Impact of Adiponectin and Leptin on Long-Term Adverse Events in Japanese Patients With Acute Myocardial Infarction – Results From the Nagoya Acute Myocardial Infarction Study (NAMIS) –

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Background: Low adiponectin levels and high leptin levels are associated with a high incidence of developing cardiovascular disease. However, the relationship between the levels of these adipokines and the development of adverse events after acute myocardial infarction (AMI) remains unclear.

Methods and Results: This study enrolled 724 Japanese subjects with AMI who underwent successful emergency percutaneous coronary intervention (PCI). Their serum adiponectin and leptin levels were measured 7 days after AMI onset. There were 63 adverse events during the 3-year follow-up. The levels of adiponectin and leptin and the leptin to adiponectin ratio, were significantly associated with adverse events [hazard ratio 2.08 (95% confidence interval (CI) 1.33–3.24), \( P=0.001 \); hazard ratio 0.62 (95% CI 0.43–0.90), \( P=0.012 \); hazard ratio 0.59 (95% CI 0.45–0.76), \( P<0.001 \), respectively]. The leptin to adiponectin ratio remained a significant independent predictor of adverse events during long-term follow-up in a multivariable analysis [adjusted hazard ratio 0.60 (95% CI 0.43–0.83), \( P=0.002 \)].

Conclusions: Higher adiponectin and lower leptin levels are associated with a high incidence of adverse events in Japanese patients after AMI, and the leptin to adiponectin ratio independently predicts prognosis after AMI. (Circ J 2013; 77: 2778–2785)

Key Words: Acute myocardial infarction; Adiponectin; Leptin; Leptin to adiponectin ratio; Prognosis

Dipokines, such as adiponectin and leptin, plasminogen activator inhibitor type 1 and tumor necrosis factor \( \alpha \), are known to regulate metabolic homeostasis. Recent studies have clarified that these adipokines have several roles linking metabolic disorder to coronary artery disease (CAD). For example, a low adiponectin level is associated with cardiovascular morbidity and mortality in the primary prevention setting. However, once cardiac disease has developed, the effect of adiponectin levels on cardiovascular mortality, re-infarction, heart failure, and revascularization is controversial. Some researchers have reported a low adiponectin level to be associated with a poor prognosis for subjects with CAD. On the other hand, a high adiponectin level was associated with a poor prognosis in subjects with heart failure, compared with those with a low adiponectin level. Leptin, which increases proportionally with the amount of body fat, reduces appetite and increases energy expenditure. It has been reported that the dysregulation of leptin is involved in metabolic disorders. Although previous studies have suggested the involvement of leptin in CAD, the association between leptin and the prognosis of patients with CAD seems to be complicated, partly because of the development of leptin...
Atherosclerotic index in patients with acute myocardial infarction (AMI). Some reports have shown that adiponectin and leptin are affected by changed hemodynamics and are regulated by an inflammatory response in the process of tissue repair. However, it remains unclear precisely how these adipokines affect the prognosis of subjects with successfully revascularized acute myocardial infarction (AMI). Some reports have shown that adiponectin and leptin are affected by changed hemodynamics and are regulated by an inflammatory response in the process of tissue repair. In addition, no previous study has examined the effects of the leptin : adiponectin ratio on the prognosis of subjects with AMI. Therefore, we aimed to clarify the effect of the serum levels of adiponectin and leptin and the leptin : adiponectin ratio measured 7 days after the onset of AMI on prognosis.

