Relation of Adiponectin to Cardiovascular Events and Mortality in Patients With Acute Coronary Syndrome

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The association between serum adiponectin levels and cardiovascular events, particularly how adiponectin predicts the development of cardiovascular events and mortality in acute coronary syndrome (ACS) patients remains unresolved. Hence, we aimed to determine whether higher adiponectin levels predict cardiovascular events and mortality in these patients. Regression analyses were performed to clarify adiponectin's ability to predict cardiovascular events and mortality among 1,641 ACS patients. Subgroup analyses were performed according to gender, age, and body mass index (BMI). The primary end point was a composite of the first all-cause death, nonfatal myocardial infarction, or nonfatal stroke event. The secondary end point was all-cause death. Hazard ratios for the primary and secondary end points per 5-μg/ml increase in adiponectin levels were 1.31 (95% confidence interval [CI], 1.13 to 1.47; p = 0.0007) and 1.32 (95% CI, 1.13 to 1.51; p = 0.001), respectively. Higher adiponectin levels were associated with increased cardiovascular events in men, patients aged ≥65 years, and those with BMI <25 kg/m^2. In conclusion, higher adiponectin levels were associated with increased cardiovascular events and all-cause mortality in ACS patients. Its predictive ability might be limited in women, patients aged <65 years, and patients with BMI ≥25 kg/m^2. **(Am J Cardiol 2021;140:7−12)**

Adiponectin is an insulin-sensitizing human hormone which possesses anti-inflammatory, antioxidant, and antiapoptotic roles, thereby mitigating key mechanisms underlying cardiovascular disease pathogenesis.[1,2] Some fundamental studies have suggested that higher adiponectin levels improve cardiovascular disease. However, several clinical studies have reported paradoxical findings where high serum levels of adiponectin were associated with increased cardiovascular events.[3] The association between serum adiponectin levels and cardiovascular events in acute coronary syndrome (ACS) patients remains controversial.[4−9] Additionally, several studies have reported that the levels of adiponectin and the actual endocrine effects of adiponectin are influenced by various patient factors, especially gender, age, and body mass index (BMI).[10−12] Thus, the predictive ability of adiponectin might also be susceptible to these changes.[13−15] However, no studies have examined the influence of gender, age, or BMI on the predictive ability of adiponectin in coronary adverse events among ACS patients. In our previous randomized controlled trial, i.e., the Heart Institute of Japan-PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER), we tested the efficacy of intensive versus conventional lipid-lowering therapy in ACS patients.[16] However, how adiponectin predicts the development of cardiovascular events and mortality in ACS patients remains unresolved. Therefore, this study aimed to examine the ability of adiponectin in predicting mortality in ACS patients and the effect of gender, age, and body mass index (BMI) on its predictive value.

Methods

This study explores a subsection of the HIJ-PROPER study. Briefly, the HIJ-PROPER study was a multicenter, prospective, randomized, open-label, blinded end point trial with an active-control design that compared 2 lipid-lowering treatment strategies involving 19 Japanese hospitals.[16] A total of 1,734 patients with ACS were randomized to intensive lipid-lowering therapy (pitavastatin + ezetimibe therapy) or conventional lipid-lowering therapy (pitavastatin monotherapy) between January 2010 and April 2013. In the HIJ-PROPER study, 13 patients failed to follow-up; thus, 1,721 patients were analyzed in the original study. In this study, we enrolled patients with baseline measurements of serum adiponectin. All participants in HIJ-PROPER had been hospitalized for ACS, and laboratory examinations were performed within 24 hours of admission. All laboratory analyses were exclusively performed at SRL Inc., an external laboratory (Hachioji, Tokyo, Japan).

The primary end point of this study was cardiovascular events, a composite end point of the first instance of all-cause death, nonfatal myocardial infarction, or nonfatal stroke during a median observational period of 3.9 years. The secondary end point was all-cause death. We examined whether adiponectin levels predict the incidence of the

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Original Trial Registration No: UMIN000002742, registered as an International Standard Randomized Controlled Trial. Registry URL: https://www.umin.ac.jp.

