. Nippon Medical School Chiba Hokusoh Hospital	*Kyouichi Mizuno*
7. Yokohama Rosai Hospital	*Kenichi Katoh*
8. Yokohama City University Medical Center	*Kazuo Kimura*
9. Toyohashi Heart Center	*Shigenori Ito (Moved to Moriyama Municipal Hospital, City of Nagoya)*
10. Nagoya Daini Red Cross Hospital	*Haruo Hirayama*
11. National Cardiovascular Center	*Hiroshi Nonogi*
12. Kansai Rosai Hospital	*Shinsuke Nanto*
13. Osaka Police Hospital	*Kazuhisa Kodama, Atsushi Hirayama*
14. Osaka City Central Hospital	*Kazuo Haze*
15. Sakurabashi Watanabe Hospital	*Kenshi Fujii*
16. Osaka Koseinenkin Hospital	*Tatsuya Sasaki*
17. Matsushita Memorial Hospital	*Hiroki Sugihara*
18. Wakayama Medical University	*Yoshiaki Tomobuchi*
19. Kobe City General Hospital	*Shigefumi Morioka*
20. Kumamoto Chuo Hospital	*Shuichi Oshima*

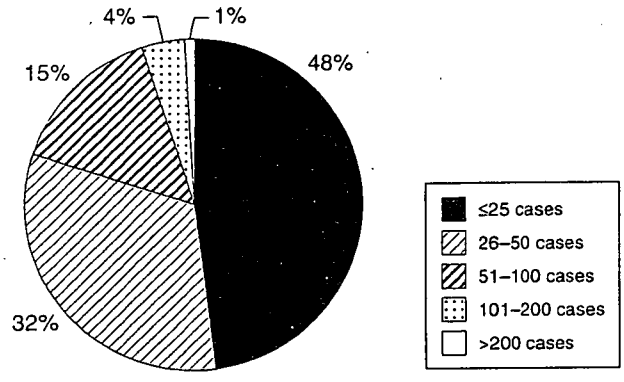


Fig 1. Approximate number of unstable angina (UA) patients hospitalized in 2000 at 582 cardiovascular care sites.

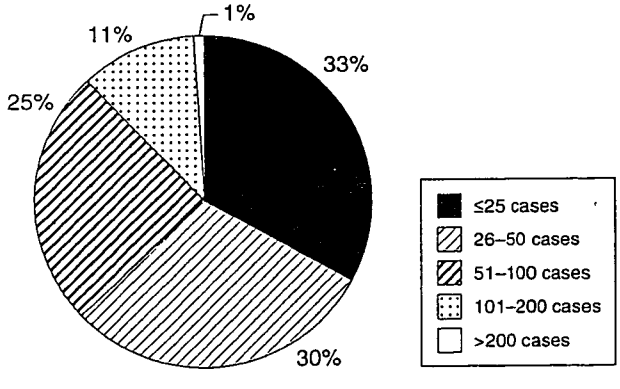


Fig 2. Approximate number of acute myocardial infarction (AMI) patients treated in 2000 at 580 cardiovascular care sites.

UA was defined according to the Braunwald Classification with creatine kinase (CK) and CK-MB isozyme values not greater than twice the respective upper limits of normal; a diagnosis of AMI was made if the CK and CK-MB values exceeded twice the upper limits of normal and the time from onset to admission was within 24 h.

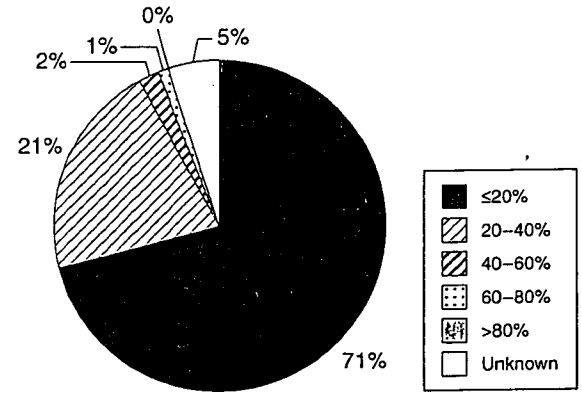


Fig 3. Approximate percentage of patients with non-ST elevation acute myocardial infarction (AMI) among all AMI patients at 574 responding sites.

