Brief episodes of ischemia before sustained coronary artery occlusion protect the heart by delaying lethal injury and significantly limiting the size of the infarct, an effect known as ischemic preconditioning.\(^1,2\) Clinical studies have confirmed that angina shortly before the onset of acute myocardial infarction (AMI) is associated with a smaller infarct size and better short- and long-term outcomes.\(^3,4,6\) However, it has been reported that in the thrombolytic era preinfarction angina limits infarct size and improves clinical outcome in nonelderly, not elderly, patients with AMI\(^7,8\) and it remains unclear whether preinfarction angina has a beneficial effect on clinical outcome in elderly patients undergoing percutaneous coronary intervention (PCI).

In this study, we assessed the relation of preinfarction angina to in-hospital outcome in nonelderly and elderly patients with anterior AMI who underwent PCI.

**Methods**

**Patients** The Japanese Acute Coronary Syndrome Study (JACSS) is a retrospective, observational multicenter trial\(^9\) involving 484 patients with anterior AMI who fulfilled the following inclusion criteria: (1) admission within 24 h (Nonelderly patients, \(n=290\)) and those aged \(\geq 70\) years (elderly patients, \(n=194\)). Angina within 24 h before AMI was present in 42% of nonelderly patients and in 37% of elderly patients. In nonelderly patients, preinfarction angina was associated with a lower in-hospital mortality rate (1% vs 7%, \(p=0.02\)). Similarly, in elderly patients, preinfarction angina was associated with a lower in-hospital mortality rate (6% vs 16%, \(p=0.03\)). Multivariate analysis showed that the absence of preinfarction angina was an independent predictor of in-hospital mortality in both nonelderly (odds ratio 4.20, 95% confidence interval (CI) 1.20–10.6, \(p=0.04\)) and elderly patients (odds ratio 3.04, 95% CI 1.06–8.1, \(p=0.04\)).

**Conclusions** Angina within the 24 h before AMI is associated with better in-hospital outcomes in elderly and nonelderly patients.\(^{\text{(Circ J 2005; 69: 630–635)}}\)

**Key Words:** Aging; Angina pectoris; Myocardial infarction; Reperfusion

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kinase concentration to more than twice the upper limit of normal. Preinfarction angina was defined as the presence of typical chest pain occurring at rest or during exercise and persisting for less than 30 min within 24 h before the onset of AMI. Preinfarction angina was defined as the presence of typical chest pain occurring at rest or during exercise and persisting for less than 30 min within 24 h before the onset of AMI.3,6 The study protocol was reviewed and approved by the ethics committee of each participating hospital.

Coronary Angiography and Coronary Intervention
Coronary angiography was performed immediately after admission to assess the perfusion status of the LAD according to the Thrombolysis in Myocardial Infarction (TIMI) study classification. The recanalization method was left to the attending physician’s discretion. Final TIMI flow grade was assessed on the final angiograms. Multivessel disease was defined as ≥75% stenosis in 1 or more vessels remote from the LAD.

Statistical Analysis
Data are expressed as mean±SD. Categorical data were compared by chi-square analyses. Student’s t-test was used to compare continuous variables. A probability value <0.05 was considered to indicate a statistically significant difference. Multiple logistic regression analysis was used to examine the determinants of in-hospital mortality. Variables used for analysis included age, sex, time to admission, prior infarction, Killip class on admission, preinfarction angina, initial occlusion status in the LAD, multivessel disease, stent implantation, final TIMI flow grade, hypertension, diabetes mellitus, hyperlipidemia, and smoking. Odds ratios and 95% confidence intervals were calculated. Analyses were done using SPSS PC software (Chicago, IL, USA).

Results

Patient Characteristics
There were 290 patients aged <70 years (nonelderly patients, mean age 58 years, range 29–69) and 194 patients...
aged ≥70 years (elderly patients, mean age 77 years, range 70–95). Overall, stent implantation was performed in 380 patients (79%). The final TIMI flow grade was ≥2 in 470 patients (97%) and 3 in 428 (89%). The baseline characteristics of all the patients are presented in Table 1. The nonelderly and elderly patient groups differed with regard to age, sex, Killip class on admission, smoking, hyperlipidemia, hypertension, time to admission, and multivessel disease. However, there were no differences in diabetes mellitus, prior infarction, the prevalence of initial or final TIMI flow grade, or stent implantation. Preinfarction angina was slightly but not significantly less frequent in elderly patients.

The baseline characteristics of the elderly patients with and without preinfarction angina are presented in Table 3. These groups were similar with regard to age, sex, coronary risk factors, prior infarction, time to admission, the prevalence of multivessel disease, initial and final TIMI flow grades, and stent implantation. The prevalence of Killip class ≥2 on admission was significantly lower in patients with preinfarction angina.

**Peak Creatine Kinase (CK) Concentration (Fig 1)**

In both nonelderly (age <70 years) and elderly patients (age ≥70 years), the peak creatine kinase concentration was significantly lower in those with (white bar) than in those without (black bar) preinfarction angina. *p<0.05 vs patients without preinfarction angina.

