admission showed a borderline positive correlation with BNP (β = 0.43, p = 0.076); however, they related with BNP and HDL as well as age at discharge. The plasma HMW-APN levels positively related only with age at admission; however they positively related with HDL and age at discharge. A relationship between APN and BNP has been demonstrated in a wide range of patients [6,7,20,25–30], and it has been shown that BNP directly increased APN production in adipocytes [31]. However, the small number of patients in our study precluded showing a clear relationship between BNP and APN in the acute phase. Invasive monitoring of hemodynamics was not performed in this study. However, APN values did not associate with the ratio of early diastolic transmitral flow velocity to mitral annular velocity, which is known to relate with the left ventricular end-diastolic pressure.

We found the higher the HMWR at admission and the larger decrease in HMWR was associated with a preferable prognosis on the exploratory survival analyses. The decrease in HMWR may reflect the treatment responsiveness of patients with acute HF. Patients with a larger decrease in HMWR had a lower left ventricular mass index, which may indicate that they had less severe left ventricular remodeling. The cardioprotective effect of APN via several cellular pathways may mediate this better prognosis [8,9,32–34].

Our prognostic results may contradict several previous studies. Several studies in chronic HF have shown that higher APN levels were associated with a worse prognosis or future deterioration of cardiac function [5–7,25,26,35]. Tsutamoto et al. showed that higher total APN levels were associated with higher mortality in chronic HF; however, HMW-APN levels were less useful to predict mortality and HMWR levels were not different between survivors and non-survivors [7]. HMW-APN may lose its functional predominance and its predictive value under specific pathophysiological conditions [36]. In chronic HF, the relevance of increased plasma APN levels as an indicator of disease severity may be more relevant than its function as a pathophysiological mediator. Our study suggested that in acute HF higher levels of HMWR and their changes may exert their predominant cardioprotective effect and be better prognostic indicators in contrast to chronic HF. Dieplinger et al. showed that the higher plasma total APN level in acute HF related to a worse prognosis; however, they did not evaluate the levels of HMW-APN [37]. Because the HMWR values varied substantially even among subjects with similar total APN levels in plasma, we have to evaluate HMW-APN and HMWR levels in the future studies on acute HF [3].

Limitations

The small number of patients means that this study lacks a statistical power to conduct a complex analysis. However, the elevation of the plasma total APN and HMW-APN levels at admission and the decrease of these values and HMWR in response to treatment were evident even in this small number of patients.

Our patients did not show marked hypertension at the acute phase. Most of the patients could be classified as having acute HF with normal or moderately elevated blood pressure rather than with elevated blood pressure [38]. The former is predominantly accompanied with systemic congestion and minimal pulmonary congestion, whereas the latter is predominantly accompanied with pulmonary congestion, more often accompanied with preserved ejection fraction and thought to be caused by abnormal blood pressure responses [39]. Our cases might have fewer symptoms related with pulmonary congestion. Although 30% of the cases were classified as New York Heart Association class II, the relative paucity of symptoms does not necessarily mean they had less severe heart failure. In fact, about half of the patients had died or were readmitted during the follow-up period. Our patients may not include most severe patients in terms of the BNP values. The results of our study should be confirmed in a wider range of patients in future studies.

Our control subjects were not completely normal. They were admitted for the treatment of supraventricular arrhythmia. They were free from symptoms of heart failure with normal range of BNP and their plasma APN levels were similar to the values of normal subjects in the previous report [13,20].

Conclusion and clinical implication

Plasma total APN and HMW-APN levels are elevated in patients with acute HF. Total APN, HMW-APN levels, and HMWR decrease in response to the treatment. The higher HMWR at admission and larger decrease in HMWR may predict a better prognosis of acute HF. Further study is warranted to evaluate the prognostic impact of the dynamic response of APN in acute HF.