See page 11 for disclosure information.

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primary and secondary end points after ACS development. Moreover, we examined adiponectin's ability to predict clinical outcomes according to patients' gender, age (younger or older than 65 years), and BMI (less than or greater than 25 kg/m^2).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institutional review board or relevant ethics committee of each participating medical center. Written informed consent for trial enrollment was obtained from all patients. The original trial number for this sub-study is registered at UMIN000002742 as an International Standard Randomized Controlled Trial (Registry URL: https://www.umin.ac.jp).

Continuous variables data are reported as means (standard deviation), non-normally distributed data as medians and interquartile ranges, and categorical data as absolute values and percentages. Normally distributed continuous data were compared using Welch's *t* Test, nonnormally distributed continuous data were compared using the Mann-Whitney U test, and categorical data were compared using Pearson's chi-squared test. Conventional Cox proportional hazard regression models were used to calculate hazard ratios (HR) and 95% confidence intervals (CIs) for each end point. The HR was calculated based on how many folds the risk increased with increase in adiponectin level per 5-μg/ml. Multivariate regression analyses were performed whereas adjusting for randomization to the treatment arm, age, gender, BMI, history of myocardial infarction, history of heart failure, presence of diabetes mellitus, glomerular filtration rate (GFR), and high-sensitivity C reactive protein. These variables were based on previous literature that reported the predictors of cardiovascular events after acute coronary syndrome.[17,18] Additionally, regression analyses were performed by classifying patients into age, gender, and BMI subgroups, as mentioned earlier. A p value <0.05 was considered to indicate statistical significance unless stated otherwise. All statistical analyses were performed using JMP Pro 14 (SAS Institute Inc., Cary, North Carolina).

Results

Of the 1,721 patients analyzed in the HIJ-PROPER original study, adiponectin level data was not available for 80 patients. Therefore, only 1,641 patients were included in this analysis. Although the patients excluded from the analysis were more likely to have a history of heart failure, most of their baseline characteristics were equivalent to those included in the analysis. (Table 1). The mean patient age was 65.5 ± 11.8 years, and 24.0% were women. The mean BMI was 24.3 ± 3.6 kg/m^2. Diabetes mellitus was present in 30.0% of the patients, and 68.2% had hypertension. The median serum adiponectin level was 6.7 μg/ml (interquartile range, 4.8, 9.9) (Figure 1).

Figure 2 shows a stepwise increase in the events rate of the primary end point and all-cause death during 3.9 years with rising adiponectin levels. Table 2 shows regression analyses of the risk of study end point for each per 5-μg/ml increase in adiponectin levels. In the unadjusted model, higher adiponectin levels were associated with increased incidence of the primary end point (HR, 1.31; 95% CI, 1.13 to 1.47; p = 0.0007) and all-cause mortality (HR, 1.32; 95% CI, 1.13 to 1.51; p = 0.001). After adjustment for patient clinical factors and laboratory findings, higher adiponectin levels remained associated with an increased incidence of the primary end point (HR, 1.32; 95% CI, 1.10 to 1.55; p = 0.004) and all-cause mortality (HR, 1.28; 95% CI, 1.04 to 1.54; p = 0.02). Moreover, the adjusted model showed an association with an increased incidence of nonfatal stroke (HR, 1.54; 95% CI, 1.09 to 2.01; p = 0.02).