Study 1: Questionnaire Survey

A questionnaire composed of the 8 questions listed below was sent to the 770 sites certified for cardiovascular care by the Japanese Circulation Society. To increase the response rate and to avoid null answers, multiple choice responses to the questions were set, as shown in parentheses below.

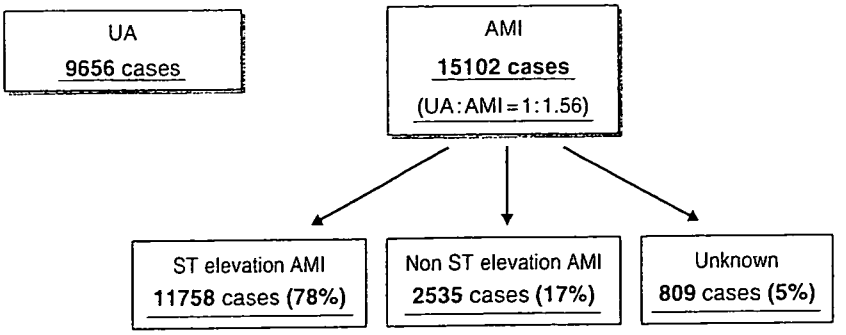
UA (1) Approximate number of hospitalized UA patients during the year from January to December 2000 (≤25; 26–50; 51–100; 101–200; >200).

(2) Treatment with heparin immediately after hospital arrival, excluding bolus administration for coronary angiography and/or revascularization (for all patients apart from those with contraindications; only for refractory patients not responding to appropriate antianginal treatment or for severe cases; not used in principle).

(3) Timing of coronary angiography (immediately after arrival at hospital; after stabilization by drug treatment; not performed if stabilized by drug treatment; no definite policy).

(4) Use of heparin after percutaneous coronary intervention (PCI) (not used in principle; for some patients; for all patients in principle).

AMI (1) Approximate number of hospitalized AMI patients during the year from January to December 2000



Number of sites sent the additional questionnaire: 387

Number of responding sites: 217 (response rate: 56.1%)

Fig4. Number and ratio of unstable angina (UA) and acute myocardial infarction (AMI) patients: results from the additional questionnaires.

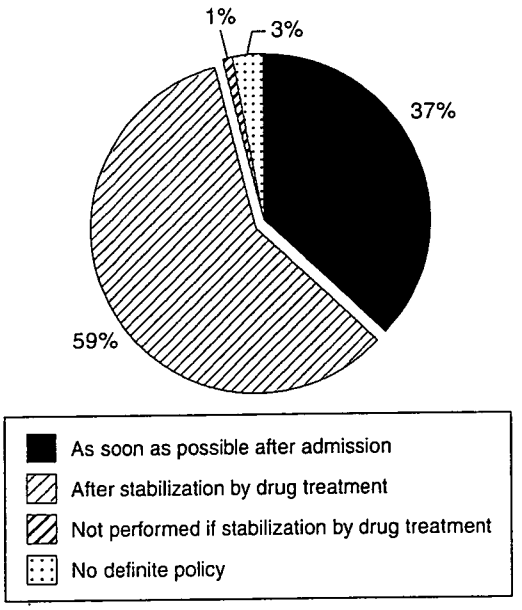


Fig5. Timing of coronary angiography for unstable angina (UA) patients. Number of responding sites: 574.

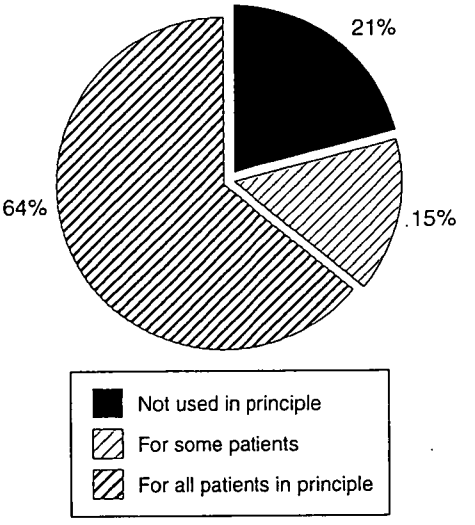


Fig7. Use of Heparin after percutaneous coronary intervention (PCI). Number of responding sites: 521.