Methods

Patients and Definitions

The Nagoya Acute Myocardial Infarction Study (NAMIS) was a prospective, multicenter observational study of AMI in which 18 collaborating hospitals in central Japan participated (registered with UMIN-CTR, no. C000000021). AMI was defined as dyspnea and/or edema that was accompanied by pulmonary congestion on the chest roentgenogram and required diuretic treatment. A diagnosis of stroke was made only when a prolonged neurological deficit was present with documentation on imaging. The independent endpoint evaluation committee strictly evaluated all events in a manner that was blind to clinical information. Patients who were taking antihypertensive drugs or whose systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg were considered to be hypertensive. Patients who were taking antihyperlipidemic drugs or whose low-density lipoprotein cholesterol (HDL-C) was ≥140 mg/dl and/or triglycerides ≥150 mg/dl and/or whose high-density lipoprotein cholesterol (HDL-C) was <40 mg/dl were considered dyslipidemic. Diabetes mellitus was diagnosed according to the criteria of the World Health Organization. Cigarette smoking was defined as current smoking. Killip class on hospital admission was assessed to evaluate patients for clinical signs of heart failure. The Human Ethics Review Committee of Nagoya University (Institutional No. 411) and each hospital approved the study protocol and signed consent forms were obtained for each subject.

Laboratory Examinations and Emergency Coronary Angiography

Emergency coronary angiography was performed in all patients and each attending physician or interventional cardiologist determined the allocation of reperfusion therapy independently of this study. Blood samples were taken every 6 h during the first 24 h for the determination of the peak CK level. Fasting venous blood samples were also obtained to measure the serum adiponectin levels, serum leptin levels, and lipid parameters, such as the levels of HDL-C, triglycerides and HDL-C, 7 days...
after admission when these measurements were considered to have returned to the basal levels.24,25 The estimated glomerular filtration rate (eGFR) was calculated using an equation developed and validated for a Japanese population.24 Serum concentrations of adiponectin were measured by a sandwich enzyme-linked immunosorbent assay (ELISA). All components of blood examinations were measured by Mitsubishi Chemical Medience Co, Ltd, Tokyo, Japan.

Follow-up
The patients were prospectively followed up every 6 months for 36 months (1,095 days), by medical questionnaires until the first occurrence of each event.

Statistical Analysis
Data of normally distributed continuous variables are expressed as median values (25–75th percentile range). Comparisons of continuous variables were performed using the unpaired t-test or the Mann-Whitney U-test, as appropriate. Categorical variables were presented by frequency counts, and intergroup comparisons were analyzed by the Chi-squared test.

We plotted the cumulative event curves using the Kaplan-Meier survival method and tested the differences among the groups by log-rank analysis. The Spearman 2-way test was used to assess the relationship between 2 quantitative variables with a non-normal distribution. Variables with a non-normal distribution were transformed logarithmically before multivariate analysis.

We also assessed the independent predictors of adverse events using the Cox proportional-hazards analysis and including variables that were significantly associated with adverse events in the univariate analysis. These analyses were performed using the SPSS software program (IBM Corp, Somers, NY, USA). Statistical significance was defined as P<0.05.

Results
Patients’ Characteristics
A total of 749 Japanese subjects (593 males, 156 females) with AMI were enrolled from January 2004 to February 2009. Of them, 13 were excluded from because of violation of inclusion criteria, 5 because blood samples were not available, and 7 revoked their informed consent, resulting in 724 subjects for analysis. The median age was 64 years, 79.7% were male, 51.1% had hypertension, 94.1% had dyslipidemia, and 26.0% had diabetes mellitus; the median body mass index (BMI) was 23.9 kg/m² (Table 1).

Association of Adipokines With Clinical Variables and Other Biomarkers
Table 2 shows the relationship between adiponectin, leptin and the leptin : adiponectin ratio and the other variables measured in this study. Elevated adiponectin levels were seen in association with older age, higher HDL-C levels, higher brain natriuretic peptide (BNP) levels and higher Killip class. In contrast, male sex, presence of dyslipidemia, BMI, LDL-C level and eGFR were all inversely correlated with the adiponectin level. Age, BMI and hypertension were all positively correlated with the leptin level. In contrast, male sex, current smoking negatively correlated with the leptin level. An elevated leptin : adiponectin ratio was associated with higher BMI, the LDL-C level, hypertension and dyslipidemia. In contrast, male sex, current smoking, the HDL-C level, age and the BNP level were all inversely correlated with the leptin : adiponectin ratio. Only age, BMI, sex and current smoking significantly correlated with all of these adipokines.