Figure 3 shows the HR for the primary end point per 5-μg/ml increase of adiponectin according to gender, age, and body mass index. Higher adiponectin levels were associated with increased cardiovascular events in men (HR, 1.37; 95% CI, 1.07 to 1.69; p = 0.02), patients aged ≥65 years (HR, 1.38; 95% CI, 1.14 to 1.65; p = 0.002), and patients with BMI <25 kg/m^2 (HR, 1.33; 95% CI, 1.09 to 1.59; p = 0.003). However, the same was not true for women (HR, 1.23; 95% CI, 0.94 to 1.55; p = 0.13), patients aged <65 years (HR, 1.57; 95% CI, 0.79 to 2.59; p = 0.17), and patients with BMI ≥25 kg/m^2 (HR, 1.36; 95% CI, 0.91 to 2.02; p = 0.13) (Supplementary Table 1 shows the individual components of the primary end point).

Discussion

Basic science studies have revealed that adiponectin ameliorates inflammation and insulin resistance, has antioxidant effects, and is expected to improve the prognosis of patients with cardiovascular disease.[19,20] However, several clinical studies have reported a positive correlation between adiponectin levels and cardiovascular events or mortality.[4–7] To the best of our knowledge, 2 studies have reported results different from those showing a positive correlation between adiponectin levels and cardiovascular events in ACS patients. Kojima et al reported that cardiovascular events after acute myocardial infarction in men were less frequent in those with baseline adiponectin levels >3.8 g/ml than in those with baseline adiponectin levels of ≤3.8 g/ml.[8] In addition, the AtheroGene study group reported that the incidence of cardiovascular events was significantly higher in the highest quartile of baseline adiponectin levels in coronary artery disease patients, but this trend was not observed in ACS patients.[9] In the former study, the fact that the analysis was limited to men and patients after acute myocardial infarction might have influenced the results significantly. In the latter, patients with higher adiponectin levels tended to have a higher event rate, albeit not significantly higher, and the authors acknowledged that the sample size might have been insufficient to find a significant difference. Moreover, there were several differences in patient characteristics, including age, gender, and BMI, between the 2 studies that did not find a positive correlation and previous studies that did find one, making it difficult to perform direct comparisons. Based on the results of past studies as well as those of ours, higher adiponectin levels are considered to be associated with increased cardiovascular events and mortality after ACS episodes.

Our study provides some new insights. In women with ACS, adiponectin might be useless as a predictor of

Table 1
Baseline characteristics of the study population

Variables	All patients (n = 1721)	Included patients (n = 1641)	Excluded patients (n = 80)	p Value*
Age (years)	65.6 ± 11.8	65.5 ± 11.8	66.8 ± 12.6	0.34
Women	421 (24.5)	394 (24.0)	27 (33.8)	0.06
Body mass index (kg/m^2)	24.3 ± 3.6	24.3 ± 3.6	24.3±3.6	0.94
Diabetes mellitus	523 (30.4)	493 (30.0)	30 (37.5)	0.17
Hypertension	1,175 (68.3)	1,119 (68.2)	56 (70.0)	0.81
Current smoker	594 (34.5)	571 (34.8)	23 (28.8)	0.28
History of heart failure	36 (20.9)	30 (1.8)	6 (7.5)	0.005
Prior myocardial infarction	130 (7.6)	123 (7.5)	7 (8.8)	0.66
History of Revascularization	155 (9.0)	145 (8.8)	10 (12.5)	0.31
Clinical presentation				
STEMI	880 (51.1)	835 (50.9)	45 (56.3)	0.36
Non-STEMI	180 (10.5)	171 (10.4)	9 (11.3)	0.85
Unstable angina pectoris	661 (38.4)	635 (38.7)	26 (32.5)	0.29
Medications				
Use of beta blockers	178 (10.3)	165 (10.1)	13 (16.3)	0.09
Use of ACEI/ARB	492 (28.6)	469 (28.6)	23 (28.8)	1.00
Use of calcium channel blocker	518 (30.1)	489 (29.8)	29 (36.3)	0.21
Use of aspirin	292 (17.0)	277 (16.9)	15 (18.8)	0.65
Total cholesterol (mg/dl)	204 [185, 231]	204 [185, 231]	207 [184, 230]	0.55
HDL-C (mg/dl)	47 [40, 56]	47 [40, 56]	49 [41, 59]	0.16
LDL-C (mg/dl)	129 [114, 151]	129 [113, 151]	130 [116, 151]	0.63
Triglyceride (mg/dl)	114 [80, 167]	115 [80, 167]	103 [57, 171]	0.44
High sensitivity CRP (mg/dl)	0.86 [0.27, 2.59]	0.86 [0.27, 2.60]	0.76 [0.05, 1.83]	0.42
GFR (mL/min/1.73m^2)	72 [60, 84]	72 [60, 84]	73 [63, 85]	0.95