Acknowledgments

This work is supported by Grants-in-aid from the Ministry of Health, Labor, and Welfare-Japan; Grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology-Japan; Grants from the Japan Cardiovascular Research Foundation; and Grants from the Japan Heart Foundation. We would like to thank Akiko Kada, MPH and Hiroyuki Uesaka, PhD (National Cerebral and Cardiovascular Center, Suita, Japan) for statistical advice. We also wish to thank Dr William C Little (Wake Forest School of Medicine, Winston-Salem, NC, USA) for assistance in preparing the manuscript. We would like to thank Ms. Mika Nishimura for the coordinating work in this project.

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ORIGINAL ARTICLE

Decreased glomerular filtration rate is a significant and independent risk for in-hospital mortality in Japanese patients with acute myocardial infarction: report from the Hokkaido acute myocardial infarction registry

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Renal dysfunction is a significant risk factor in the prognosis of patients with cardiovascular diseases. We sought to determine the relationship between estimated glomerular filtration rate (eGFR) values and in-hospital mortality in Japanese acute myocardial infarction (AMI) patients. A total of 2266 consecutive AMI patients admitted to 22 hospitals in Hokkaido were registered. The eGFR values were determined using the following equation: $eGFR=194\times(\text{serum creatinine})^{-1.094}\times(\text{age})^{-0.287}$ ($\times 0.739$ if female). Patients were classified into four groups according to their eGFR values: $\geqslant 60$ (n=1304), 30–59 (n=810), 15–29 (n=87) and $<15\,ml\,min^{-1}$ per 1.73 m^2 (n=65). A total of 110 patients (4.9%) died during hospitalization. The in-hospital mortality rate was significantly higher in patients with reduced eGFR values at 2.3, 5.4, 24.1 and 23.1% for eGFR values of $\geqslant 60$, 30–59, 15–29, and $<15\,ml\,min^{-1}$ per 1.73 m^2, respectively. The odds ratios for in-hospital all cause death were 8.26 (95% confidence interval (CI): 2.22–30.77) for eGFR$<15\,ml\,min^{-1}$ per 1.73 m^2 and 3.42 (95% CI: 1.01–11.61) for eGFR 15–29 $ml\,min^{-1}$ per 1.73 m^2 compared with eGFR $\geqslant 60\,ml\,min^{-1}$ per 1.73 m^2. Similarly, the odds ratios for in-hospital cardiac death were 8.43 (95% CI: 1.82–39.05) for eGFR$<15\,ml\,min^{-1}$ per 1.73 m^2 and 5.47 (95% CI: 1.51–19.80) for eGFR 15–29 $ml\,min^{-1}$ per 1.73 m^2. In conclusion, the eGFR of $<30\,ml\,min^{-1}$ per 1.73 m^2 was a significant and independent risk for in-hospital mortality in abroad cohort of Japanese patients with AMI.

Hypertension Research (2012) **35,** 463–469; doi:10.1038/hr.2011.224; published online 19 January 2012

Keywords: acute myocardial infarction; chronic kidney disease; estimated glomerular filtration rate; mortality

INTRODUCTION

Chronic kidney disease (CKD) is increasingly becoming recognized as a global public health problem.[1] The National Kidney Foundation has published clinical guidelines on the evaluation, classification and risk stratification in patients with CKD.[2] Despite the recognized association between a reduced estimated glomerular filtration rate (eGFR) and poor prognosis, screening for CKD is frequently limited to the measurement of serum creatinine,[3,4] which does not accurately reflect the GFR. As a result, the management of this risk is often not optimized. The risks of CKD included not only the progression to end-stage renal failure but also the occurrence of adverse cardiovascular outcomes.[5–9] Previous studies have demonstrated that CKD is an independent risk factor for morbidity and mortality in the general population,[10] as well as in patients with cardiovascular diseases such as post acute myocardial infarction (AMI).[11] Anavekar *et al.*[11] reported that CKD was a common and significant independent risk factor for cardiovascular events in AMI patients based on data from the Valsartan in Acute Myocardial Infarction Trial (VALIANT). The risk was progressive, and each 10 unit reduction in the eGFR was significantly associated with a 10% increase in the relative risk of death or nonfatal cardiovascular complications.[11] However, the patients in the VALIANT study had heart failure, left ventricular dysfunction, or both as a complication of AMI, and patients with a baseline serum creatinine level $>2.5\,mg\,dl^{-1}$ were excluded. Therefore, the patients enrolled in the study by Anavekar *et al.*[11] were not representative of the general AMI population routinely encountered in clinical practice. It is critically important to determine the prognostic impact of CKD in the registry data of Japanese patients with AMI.