Clinical Outcomes and Their Association With Baseline Variables and Biomarkers
During the 36-month follow-up, there were 12 cases of cardiac death, 24 of acute coronary syndrome, 26 of heart failure, and 11 of stroke. The combined endpoint of cardiac death, acute coronary syndrome, heart failure, or stroke occurred in 63 subjects. The high adiponectin/low leptin patients were significantly associated with poor prognosis in 4 groups divided according to serum adiponectin and leptin levels (Figure S1). Table 3 shows the results of the univariate analysis that evaluated for a combined outcome. Older age, higher BNP level, diabetes mellitus, previous MI and higher adiponectin level were positive predictors of adverse events. In contrast, higher

| Variable                        | P value   | P value   | P value   | P value   |
|---------------------------------|-----------|-----------|-----------|-----------|
| Adiponectin                     | ρ         | P value   | ρ         | P value   |
| Age                             | 0.336     | <0.0001   | 0.096     | 0.010     |
| sex, male                       | -0.333    | <0.0001   | -0.434    | <0.0001   |
| BMI                             | -0.311    | <0.0001   | 0.467     | <0.0001   |
| Peak CK level                   | -0.039    | 0.299     | -0.054    | 0.146     |
| HDL-C                           | 0.287     | <0.0001   | 0.016     | 0.667     |
| LDL-C                           | -0.161    | <0.0001   | 0.039     | 0.292     |
| eGFR                            | -0.142    | <0.0001   | -0.103    | 0.005     |
| BNP                             | 0.323     | <0.0001   | -0.039    | 0.294     |
| Hypertension                    | -0.007    | 0.848     | 0.162     | <0.0001   |
| Diabetes mellitus               | -0.013    | 0.734     | 0.055     | 0.140     |
| Dyslipidemia                    | -0.177    | <0.0001   | 0.012     | 0.750     |
| Previous MI                     | 0.047     | 0.204     | 0.059     | 0.114     |
| Current smoking                 | -0.139    | <0.0001   | -0.271    | <0.0001   |
| Killip class ≥2                 | 0.085     | 0.022     | 0.049     | 0.189     |
| LAD as culprit                  | 0.033     | 0.371     | -0.057    | 0.123     |

The Spearman correlation coefficients are provided. Abbreviations as in Table 1.
Effect of Adipokines after AMI

Multivariate Analysis of Adipokines

The association of adipokine and BNP levels with adverse events was examined using different proportional hazard regression models to assess the value of these adipokines as biomarkers. First, we used a model adjusting for age (model 1) and then a model adjusting for additional variables that correlated with all the adipokines (sex, BMI and current smoking: model 2). Next, we used an additional model that was also adjusted for variables that were associated with adverse events (diabetes mellitus and previous MI: model 3). Finally, model 4 was additionally adjusted for BNP.

The results of the analyses are summarized in Table 5. The levels of adiponectin and leptin, the leptin : adiponectin ratio and BNP level were all related to the event-free survival in

leptin level and higher leptin : adiponectin ratio were negative predictors of adverse events. Table 4 shows the result of univariate analysis of each component. Previous MI, higher BNP level and higher adiponectin level were positive predictors of cardiac death. In contrast, higher leptin level and a higher leptin : adiponectin ratio were negative predictors of cardiac death. No factor correlated with acute coronary syndrome. Only a higher leptin : adiponectin ratio was a negative predictor of stroke. Older age, diabetes mellitus, higher BNP level and higher adiponectin level were positive predictors of heart failure. In contrast, higher eGFR and a higher leptin : adiponectin ratio were negative predictors of heart failure. Only the leptin : adiponectin ratio significantly related to 3 components.

*Analyzed after logarithmic transformation.
Abbreviations as in Tables 1, 3.