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CRP = C-reactive protein; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; STEMI = ST-elevation myocardial infarction.

Data are expressed as mean ± standard deviation, median (interquartile range), or as number (percentage).

* p Value refers to comparison between included patients and excluded patients.

composite cardiovascular events, or all-cause mortality. Similar clinical findings have been reported by Menzahi et al, who suggested that a paradoxical relationship between adiponectin levels and cardiovascular mortality was observed in men but not in women with type 2 diabetes mellitus.[13] The authors posited that this gender-specific difference might be due to an interaction between adiponectin and gender-linked genes or gender hormones. Other reports suggested that the difference in adiponectin resistance or degree of expression of the adiponectin-elevating alleles between women and men impacts its predictive ability.[21,22] The predictive value of adiponectin might also be diminished in patients aged <65 years and those with BMI >25 kg/m^2. Few studies have examined the influence of age or BMI on the ability of adiponectin to predict

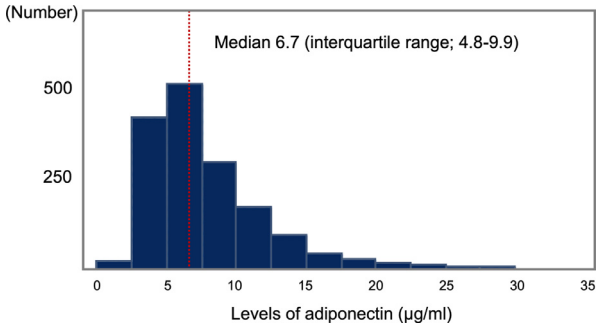

Figure 1. Distribution of adiponectin in this study.

cardiovascular events. Similar to a previous study that reported the relationship between age, GFR, and adiponectin,[23] GFR level in our study was independently and inversely associated with adiponectin levels in patients aged >65 years but not in those aged <65 years (Supplementary Table 2) (Supplementary Figure 1). There is a wealth of data demonstrating a strong association between lower GFR and increased cardiovascular events.[24,25] The age-specific difference in predictive value might be due to an interaction between adiponectin and renal function in patients aged >65 years. Regarding BMI, Sung et al. reported that adiponectin predicted mortality in normal-weight patients but not in overweight patients undergoing coronary artery bypass grafting.[15]

Interestingly, in the current analysis, higher adiponectin levels tended to be associated with an increased incidence of nonfatal stroke, especially in women, patients aged >65 years, and those with BMI <25 kg/m^2 (Supplementary Table 1). Although previous studies have suggested that adiponectin was not associated with the risk of stroke,[26–29] the patients enrolled in these studies did not have cardiovascular disease at baseline. Higher adiponectin levels might indeed be associated with increased incidence of stroke after ACS, with specific considerations in terms of gender, age, and BMI.

