Modern state of acute myocardial infarction in the interventional era: Observational case—control study—Japanese acute coronary syndrome study (JACSS)

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Summary  The Japanese acute coronary syndrome study (JACSS) is a retrospective and multicenter observational study conducted in 35 medical institutions across Japan. The JACSS database included 5325 consecutive patients hospitalized at the participating institutions within 48 h after the onset of symptoms of acute myocardial infarction (AMI) between January 2001 and December 2003. The JACSS data vividly displayed the modern state of AMI in the interventional era. Percutaneous coronary intervention (PCI) including balloon angioplasty and stent implantation was performed in 80% of the patients and approximately 90% of the treated patients had successful coronary recanalization during the acute phase of MI. The results showed very low rates of all-cause mortality and cardiovascular deaths during hospitalization. Various types of novel information have been produced from JACSS data by several leading clinical researchers in Japan and this may also be helpful in making plans for a prospective study.

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Introduction

The Japanese acute coronary syndrome study (JACSS) is a retrospective and multicenter observational study conducted in 35 medical institutions across Japan. The JACSS database included 5325 consecutive patients hospitalized at the participating institutions within 48 h after the onset of symptoms of acute myocardial infarction (AMI) between January 2001 and December 2003. Tables 1A and 1B show the clinical and angiographic characteristics of the patients and the state of AMI in the intervention era. Percutaneous coronary intervention (PCI) including balloon angioplasty and stent implantation was performed in 80% of the patients and approximately 90% of the treated patients had successful coronary recanalization (thrombolysis in myocardial infarction [TIMI] [1] III) during the acute phase of MI. The results showed very low rates of all-cause mortality (8%) and cardiovascular deaths (7%) during hospitalization. Several leading clinical researchers in Japan have used data of the JACSS in their analysis [2–14].

Risk factors for AMI in Japanese men and women

Current knowledge about the prevention of coronary heart disease and cardiovascular disease is mainly derived from studies in European populations [15]. However, the extent to which these findings apply worldwide is unknown. Some studies reported that risk factors for coronary artery disease vary in different geographic regions, especially Asian countries. For example, dyslipidemia is not a risk factor for coronary artery disease in India [16] and hypertension is more important in China [17]. In addition, the incidence of ischemic heart disease in Japan has been reported to be the lowest among the developed countries [18,19]. The differences between Japan and western countries may stem, in part, from genetic factors, but it is more likely that eating habits are the cause; for example, the average plant-based low-fat diet. Kawano et al. [9] clarified the risk factors for AMI in the Japanese population. Risk factors were assessed in patients with a first AMI and age- and sex-matched population-based controls. Hypertension, diabetes,.
current smoking, family history, and hypercholesterolemia were all independent risk factors for AMI (in both men and women) (Fig. 1A). However, obesity was not. Hypertension, current smoking, and diabetes were all independent risk factors for AMI in men. In contrast, only current smoking, diabetes, and hypertension were independent risk factors for AMI in women. Hypercholesterolemia was an independent risk factor for AMI in men, but not in women (Fig. 1B). In conclusion, hypertension, diabetes, current smoking, family history, and hypercholesterolemia are associated with AMI in Japanese patients. In addition, there are sex differences in the order of importance related to risk factors for AMI. Hypertension, current smoking, diabetes, and family history are the most important risk factors in men, whereas current smoking, diabetes, hypertension, and family history are the most important risk factors in women. Hypercholesterolemia is an independent risk factor for AMI in men, but not in women. This is the first clinical study that defines the relative importance of risk factors for AMI in Japanese patients.

### Beneficial effects of preinfarction angina on in-hospital outcome

In experimental animals, brief episodes of ischemia before sustained coronary occlusion significantly decrease infarct size [20–22]. This phenomenon, known as ischemic preconditioning, also occurs in humans. Several clinical studies have demonstrated that angina attacks shortly before the onset of AMI limit infarct size and improve both short- and long-term outcomes [23–26]. However, the clinical significance of preinfarction angina in patients with AMI who undergo PCI is not known. Kosuge et al. [2] assessed the relationship between preinfarction angina, infarct size, and in-hospital outcome after PCI for AMI. They reported that preinfarction angina occurring ≤24 h before the onset of AMI was associated with lower peak creatine kinase levels (Fig. 2A) and lower in-hospital mortality in patients who underwent PCI for anterior infarction (Fig. 2B). This beneficial effect of preinfarction angina on in-hospital outcome was less obvious in patients with non-anterior infarction. A previous report described a favorable effect of preinfarction angina on in-hospital outcome in both anterior and non-anterior infarctions although only 19% of patients underwent PCI [27].
Leukocyte count and predictor of mortality