**In-hospital mortality (Fig 2)**

In both nonelderly patients (age <70 years) and elderly patients (age ≥70 years), in-hospital mortality was significantly lower in those with (white bar) than in those without (black bar) preinfarction angina. *p<0.05 vs patients without preinfarction angina.

The baseline characteristics of the elderly patients with and without preinfarction angina are presented in Table 3. These groups were similar with regard to age, sex, coronary risk factors, prior infarction, time to admission, the prevalence of multivessel disease, initial and final TIMI flow grades, and stent implantation. The prevalence of Killip class ≥2 on admission was significantly lower in patients with preinfarction angina.

**Peak Creatine Kinase (CK) Concentration (Fig 1)**

The peak CK concentration was significantly lower in elderly patients than in nonelderly patients, but in both groups, preinfarction angina was associated with a lower peak CK.

**In-Hospital Mortality (Fig 2)**

During hospitalization (mean 14 days), 36 patients (7.4%) died; 86% of in-hospital deaths were related to cardiac causes. In-hospital mortality was significantly higher in elderly patients than nonelderly patients. In both groups, preinfarction angina was associated with lower in-hospital mortality. Multivariate analysis revealed that the absence of preinfarction angina was an independent
Preinfarction Angina than in those without it.6 Experimentally, lytic therapy, recanalization of an occluded infarct-related artery has been shown to enhance brief antecedent ischemia has been shown to enhance cardioprotective effect of ischemic preconditioning, collater al circulation, and intermittent occlusion.13 Ischemic preconditioning is a cardioprotective phenomenon in which short periods of myocardial ischemia make the myocardium more resistant to subsequent episodes.1,2 In the present study we showed that preinfarction angina per se, apart from the perfusion status of the infarct-related artery before and after recanalization, was related to improved inhospital survival. These findings suggest that the beneficial effects of preinfarction angina on clinical outcome may be related to the cardioprotective effect of ischemic preconditioning.

### Discussion

In the present study preinfarction angina occurring within 24 h of the onset of anterior AMI was associated with a lower peak CK concentration and lower in-hospital mortality after PCI in elderly and nonelderly patients. Multivariate analysis showed that the absence of preinfarction angina was an independent predictor of in-hospital mortality in both groups of patients. These findings suggest that the beneficial effects of preinfarction angina on in-hospital outcome is preserved independently of age in patients undergoing PCI for anterior AMI.

### Preinfarction Angina

Clinical studies have reported that in the thrombolytic era the presence of preinfarction angina is associated with a smaller infarct and better survival.1,2 Andreetti et al have shown that thrombolytic therapy results in more rapid recanalization in patients with preinfarction angina than in those without it! Ishihara et al found that after thrombolytic therapy, recanalization of an occluded infarct-related artery is more frequently achieved in patients with preinfarction angina than in those without it.6 Experimentally, brief antecedent ischemia has been shown to enhance recombinant tissue plasminogen activator-induced thrombolysis.12 Taken together, these findings suggest that early implementation of thrombolytic therapy may partly contribute to better outcomes in patients with preinfarction angina who undergo this treatment. The beneficial effects of preinfarction angina may also be explained by other mechanisms, including ischemic preconditioning, collateral circulation, and intermittent occlusion.13 Ischemic preconditioning is a cardioprotective phenomenon in which short periods of myocardial ischemia make the myocardium more resistant to subsequent episodes.1,2 In the present study we showed that preinfarction angina per se, apart from the perfusion status of the infarct-related artery before and after recanalization, was related to improved inhospital survival. These findings suggest that the beneficial effects of preinfarction angina on clinical outcome may be related to the cardioprotective effect of ischemic preconditioning.

### Ischemic Preconditioning and Aging

Experimental studies have demonstrated that the effects of ischemic preconditioning are attenuated with age and several mechanisms have been proposed for this phenomenon, including decreased adenosine triphosphate concentrations or superoxide dismutase activity, reduced production of stress-induced proteins, reductions in norepinephrine release and ß-adrenergic receptor stimulation, increased intracellular calcium concentrations, increased vulnerability of myocardium to ischemia, and attenuated activation of the KATP channels.14–18 On the other hand, Przyklenk et al have shown that ischemic preconditioning reduces infarct size in both middle-aged and old rabbits independently of morphologic and functional cardiovascular aging, characterized by myocyte hypertrophy, increased myocardial fibrosis, and attenuated responsiveness to ß-adrenergic stimulation.19 These findings are supported by studies done by Loubani et al demonstrating in experimental models that necrosis induced by severe ischemic insults to the human myocardium is not exacerbated by increasing age and that ischemic preconditioning equally protects the myocardium in both elderly and younger patients. Thus, the relation between aging and the implications of ischemic preconditioning remain a matter of debate.