An increase in adiponectin levels is likely a compensatory mechanism due to the development of adiponectin resistance.[30] Although several explanations have been proposed,[31] the biological mechanism that underlies the

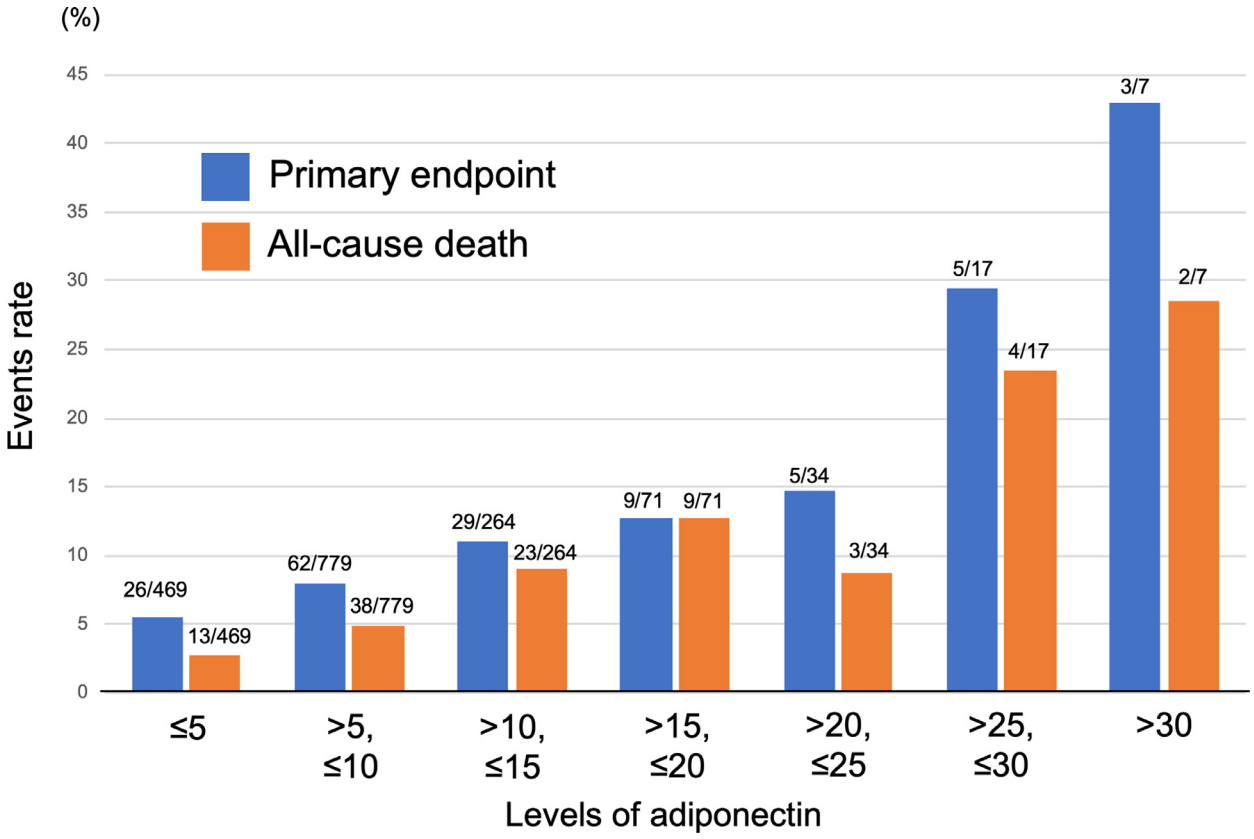

Figure 2. The event rates of primary end point (all-cause death, myocardial infarction, stroke) and all-cause death per 5-μg/ml increase in adiponectin levels.

paradoxical relationship between higher adiponectin levels and cardiovascular events is unknown. Risk stratification of ACS patients can be performed by measuring serum adiponectin early in the course of hospitalization. However, the clinical significance of adiponectin levels may be variable in women, patients aged <65 years, and patients with BMI ≥25 kg/m^2. Further prospective studies are needed to validate and further elucidate our findings.

This study has some limitations that must be acknowledged. First, it was retrospective and based on a subgroup of a prospective study. Second, our study population consisted entirely of Japanese ACS patients, which could influence the generalizability of our findings to non-Japanese patients. There are significant differences in adiponectin levels in Asian versus Caucasian (and other) populations.[32] Moreover, some reports show that the biological characteristics of adiponectin vary not only with race but also with the genotype of adiponectin. Thus, the results are not universal and are influenced by many factors, including race, as well as gender, age, and BMI.