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Received 19 May 2011; revised 9 October 2011; accepted 17 October 2011; published online 19 January 2012

The aim of the present study was to examine the prognostic significance of eGFR values on the in-hospital mortality in Japanese AMI patients in routine clinical practice.

METHODS

Patients

The study patients consisted of 2266 consecutive patients hospitalized because of AMI in 22 hospitals in Hokkaido from 2005 to 2007.

AMI was defined by the presence of at least two of the following criteria:[12–14] (1) a clinical history of chest pain persisting for $\geqslant$30 min, (2) ischemic electrocardiographic changes and (3) a peak creatine kinase level equivalent to more than twice the upper limit of normal. All patients underwent coronary catheterization within 24 h after the onset of AMI. Body weight and height were measured in the morning after fasting. Body mass index was calculated as body weight (kg) divided by squared height (m). Smoking habits were determined using a self-reported questionnaire. Patients who had never smoked and ex-smokers were classified as 'nonsmokers'. Hypertension was defined as a history of systolic blood pressure $\geqslant$140 mm Hg and/or diastolic blood pressure $\geqslant$90 mm Hg or the use of oral antihypertensive drugs. Dyslipidemia was defined as a fasting total cholesterol $\geqslant$220 mg per 100 ml or the use of anti-hypercholesterol drugs. Diabetes mellitus was defined as fasting plasma glucose $\geqslant$126 mg per 100 ml or the use of oral hypoglycemic drugs or insulin. Patients who had suffered from myocardial infarction and stroke were defined as 'prior cardiovascular disease'. Blood samples were obtained after an overnight fast in the hospital. The creatine kinase values were measured every 4 h after admission to determine the peak value. The information regarding all cause death and cardiac death during hospitalization was obtained by physicians in the hospitals where the patients were admitted. Cardiac death was defined as a death due to heart failure, fatal arrhythmia, cardiac rupture or recurrent myocardial infarction. The patient data were registered in each hospital and reported to the data management office at Hokkaido University. Written informed consent was obtained from each patient or a family member. The study protocol was approved by the ethics committee at Hokkaido University School of Medicine.

Measurement of the eGFR

To calculate the eGFR, serum creatinine was measured using the compensated Jaffe creatinine method at the time of admission to the hospital. The eGFR was calculated using the equation for Japanese as follows:[15] eGFR=194$\times$(serum creatinine)$^{-1.094}\times$(age)$^{-0.287}$ ($\times$0.739 if female) ml min^{-1} per 1.73 m^2.

Statistical analysis

The characteristics of the study subjects were expressed as means $\pm$ s.d. for continuous variables, median (and interquartile range) for skewed distribution variables, and percentages for categorical variables according to the eGFR values. The differences in variables among groups were examined by analysis of variance, Kruskal–Wallis test or chi-square test. The association between the risk factors and in-hospital deaths of AMI patients was assessed using multiple logistic regression analysis. The principal model included the following candidate variables: demographics (age, sex, body mass index, smoking, prior cardiovascular disease), medical history (hypertension, diabetes mellitus, dyslipidemia, Q wave myocardial infarction and peak creatine kinase), angiographic data (number of diseased vessels, Killip classification, thrombolysis in myocardial infarction flow grade 0 at admission and thrombolysis in myocardial infarction flow grade 3 after treatment) and procedural information (mechanical support and treatment). Variables that were regarded as significant (P<0.05) were included in subgroup multivariate analyses. A P-value of <0.05 indicated statistical significance. All statistical analyses were performed using the SPSS statistical package for Windows version 11.0 (Chicago, IL, USA).