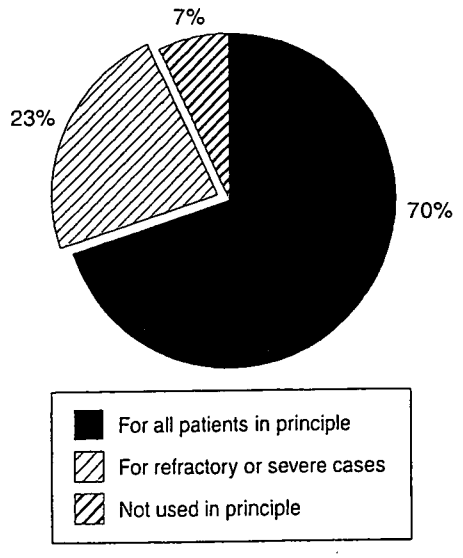


Fig6. Treatment with heparin immediately after admission. Number of responding sites: 582.

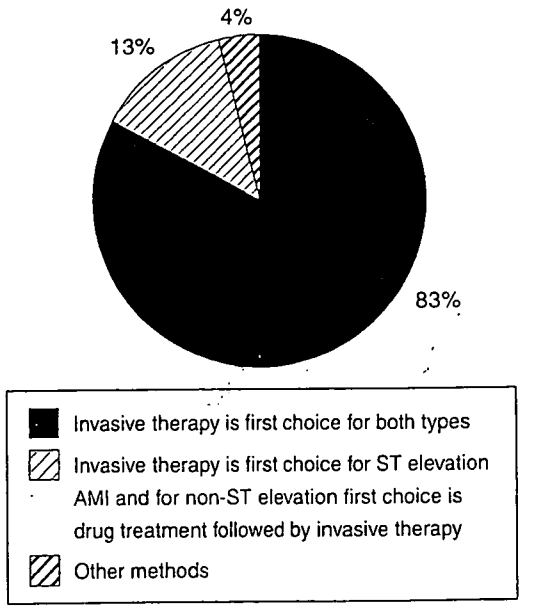


Fig8. Treatment principles for ST elevation and non-ST elevation acute myocardial infarction (AMI) at 576 responding sites.

Table 2 Baseline Characteristics of Patients With UA

Sex	
M	652 (74%)
F	233 (26%)
Age (years)	
Median	67 (Max: 93 Min: 27)
Mean±SD	66.2±10.8
Concomitant disease	
Hypertension	
Yes	514 (58%)
No	371 (42%)
Diabetes	
Yes	328 (37%)
No	557 (63%)
Hyperlipidemia	
Yes	373 (42%)
No	512 (58%)
Cerebrovascular disease	
Yes	75 (8%)
No	810 (92%)
Renal disease	
Yes	81 (9%)
No	804 (91%)
Liver disease	
Yes	24 (3%)
No	861 (97%)
Previous disease	
MI	
Yes	221 (25%)
No	664 (75%)
History of PTCA, stent	
Yes	198 (22%)
No	684 (77%)
Unknown	3 (0.3%)
History of CABG	
Yes	39 (4%)
No	845 (95%)
Unknown	1 (0.1%)
Time from onset to admission (h)	
Median	15.75 (Max: 1,258 Min: 0)
Mean±SD	70.11±140.8
Duration of hospitalization (days)	
Median	12 (Max: 259 Min: 0)
Mean±SD	18.35±22.10
Braunwald class	
I	225 (25%)
II	112 (13%)
III	548 (62%)
A	87 (10%)
B	775 (88%)
C	23 (3%)
ECG abnormality on admission	
ST deviation	
No change	376 (42%)
Elevation	130 (15%)
Depression	364 (41%)
Elevation + Depression	4 (0.5%)
Unknown	11 (1%)