Table 3. Crude Hazard Ratios (HR) for Primary Endpoint for Various Factors

|                | HR   | 95% CI     | P value |
|----------------|------|------------|---------|
| Age, year increase | 1.05 | 1.02–1.08  | 0.001   |
| sex, male        | 0.99 | 0.54–1.82  | 0.978   |
| BMI, 1-unit increase | 0.94 | 0.87–1.02  | 0.166   |
| Hypertension, yes | 1.58 | 0.95–2.63  | 0.078   |
| Diabetes mellitus, yes | 2.28 | 1.38–3.76  | 0.001   |
| Dyslipidemia, yes | 1.27 | 0.40–4.04  | 0.690   |
| Previous MI, yes | 2.71 | 1.17–6.28  | 0.020   |
| Current smoking, yes | 0.88 | 0.53–1.44  | 0.602   |
| LAD as culprit artery, yes | 1.34 | 0.81–2.19  | 0.252   |
| HDL-C, 1-unit increase* | 0.45 | 0.16–1.28  | 0.134   |
| LDL-C, 1-unit increase* | 0.46 | 0.18–1.22  | 0.119   |
| eGFR, 1-unit increase | 0.99 | 0.98–1.01  | 0.277   |
| BNP, 1-unit increase* | 1.87 | 1.47–2.37  | <0.001  |
| Adiponectin, 1-unit increase* | 2.08 | 1.33–3.24  | 0.001   |
| Leptin, 1-unit increase* | 0.62 | 0.43–0.90  | 0.012   |
| LAR, 1-unit increase* | 0.59 | 0.45–0.76  | <0.001  |

*Analyzed after logarithmic transformation.
CI, confidence interval; LAR, leptin : adiponectin ratio. Other abbreviations as in Table 1.

Table 4. Crude Hazard Ratios (HR) for Each Component of Secondary Endpoint for Various Factors

Cardiac death | Acute coronary syndrome | Stroke | Heart failure

|                | HR   | 95% CI     | P value | HR   | 95% CI     | P value | HR   | 95% CI     | P value |
|----------------|------|------------|---------|------|------------|---------|------|------------|---------|
| Age            | 1.05 | 0.99–1.12  | 0.120   | 1.04 | 1.00–1.09  | 0.073   | 1.02 | 0.95–1.08  | 0.630   | 1.08 | 1.03–1.13  | <0.001 |
| sex, male      | 1.28 | 0.28–5.84  | 0.750   | 1.29 | 0.44–3.77  | 0.643   | 2.60 | 0.33–20.27 | 0.363   | 0.87 | 0.34–2.11  | 0.725  |
| BMI            | 0.85 | 0.70–1.03  | 0.097   | 0.91 | 0.80–1.05  | 0.189   | 0.94 | 0.77–1.14  | 0.526   | 0.99 | 0.87–1.12  | 0.859  |
| Hypertension   | 2.90 | 0.79–10.71 | 0.110   | 0.57 | 0.25–1.31  | 0.189   | 4.42 | 0.95–20.46 | 0.057   | 2.20 | 0.96–5.05  | 0.064  |
| Diabetes mellitus | 1.44 | 0.43–4.80  | 0.548   | 1.76 | 0.77–4.02  | 0.181   | 2.44 | 0.75–8.01  | 0.140   | 2.97 | 1.38–6.40  | 0.006  |
| Dyslipidemia   | 0.32 | 0.07–1.44  | 0.137   | >100 | 0.00–>999  | 0.997   | >100 | 0.00–>999  | 0.998   | 0.75 | 0.18–3.16  | 0.691  |
| Previous MI    | 12.69 | 3.82–42.16 | <0.001  | 2.38 | 0.56–10.11 | 0.241   | 0.00 | 0.00–999   | 0.998   | 1.01 | 0.14–7.45  | 0.992  |
| Current smoking | 0.32 | 0.09–1.18  | 0.087   | 0.96 | 0.43–2.14  | 0.923   | 1.69 | 0.50–5.78  | 0.402   | 0.82 | 0.38–1.77  | 0.615  |
| LAD as culprit artery | 1.58 | 0.50–4.98  | 0.435   | 0.80 | 0.36–1.81  | 0.596   | 0.95 | 0.29–3.11  | 0.932   | 2.15 | 0.96–4.82  | 0.064  |
| HDL-C*         | 0.47 | 0.04–5.12  | 0.533   | 0.45 | 0.04–1.17  | 0.075   | 1.18 | 0.10–14.06 | 0.897   | 0.65 | 0.13–3.30  | 0.606  |
| LDL-C*         | 0.13 | 0.02–1.10  | 0.062   | 0.63 | 0.13–3.09  | 0.573   | 0.38 | 0.04–3.84  | 0.410   | 0.35 | 0.08–1.55  | 0.165  |
| eGFR           | 0.97 | 0.94–1.01  | 0.116   | 1.00 | 0.97–1.02  | 0.869   | 1.03 | 1.00–1.06  | 0.082   | 0.98 | 0.95–1.00  | 0.048  |
| BNP*           | 3.25 | 1.80–5.85  | <0.001  | 1.11 | 0.77–1.62  | 0.574   | 1.20 | 0.69–2.10  | 0.515   | 2.76 | 1.88–4.06  | <0.001 |
| Adiponectin*   | 3.21 | 1.16–8.91  | 0.025   | 1.15 | 0.57–2.60  | 0.696   | 1.03 | 0.88–1.20  | 0.737   | 1.17 | 1.10–1.24  | <0.001 |
| Leptin*        | 0.36 | 0.15–0.85  | 0.020   | 0.76 | 0.42–1.38  | 0.363   | 0.76 | 0.76–1.02  | 0.071   | 0.95 | 0.85–1.06  | 0.327  |
| LAR*           | 0.40 | 0.23–0.71  | 0.001   | 0.81 | 0.52–1.25  | 0.346   | 0.26 | 0.07–0.96  | 0.043   | 0.51 | 0.28–0.93  | 0.029  |