RESULTS

Patient characteristics

Figure 1 shows the distribution of the eGFR in the study patients. The mean eGFR value was 64.4 $\pm$ 23.7 ml min^{-1} per 1.73 m^2, ranging from 3.3 to 171.2 ml min^{-1} per 1.73 m^2 for 2254 patients. In all, 12 patients under hemodialysis were included in the group of eGFR values

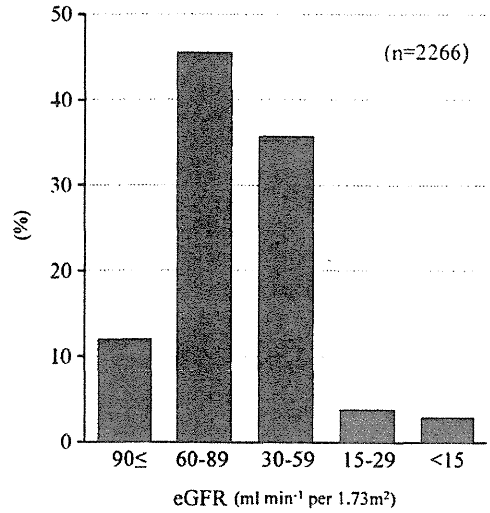

Figure 1 The distribution of the eGFR in the study patients.

<15 ml min^{-1} per 1.73 m^2. In all, 962 (42.5%) patients had an eGFR <60 ml min^{-1} per 1.73 m^2 or dialysis treatment.

Table 1 shows the baseline demographic and medical characteristics of the patients according to eGFR levels. The mean age of the patients was 66 $\pm$ 12 years and 72.0% were men. Patients with a reduced eGFR were older and more often women. They were more likely to have hypertension, diabetes mellitus, dyslipidemia and prior cardiovascular disease.

Table 2 shows the baseline angiographic and procedural characteristics of the patients according to eGFR levels. Patients with a reduced eGFR were more likely to have severe coronary artery stenosis, severe heart failure symptoms based on Killip classifications and higher use of mechanical supports such as intraaortic balloon pumping or percutaneous cardiopulmonary support. The prevalence of thrombolysis in myocardial infarction flow grade 0 at admission and thrombolysis in myocardial infarction flow grade 3 after treatment was lower with reduced eGFR levels. The performance of percutaneous coronary intervention by stent implantation was lower and that of thrombolysis, balloon angioplasty and coronary artery bypass grafting was higher with reduced eGFR levels.

Outcomes

A total of 110 (4.9%) patients died because of any causes and 84 (3.7%) patients died because of cardiac events during hospitalization during the follow-up period of 20 $\pm$ 17 (2–92) days.

Table 3 shows the odds ratios and 95% confidence interval (CI) for all cause and cardiac death according to eGFR levels. The rates of all cause death were 2.3, 5.4, 24.1 and 23.1% in patients with eGFR values $\geqslant$60, 30–59, 15–29 and <15 ml min^{-1} per 1.73 m^2, respectively. The rates of cardiac death were 1.8, 4.1, 19.5 and 15.4% in subjects with eGFR values $\geqslant$60, 30–59, 15–29 and <15 ml min^{-1} per 1.73 m^2, respectively. Decreases in the eGFR levels were associated with a significant progressive elevation of risk for all cause (P<0.05 for trend) and cardiac death (P<0.01 for trend). By multivariate analysis with an eGFR $\geqslant$60 ml min^{-1} per 1.73 m^2 as the reference, patients with eGFR of 15–29 and <15 ml min^{-1}per 1.73 m^2 had a significantly elevated risk for all cause death (OR 3.42, 95% CI 1.01–11.61 and OR 8.26, 95% CI 2.22–30.77, respectively) and cardiac death (OR 5.47, 95% CI 1.51–19.80 and OR 8.43, 95% CI 1.82–39.05, respectively). By multiple logistic regression analysis, age, Killip classification $\geqslant$II at admission, prior cardio-