Inflammation is a significant risk factor for the development of coronary artery disease [28—30]. Recently, there has been a renewed interest in leukocyte count as a prognostic indicator of acute coronary syndrome [31]. The leukocyte count is a simple and universally available marker of inflammation and acute-phase reactants. Leukocytosis was also considered a high risk factor for adverse events following AMI in the era before coronary reperfusion therapy [32—34]. Kojima et al. [3] evaluated whether leukocyte count in the acute phase of MI predicts adverse in-hospital clinical outcomes and long-term prognosis in the coronary interventional era. Leukocyte count was significantly associated with smoking, sudden onset AMI, and the no-reflow phenomenon during PCI, as were age, peak creatine kinase level, and Killip class. Leukocytosis was significantly associated with higher risk of in-hospital mortality (Fig. 3). Patients in the
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Figure 3 Event-free survival of patients after AMI by quartile of the leukocyte count. Quartile 1: leukocyte count \( \leq 7800/\text{mm}^3 \); Quartile 2: \( 7800/\text{mm}^3 < \text{leukocyte count} \leq 9750/\text{mm}^3 \); Quartile 3: \( 9750/\text{mm}^3 < \text{leukocyte count} < 12,100/\text{mm}^3 \); Quartile 4: \( 12,100/\text{mm}^3 < \text{leukocyte count} \).

The highest quartile of leukocyte count were about three times more likely to have a poor prognosis after AMI compared to those in the lowest quartile, after adjusting for independent factors which were closely associated with leukocyte count. They concluded that the leukocyte count is of great significance for stratifying patient risk and recommended its use as a marker for predicting future adverse events following treatment for AMI.

Hyperglycemia and adverse outcomes

An increase in plasma glucose concentration is often observed during the early hours after the onset of AMI not only in diabetic patients but also in patients free of diabetes mellitus [35]. It has been reported that both acute hyperglycemia and diabetes mellitus are independently associated with adverse outcomes after AMI in the pre-reperfusion era and in the thrombolytic era [36–41]. Ishihara et al. [7] assessed the association between acute hyperglycemia and in-hospital outcome after AMI in the contemporary PCI era. In addition, because acute hyperglycemia was often confused with chronic hyperglycemia, the association between diabetes mellitus and outcome after AMI in the PCI era was also investigated. The in-hospital mortality rate was significantly higher in patients with acute hyperglycemia than in patients without. However, there was no significant difference in mortality between diabetic and non-diabetic patients. Acute hyperglycemia was associated with a higher in-hospital mortality rate both in non-diabetic patients and in diabetic patients. The in-hospital mortality increased as plasma glucose increased (2% in patients with plasma glucose \( \leq 90 \text{mg/dL} \), 3% in patients with plasma glucose 90–126 mg/dL, 5% in patients with plasma glucose 126–162 mg/dL, 10% in patients with plasma glucose 162–198 mg/dL, 12% in patients with plasma glucose 198–234 mg/dL, and 18% in patients with plasma glucose > 234 mg/dL; \( P < 0.001 \)).

Figure 4 The in-hospital mortality rate increased as plasma glucose increased (2% in patients with plasma glucose \( \leq 90 \text{mg/dL} \), 3% in patients with plasma glucose 90–126 mg/dL, 5% in patients with plasma glucose 126–162 mg/dL, 10% in patients with plasma glucose 162–198 mg/dL, 12% in patients with plasma glucose 198–234 mg/dL, and 18% in patients with plasma glucose > 234 mg/dL; \( P < 0.001 \)).

Acute hyperglycemia was associated with a higher incidence of no-reflow during PCI but diabetes was not. They concluded that acute hyperglycemia, but not diabetes, was a predictor of in-hospital mortality after AMI in the PCI era. No-reflow occurred more frequently during PCI in patients with acute hyperglycemia, suggesting that microvascular dysfunction might contribute to the adverse outcome of such patients.