*Analyzed after logarithmic transformation.
Abbreviations as in Tables 1, 3.
long-term adverse events. Measured 7 days after AMI onset is a significant predictor of events. These results suggest that the leptin : adiponectin ratio was associated with a 0.51-fold cally important covariates listed for model 4, a 1-tertile increase was excluded from the analysis. After adjusting for the clini-

tertile was more likely to develop adverse events than the groups according to tertiles of the ratio ($\text{Figure}$). The lower $P=0.002$, respectively. 

The major finding of the present study was that a higher serum adiponectin level, lower serum leptin level and lower leptin : adiponectin ratio measured 7 days after the onset of AMI predicted a poor prognosis in Japanese subjects. The associa-
tion of the leptin : adiponectin ratio with adverse events was statistically significant even after adjusting for age, sex, BMI, diabetes mellitus, HDL-C, previous MI and BNP, and its stati-
tical power was comparable to that of BNP. Adiponectin is exclusively secreted from adipose tissue, and the serum adiponectin level inversely correlates with the body fat percentage in adults. Adiponectin exerts vasculoprotective effects through its insulin-sensitizing and anti-inflammatory functions in the setting of primary prevention. Pischon et al reported that high serum adiponectin levels were associated with a low occurrence of CAD in the primary prevention setting. However, after the onset of AMI, the effect of adiponectin on prognosis appear to change paradoxically. 

### Table 5. Hazard Ratios (HR) for Future Adverse Events According to the Adiponectin Level, Leptin Level and Leptin : Adiponectin Ratio in Continuous Analysis (Analysis After Logarithmic Transformation)

|          | Adiponectin | Leptin | Leptin : adiponectin ratio | BNP |
|----------|-------------|--------|---------------------------|-----|
| Model 1  | HR          | 1.71   | 0.58                      | 0.62| 1.73|
|          | 95% CI      | 1.07–2.73 | 0.40–0.83                 | 0.48–0.81 | 1.34–2.23 |
|          | P value     | 0.026 | 0.003                      | <0.001 | <0.001 |
| Model 2  | HR          | 1.92   | 0.47                      | 0.54| 1.79|
|          | 95% CI      | 1.14–3.25 | 0.28–0.78                 | 0.39–0.75 | 1.38–2.32 |
|          | P value     | 0.014 | 0.004                      | <0.001 | <0.001 |
| Model 3  | HR          | 1.88   | 0.47                      | 0.55| 1.73|
|          | 95% CI      | 1.12–3.17 | 0.28–0.77                 | 0.39–0.76 | 1.33–2.39 |
|          | P value     | 0.018 | 0.003                      | <0.001 | <0.001 |
| Model 4  | HR          | 1.56   | 0.49                      | 0.60| –|
|          | 95% CI      | 0.93–2.62 | 0.30–0.81                | 0.43–0.83 | –|
|          | P value     | 0.090 | 0.005                      | 0.002 | –|