Table 1 Demographic and medical characteristics of the patients according to eGFR levels

		eGFR				
	Total (n=2266)	*≥60 (n=1304)*	*30–59 (n=810)*	*15–29 (n=87)*	*<15 (n=65)*	P-*value*
Age (years)	66±12	63±12	71±11	77±9	78±11	<0.001
Male (%)	72.0	76.5	67.9	55.2	56.4	<0.001
Body mass index (kg m^{-2})	24.4±3.7	24.5±3.6	24.3±3.5	23.5±4.4	24.2±6.5	0.15
Smoking (%)	50.5	57.3	41.8	30.8	48.3	<0.001
Hypertension (%)	44.6	36.1	53.0	69.4	76.2	<0.01
Diabetes mellitus (%)	22.7	19.5	23.8	38.8	50.0	<0.001
Dyslipidemia (%)	20.6	18.7	23.0	28.0	20.0	<0.05
Prior cardiovascular disease (%)	20.7	16.5	26.1	26.4	29.7	<0.01
Q wave myocardial infarction (%)	66.1	72.3	55.7	67.5	70.2	0.57
Peak creatine kinase (IU per 100 ml)	2559 (1441–4201)	2623 (1486–4275)	2492 (1440–4107)	2505 (1018–3692)	2604 (1112–4281)	0.26

Abbreviation: eGFR, estimated glomerular filtration rate.
Values are means±s.d., median (and interquartile range) and percentage.

Table 2 Angiographic and procedural characteristics of the patients according to eGFR levels

		eGFR				
	Total (n=2266)	*≥60 (n=1304)*	*30–59 (n=810)*	*15–29 (n=87)*	*<15 (n=65)*	P-*value*
Number of diseased vessels (%)						
LMT	4.3	2.8	5.1	9.2	16.9	<0.001
One vessel	55.1	59.6	50.9	47.8	29.2	<0.001
Two vessel	27.3	26.1	29.1	22.1	35.4	<0.01
Three vessel	13.3	11.5	14.9	20.9	18.5	<0.001
Killip classification ≥II						
At admission (%)	18.5	11.7	24.5	47.1	43.5	<0.01
Mechanical support (IABP/PCPS) (%)	13.7	10.8	15.6	26.4	30.8	<0.001
TIMI flow grade 0 at admission (%)	68.8	69.7	69.9	57.5	53.8	<0.01
TIMI flow grade 3 after treatment (%)	99.1	99.4	98.9	97.3	96.2	<0.05
Treatment (%)						
Thrombolysis	6.8	5.2	8.1	13.8	13.9	<0.001
Balloon angioplasty	6.6	6.6	6.3	5.8	12.3	<0.001
Coronay stent	85.9	87.5	85.1	79.3	72.3	<0.001
CABG	0.7	0.7	0.5	1.1	1.5	<0.001

Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; IABP, intraaortic balloon pumping; LMT, left main trunk; PCPS, percutaneous cardiopulmonary support; TIMI, thrombolysis in myocardial infarction.

vascular disease, peak creatine kinase and eGFR values were significant and independent predictors for all cause death. Age, the use of mechanical support, peak creatine kinase and eGFR values were significant and independent predictors for cardiac death (Table 4).

Table 5 shows the results of subgroup analysis for all cause death according to eGFR levels stratified by sex, age (≥65 *vs.* <65 years) and comorbidities (hypertension *vs.* no hypertension and diabetes mellitus *vs.* no diabetes mellitus). The eGFR <30 ml min^{-1} per 1.73 m^2 was associated with poor outcomes in each subgroup, which is in agreement with the results of the primary analysis.

DISCUSSION

The present study demonstrated that the prevalence of AMI patients with an eGFR <60 ml min^{-1} per 1.73 m^2 was 42.5% based on a large-scale, multicenter trial. A reduced eGFR was a significant and independent risk for in-hospital all-cause and cardiac mortality. Moreover, AMI patients with eGFR values <30 ml min^{-1} per 1.73 m^2 had a significantly greater mortality risk than patients with values ≥60 ml min^{-1} per 1.73 m^2.