UA, unstable angina; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

Table 3 Baseline Characteristics of Patients With AMI

Sex	
M	727 (78%)
F	210 (22%)
Age (years)	
Median	66 (Max: 96 Min: 28)
Mean±SD	65.2±12.2
Concomitant disease	
Hypertension	
Yes	512 (55%)
No	425 (45%)
Diabetes	
Yes	312 (33%)
No	625 (67%)
Hyperlimidemia	
Yes	349 (37%)
No	588 (63%)
Cerebrovasculer disease	
Yes	68 (7%)
No	869 (93%)
Renal disease	
Yes	63 (7%)
No	874 (93%)
Liver disease	
Yes	16 (2%)
No	921 (98%)
Previous disease	
MI	
Yes	149 (16%)
No	785 (84%)
Unknown	3 (0.3%)
History of PTCA, stent	
Yes	97 (10%)
No	838 (89%)
Unknown	2 (0.2%)
History of CABG	
Yes	25 (3%)
No	911 (97%)
Unknown	1 (0.1%)
Time from onset to admission (h)	
Median	3.0 (Max: 29 Min: 0)
Mean±SD	5.35±5.75
Duration of hospitalization (days)	
Median	21 (Max: 257 Min: 0)
Mean±SD	25.53±22.24
ECG abnormality on admission	
Elevation	782 (83%)
ST deviation	
Non elevation	133 (14%)
No change	34
Depression	99
Elevation + Depression	15 (2%)
Unknown	7 (1%)

AMI, acute MI. Other abbreviations as in Table 2.

(≤25; 26–50; 51–100; 101–200; >200).

(2) Approximate percentage of patients with ST-elevation AMI among all AMI patients (≥80%; 60–80%; 40–60%; 20–40%; ≤20%; unknown).

(3) Treatment principles (first-line treatment) for ST-elevation and non-ST-elevation AMI (invasive therapy is first choice for both types; invasive therapy is first choice for ST-elevation and for non-ST-elevation first choice is drug treatment followed by invasive therapy; other methods).

Study 2: Case Report Investigation

Twenty sites (Table 1) were randomly selected from among those participating in the questionnaire survey (study 1) and were requested to submit case reports for 50 consecutive patients treated for UA and 50 treated for AMI after January 2000. A case report was to include the following information.

Demographic Data and Clinical Profile Sex, age, concomitant disease, previous disease, time from onset to admission, Braunwald classification (only for UA patients), and ECG findings. Hypertension, hyperlipidemia, diabetic, kidney disease, and liver disease that were concomitant diseases were diagnosed by individual investigator based on the diagnostic standard of each site.

Treatment Findings of coronary angiography, details

Table 4 Details of Treatment of Patients With UA

Coronary Angiography	
Yes	*810 (92%)*
No	*75 (8%)*
Time from admission to angiography (h)	
Median	*28.4 (Max: 333 Min: 0)*
Mean ± SD	*58.02±68.44*
Coronary vessel with significant stenosis before intervention	
0 vessel	*78*
1 vessel	*360*
2 vessels	*217*
3 vessels	*170*
LMT	*59*
Unknown	*4*
Culprit vessel	
LMT	*43*
LAD	*424*
LCX	*178*
RCA	*229*
Graft or other	*13*
Stenosis of culprit vessel before intervention	
100%	*85*
99%	*229*
90%	*339*
75%	*73*
50%	*6*
25%	*5*
0%	*59*
Unknown	*14*
TIMI flow past the culprit lesion before intervention	
0	*73*
1	*39*
2	*142*
3	*505*
Unknown	*56*
Revascularization	
Yes	*647 (73%)*
No	*238 (27%)*
Interventional procedure	
PTCA	*519 (80%)*
Stent	*406 (63%)*
ICT	*13 (2%)*
IVCT	*5 (1%)*
CABG	*101 (16%)*
Other	*31 (5%)*
Time from admission to revascularization (h)	
Median	*57 (Max: 5,857.25 Min: 0)*
Mean ± SD	*144.97±296.28*
Stenosis after intervention	
100%	*5*
99%	*2*
90%	*4*
75%	*1*
50%	*30*
25%	*214*
0%	*280*
Unknown	*111*
TIMI Flow after intervention	
0	*11*
1	*1*
2	*3*
3	*508*
Unknown	*124*
Treatment with continuous heparin infusion	
Yes	*606 (68%)*
No	*279 (32%)*
Max daily dosage (units)	
Median	*12,000 (Max: 38,400 Min: 480)*
Mean ± SD	*12,692±4,236*
Duration (days)	
Median	*3 (Max: 43 Min: 1)*
Mean ± SD	*4.31±3.51*
Treatment with antiplatelet medication after admission	
Yes	*842 (95%)*
No	*43 (5%)*
ASA alone	*286*
Ticlopidine alone	*14*
ASA + Ticlopidine	*349*
ASA + Other	*61*
Ticlopidine + Other	*3*
Other alone	*16*
ASA + Ticlopidine + Other	*99*
Unknown	*14*