Model 1 is adjusted for age. Model 2 is adjusted for age, sex, BMI, and current smoking. Model 3 is adjusted for age, sex, BMI, and current smoking, diabetes mellitus, previous myocardial infarction. Model 4 is adjusted for age, sex, BMI, current smoking, diabetes mellitus, previous MI, and BNP level. 

Abbreviations as in Tables 1,3.
leptin deficient ob/ob mice exhibit severe cardiac dysfunction, which can be rescued by leptin administration.\textsuperscript{32} Experimental MI mice treated with 4-week infusions of leptin had improved systolic function and LV remodeling.\textsuperscript{33} Furthermore, proinflammatory cytokines, such as tumor necrosis factor α and interleukin-1, seem to be involved in the augmentation of leptin after AMI.\textsuperscript{34,35} Those reports suggest that the serum leptin level induced by inflammation after AMI may exert favorable effects on prognosis through its cardioprotective effect. However, a previous study revealed that a high serum leptin level was associated with a high occurrence of CAD in primary prevention.\textsuperscript{36} Therefore, the clinical significance of leptin appears complex, partly because of the development of “leptin resistance”.\textsuperscript{37,38} Although circulating leptin prevents toxic lipid accumulation,\textsuperscript{39} hyperleptinemia under basal conditions may be caused, at least partly, by insensitivity to leptin, particularly in obese subjects or those with multiple risk factors. In fact, the BMI of the patients in the present study was considerably lower than that reported in the previous study, thus suggesting that the association between the leptin level and clinical outcomes may differ with the characteristics of the study population.

Recently, some groups proposed using the leptin : adiponec-

**Figure.** Kaplan-Meier curves for event-free survival according to tertiles of the leptin to adiponectin ratio. Major adverse cardiac events (MACE) with (A) and (B) without heart failure. The P value, calculated using the log-rank test, is given for the comparisons of all groups at 1,095 days.
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**Appendix**

**The Steering Committee**

Toyoaki Murohara, Takahisa Kondo, Kengo Maeda, Hideki Ishii, Hirotugu Mitsuhashi, Kyoko Matsudaira, Daiji Yoshikawa, Naoki Okumura and Yasuhiro Morita, all from the Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

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The lead investigators included: Masahito Watarai, Anjo Kosei Hospital; Naoya Tsuboi, Chukyo Hospital; Nobuyuki Marui, Chubu Rosai Hospital; Miyoshi Ohno, Haruo Kamiya, Japanese Red Cross Nagoya Daiichi Hospital; Toshihiro Obayashi, Yuji Yamanaka, Kariya Toyota General Hospital; Akihiro Terasawa, Kasugai Municipal Hospital; Taizo Kondo, Komaki City Hospital; Takeshi Shimizu, Ichinomiya Municipal Hospital; Haruo Hirayama, Nagoya Daini Red Cross Hospital; Rinya Kato, Nagoya Ekisaikai Hospital; Tomoki Kitano, Nagoya Medical Center; Takahito Sone, Ogaki Municipal Hospital; Kazuyoshi Sakai, Tosei General Hospital; Hitoshi Kanayama, Masanori Shinoda, Toyota Kosei Hospital; Haruo Inagaki, Toyota Memorial Hospital; and Satoshi Ichimiya, Yokkaichi Municipal Hospital.

**The Endpoint Evaluation Committee**

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**Supplementary Files**

**Supplementary File 1**

Figure S1. (A) MACE with heart failure. (B) MACE without heart failure.

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