In conclusion, higher adiponectin levels were associated with an increased incidence of cardiovascular events and all-cause mortality in ACS patients. The value of adiponectin in predicting cardiovascular events among ACS patients might be limited in women, patients aged <65 years, and patients with BMI >25 kg/m^2.

Table 2
Hazard ratio for the primary and secondary end point per 5 μg/ml increase of adiponectin

		Nonadjusted model			Adjusted model		
	Number of events, n (%)	HR*	95% CI	p value	HR*	95% CI	p value
Primary endpoint	139 (8.5 %)	1.31	1.13-1.47	0.0007	1.32	1.10-1.55	0.004
All-cause death	93 (5.7 %)	1.32	1.13-1.51	0.001	1.28	1.04-1.54	0.02
Non-fatal myocardial infarction	20 (1.2 %)	0.86	0.34-1.49	0.67	0.74	0.34-1.63	0.46
Non-fatal stroke	34 (2.1 %)	1.35	0.98-1.67	0.07	1.54	1.09-2.01	0.02

CI = confidence interval; HR = hazard ratio.

Primary end point is defined as the composite end point of all-cause death, nonfatal myocardial infarction, and nonfatal stroke.

Adjusted model was adjusted by randomized treatment arm, age, gender, body mass index, the prevalence of diabetes mellitus, history of myocardial infarction, history of heart failure, baseline levels of glomerular filtration rate, and high-sensitivity C-reactive protein.

* per 5 μg/ml increase of adiponectin.

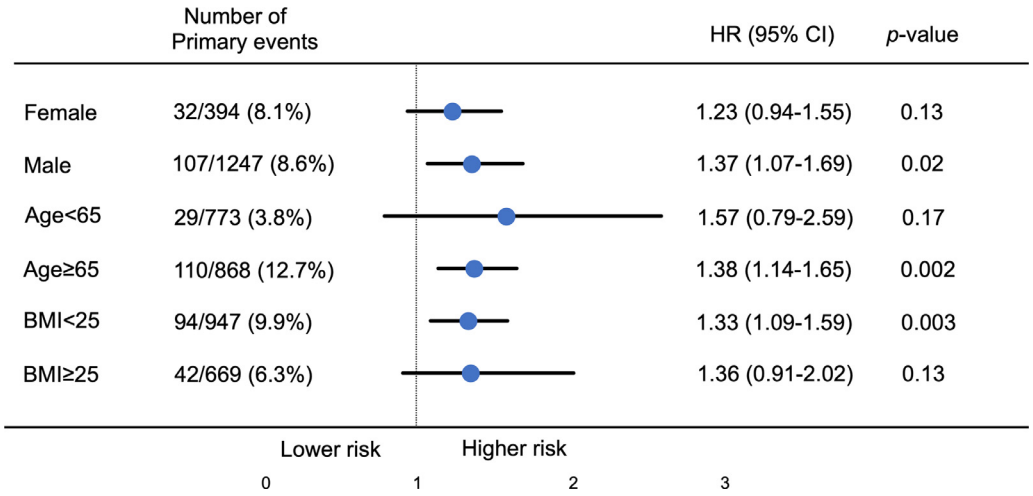

Figure 3. Hazard ratio for the primary end point per 5-μg/ml increase of adiponectin according to gender, age, and body mass index. Analyses were adjusted by patient clinical factors and laboratory findings.
BMI = body mass index.

Authors' Contributions

HA, JY, HO, and NH conceptualized and designed the original study. HA collected the data and enrolled and followed the patients. HN and HA analyzed and interpreted the data. HN and HA drafted and wrote the manuscript. JY, HO, and NH reviewed the manuscript. All authors, external and internal, had full access to all data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the analysis.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.10.053.

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