Other prognostic indicators of AMI

Other prognostic indicators of AMI in addition to leukocyte count and hyperglycemia were examined. Post-AMI hyperuricemia was associated with the development of heart failure [5]. Serum uric acid level on admission was a suitable marker for predicting AMI-related future adverse events (Fig. 5A), and the combination of Killip class and post-AMI serum uric acid level was a good predictor of mortality of patients with AMI (Fig. 5B) [5]. Leukocyte count and plasma glucose level were independently associated with in-hospital mortality suggesting that a simple combination of these two parameters might provide further information regarding prediction of outcome in patients with AMI (Fig. 6) [10]. In another study, risk stratification based on the combined use of leukocyte count,
Figure 5  (A) Survival without all-cause mortality in patients after acute myocardial infarction based on serum uric acid concentrations of < 4.6 mg/dL in quartile 1 (thin solid line), 4.6 to 5.6 mg/dL in quartile 2 (short-dash line), 5.6—6.7 mg/dL in quartile 3 (long-dash line), and > 6.7 mg/dL in quartile 4 (thick solid line).  (B) Survival without all-cause mortality in patients after acute myocardial infarction based on combinations of the best uric acid cut-off concentration of 7.5 mg/dl for predicting survival and Killip's class: Killip’s classes I and II plus a uric acid concentration ≤ 7.5 mg/dl (thin solid line), Killip’s classes I and II plus a uric acid concentration > 7.5 mg/dl (short-dash line), Killip’s classes III and IV plus a uric acid concentration ≤ 7.5 mg/dl (long-dash line), and Killip’s classes III and IV plus a uric acid concentration > 7.5 mg/dl (thick solid line).  AMI, acute myocardial infarction.

Figure 6  In-hospital mortality across tertiles of leukocyte count (low < 8300/mm³, medium 8300—11,000/mm³, high > 11,000/mm³) and plasma glucose level (low < 133 mg/dl, medium 133—182 mg/dl, high > 182 mg/dl).

plasma glucose, and glomerular filtration rate on admission provided important prognostic information and facilitated early risk stratification (Fig. 7) [14].

Patients with AMI on a weekday or on the weekend

Studies from North America report outcome differences between patients admitted to acute care hospitals on a weekday vs the weekend; that is, the mortality rate of patients admitted on weekends tended to be higher [42,43]. The difference was interpreted to be related to low staffing levels and availability of emergency procedures on the weekends compared with weekdays [44,45]. However, it is not clear whether this is also applicable to Japanese patients and hospitals. Matsui et al. [12] assessed the clinical outcomes for weekday and weekend admission to hospitals for patients with AMI in Japanese acute care hospitals. This study included AMI patients with weekday onset (Monday through Friday) and those with weekend onset (Saturday and Sunday). There were no significant differences between the 2 groups in patient background and clinical features. The proportions of patients who underwent emergency catheterization and reperfusion therapy were also similar. There were no differences between the 2 groups
in the in-hospital, 30-day, and 1-year mortality rates. Even after various adjustments, there was no difference in the risk of death associated with weekend versus weekday onset of AMI. In conclusion, the results of that study showed similar outcomes for patients who developed acute MI on a weekday or on the weekend. The results express the similar quality of care in Japanese hospitals, regardless of the day of the week.

Is it true that nitrate treatment increases future cardiac events?

In the coronary pre-interventional era, two Japanese studies examined the effects of nitrate treatment in MI patients. However, the overall randomization rate was rather low and data were not adjusted for patient background. There is no clinical evidence for clinical benefits from nitrate treatment in patients undergoing PCI in the acute phase of MI. Another study was designed to determine the effects of long-term nitrate therapy on adverse events in patients with AMI in the coronary interventional era [11]. The results showed that all-cause mortality, cardiac, and cardiovascular events were lower in patients treated with nitrates than untreated controls. However, these crude comparisons included several confounding factors on nitrate prescription. To minimize the effect of selection bias on outcomes, the technique of propensity score matching for clinical characteristics was used and distortion of effective nitrate treatment was excluded. The results of propensity score matching showed that nitrate therapy had no impact on all-cause mortality (Fig. 8A) and cardiovascular events (cardiac death, non-fatal reinfarction, unstable angina, heart failure requiring rehospitalization, and stroke) at 30-day, 60-day, 90-day, 6-month, 1-year, and 2-year follow-up periods (Fig. 8B). The study concluded that long-term nitrate therapy after AMI neither improves nor aggravates prognosis. Prospective randomized clinical trials are warranted to determine the long-term effects of nitrate therapy on secondary prevention of AMI.

Conclusions

There are prospective and retrospective studies in a longitudinal method. The evidence level in prospective studies is higher than that in retrospective studies because prospective studies have less various biases. It takes much time to get the final result in prospective studies while retrospective
studies are advantageous to form hasty conclusions. Therefore, retrospective studies show their ability to solve the urgent problems. The JACSS database included more than 5000 consecutive AMI patients and such a large database has not been generally observed in Japanese retrospective studies regarding AMI. The results from JACSS data vividly displayed the modern state of AMI in the interventional era. They may be also helpful to make plans for a novel prospective study. However, there were several problems such as striking missing data in the JACSS database. Therefore, we are now planning to perform a prospective study on AMI (New JACSS) to solve these problems.

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