LMT, left main trunk; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; ICT, intracoronary thrombolysis; IVCT, intravenous thrombolysis; ASA, acetylsalicylic acid. Other abbreviations as in Table 2.

Table 5 Details of Treatment of Patients With AMI

Coronary angiography	
Yes	*917 (98%)*
No	*20 (2%)*
Time from admission to reperfusion therapy (h)	
Median	*1.0 (Max: 1,426.5 Min: 0)*
Mean ± SD	*15.6±81.1*
Coronary vessel with significant stenosis before reperfusion	
0 vessel	*10 (1%)*
1 vessel	*481 (52%)*
2 vessels	*253 (28%)*
3 vessels	*161 (18%)*
LMT	*33 (4%)*
Unknown	*1 (0.1%)*
Culprit vessel	
LMT	*22 (3%)*
LAD	*436 (51%)*
LCX	*163 (19%)*
RCA	*321 (38%)*
Graft or other	*9 (1%)*
Unknown	*70 (7%)*
Stenosis of culprit vessel before reperfusion	
100%	*496*
99%	*229*
90%	*107*
75%	*13*
50%	*3*
25%	*5*
0%	*0*
Unknown	*64*
TIMI flow past the culprit lesion before reperfusion	
0	*479*
1	*89*
2	*140*
3	*136*
Unknown	*73*
Reperfusion therapy	
Yes	*855 (91%)*
No	*82 (9%)*
Reperfusion therapy modality	
PTCA	*765 (89%)*
Stent	*558 (65%)*
ICT	*72 (8%)*
IVCT	*62 (7%)*
CABG	*36 (4%)*
Other	*59 (7%)*
Time from admission to reperfusion (h)	
Median	*1.5 (Max: 2,798.75 Min: −22.5)*
Mean ± SD	*27.76±163.44*
Stenosis after reperfusion therapy	
100%	*15 (1.8%)*
99%	*11 (1.3%)*
90%	*5 (0.6%)*
75%	*15 (1.8%)*
50%	*81 (9.5%)*
25%	*317 (37.1%)*
0%	*362 (42.3%)*
Unknown	*49 (5.7%)*
TIMI flow after reperfusion therapy	
0	*20 (2%)*
1	*13 (2%)*
2	*45 (5%)*
3	*703 (82%)*
Unknown	*74 (8%)*
Treatment with continuous heparin infusion	
Yes	*766 (82%)*
No	*170 (18%)*
Unknown	*1 (0.1%)*
Max daily dosage (units)	
Median	*14,400 (Max: 80,000 Min: 480)*
Mean ± SD	*14,051±5,304*
Duration (days)	
Median	*4 (Max: 212 Min: 1)*
Mean ± SD	*5.09±8.71*
Treatment with antiplatelet medication after admission	
Yes	*905 (97%)*
No	*32 (3%)*
ASA alone	*218*
Ticlopidine alone	*11*
ASA + Ticlopidine	*394*
ASA + Other	*71*
Ticlopidine + Other	*2*
Other alone	*2*
ASA + Ticlopidine + Other	*190*
Unknown	*17*

Abbreviations as in Tables 2–4.

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)*		*46*	*7*	*10*	*6*	*2*
Inferior	*13.2% (43/326)*		*21*	*3*	*11*	*7*	*1*
Lateral	*12.0% (9/75)*	*0.6351*	*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*