### Preinfarction Angina and Aging

In contrast to previous studies,8 our observational multicenter study found that the presence of angiina within 24 h of infarction was associated with a smaller infarct and a better in-hospital outcome in elderly and nonelderly patients. Several reasons may account for inconsistencies with the results of prior studies. First, in the study by Abete et al,7 coronary angiography was not performed in most of the patients. Second, only 34% of elderly patients with preinfarction angina received thrombolytic therapy in their study, which might have contributed to a poorer outcome. Preinfarction angina has been shown to provide no benefit in the absence of reperfusion.21 In our study, a final TIMI flow of grade ≥2 was achieved in 97% of the patients. The study by Ishihara et al demonstrated that preinfarction angina is associated with better short- and long-term outcomes in nonelderly patients than in elderly patients who underwent emergency cardiac catheterization.8 Their study was performed between 1981 and 1994, whereas our study

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**Table 4** Multivariate Analysis of Factors Associated With In-Hospital Mortality in Nonelderly (<70 Years Old) and Elderly (≥70 Years Old) Patients According to the Presence or Absence of Preinfarction Angina

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonelderly (&lt;70 years old)</th>
<th>Elderly (≥70 years old)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95%CI) p value</td>
<td>Odds ratio (95%CI) p value</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (0.93–1.13) 0.603</td>
<td>1.19 (1.04–1.37) 0.008</td>
</tr>
<tr>
<td>Female</td>
<td>0.84 (0.12–5.72) 0.858</td>
<td>1.70 (0.38–7.64) 0.489</td>
</tr>
<tr>
<td>Time to admission</td>
<td>0.95 (0.77–1.19) 0.673</td>
<td>0.96 (0.81–1.15) 0.680</td>
</tr>
<tr>
<td>Prior infarction</td>
<td>7.20 (1.44–36.0) 0.016</td>
<td>4.96 (1.02–24.2) 0.048</td>
</tr>
<tr>
<td>Killip class 2/2</td>
<td>4.82 (1.12–20.8) 0.035</td>
<td>32.2 (7.38–49.4) &lt;0.001</td>
</tr>
<tr>
<td>Absence of preinfarction angina</td>
<td>4.20 (1.20–10.6) 0.037</td>
<td>3.04 (1.06–18.1) 0.044</td>
</tr>
<tr>
<td>TIMI flow grade 0 at initial CAG</td>
<td>1.63 (0.34–7.75) 0.537</td>
<td>3.46 (0.66–18.1) 0.141</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.10 (0.19–2.00) 0.264</td>
<td>1.05 (0.21–1.68) 0.220</td>
</tr>
<tr>
<td>Stent implantation</td>
<td>1.58 (0.31–8.00) 0.584</td>
<td>0.61 (0.12–3.05) 0.551</td>
</tr>
<tr>
<td>Final TIMI flow grade</td>
<td>0.86 (0.36–2.10) 0.752</td>
<td>0.09 (0.02–0.38) 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.77 (0.96–22.6) 0.058</td>
<td>1.53 (0.37–6.34) 0.561</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.92 (0.76–11.3) 0.120</td>
<td>1.02 (0.16–1.77) 0.191</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.67 (0.16–2.72) 0.571</td>
<td>0.26 (0.08–1.74) 0.164</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.01 (0.25–4.02) 0.995</td>
<td>0.58 (0.10–4.30) 0.592</td>
</tr>
</tbody>
</table>

95%CI, 95% confidence interval; TIMI, Thrombolysis in Myocardial Infarction; CAG, coronary angiography.
period was in 2001. The recent improvements in cardiac catheterization including PCI treatment and patient care may partially explain the discrepancy between their findings and ours. Another likely reason for the inconsistent results is the definition of “elderly”, which seems to have changed over time. Indeed, over the past 20 years, the definition of “elderly” in studies of outcome in patients undergoing cardiac surgery and related procedures has gradually increased from ≥65 years old to ≥80 years old.\(^{23-25}\) Unspecified or unmeasured baseline characteristics of patients aged ≥70 years may also have differed our study and previous investigations. We limited our study group to patients undergoing emergency PCI, a decision that might be at least in part related to the patients’ daily activities. Elderly patients in our study may have thus had a relatively high level of physical activity. Experimental studies have shown that exercise training restores the protective effect of ischemic preconditioning in the aging heart by increasing norepinephrine release.\(^{26}\)

**Study Limitations**

This was a small, retrospective, observational, nonrandomized study. Furthermore, the subjects were limited to those with anterior AMI who underwent PCI because we recently showed that preinfarction angina improves in-hospital outcome after PCI in patients with anterior AMI, but not in those with nonanterior AMI.\(^{27}\) The inclusion of these latter patients would have confounded assessment of the effect of preinfarction angina on in-hospital outcome. Another major limitation is the quantification of ischemic episodes. Because episodes of preinfarction angina were ascertained on the basis of patient history, silent ischemia was not taken into account. Silent ischemia has been shown to occur frequently in elderly patients.\(^{28}\) In our study, preinfarction angina was slightly less frequent in elderly patients, but if we had taken silent ischemia into account, the benefits of preinfarction angina may have become clearer in elderly patients. Further prospective studies are needed to confirm whether the beneficial effects of preinfarction angina are preserved in elderly patients.

**Conclusion**

The presence of angina within 24 h of an anterior AMI is associated with a smaller infarct and better in-hospital outcome in elderly and nonelderly patients undergoing PCI.

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**References**

Appendix I

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