Previous studies used serum creatinine levels rather than the eGFR to detect renal dysfunction.[3,4] However, the accuracy of serum creatinine levels is limited as a marker of renal function because significant kidney dysfunction can be present despite a normal serum creatinine concentration. Serum creatinine has a nonlinear association with eGFR according to age, sex and lean body mass.[16,17] The National Kidney Foundation[2] and Kidney Disease Improving Global Outcomes (KDIGO)[18] have recommended using an eGFR estimated by serum creatinine, and eGFR <60 ml min^{-1} per 1.73 m^2 is selected as the cutoff value for the diagnosis of CKD. The eGFR values were generally estimated by the modification of diet in renal disease or creatinine clearance. Imai *et al.*[19] reported that the modification of diet in renal disease equation might overestimate the GFR in Japanese populations compared with the GFR measured using insulin clearance. Matsuo *et al.*[15] demonstrated that the accuracy of the eGFR estimation was

Table 3 The odds ratios and 95% CI for all cause and cardiac death according to eGFR values

	eGFR				
	⩾60 (n=1304)	30–59 (n=810)	15–29 (n=87)	<15 (n=65)	P for trend
All cause death					
n (%)	30 (2.3)	44 (5.4)	21 (24.1)	15 (23.1)	
Model 1, odds ratio (95% CI)	1.00	1.66 (1.01–2.73)	7.58 (3.95–14.53)	10.64 (5.31–21.30)	<0.001
Model 2, odds ratio (95% CI)	1.00	1.58 (0.99–2.81)	6.24 (3.03–12.85)	9.55 (4.39–20.77)	<0.001
Model 3, odds ratio (95% CI)	1.00	1.05 (0.47–2.36)	3.42 (1.01–11.61)	8.26 (2.22–30.77)	<0.05
Cardiac death					
n (%)	24 (1.8)	33 (4.1)	17 (19.5)	10 (15.4)	
Model 1, odds ratio (95% CI)	1.00	1.52 (0.87–2.67)	7.49 (3.67–15.29)	8.90 (4.01–20.00)	<0.001
Model 2, odds ratio (95% CI)	1.00	1.46 (0.85–2.52)	7.10 (3.31–15.20)	8.88 (3.74–21.04)	<0.001
Model 3, odds ratio (95% CI)	1.00	1.02 (0.41–2.53)	5.47 (1.51–19.80)	8.43 (1.82–39.05)	<0.01

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
Model 1, adjusted for demographic (age and sex) variables.
Model 2, adjusted for demographic (age and sex) and medical (hypertension, diabetes mellitus and dyslipidemia) variables.
Model 3, adjusted for demographic (age and sex), medical (body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, prior cardiovascular disease, Q wave myocardial infarction and peak creatine kinase), angiographic (number of diseased vessles and killip classification ⩾II) and procedural (mechanical support, TIMI (thrombolysis in myocardial infarction) flow grade 0 at admission and TIMI flow grade 3 after treatment) variables.

Table 4 Multivariate predictors of outcomes by multiple logistic regression analysis

	Odds ratio	95% CI	P-value
All cause death			
Age (per 1 year increase)	1.06	1.02–1.10	<0.01
Killip classification ⩾II at admission	2.60	1.19–5.69	<0.05
Prior cardiovascular disease	2.21	1.02–4.79	<0.05
Peak creatine kinase (per 100 IU per 100 ml increase)	1.02	1.01–1.03	<0.01
eGFR (per 10 ml min^{-1} per 1.73 m^2 decrease)	1.36	1.14–1.62	<0.01
Cardiac death			
Age (per 1 year increase)	1.06	1.02–1.10	<0.01
Mecanical support (IABP/PCPS)	3.51	1.39–8.84	<0.01
Peak creatine kinase (per 100 IU per 100 ml increase)	1.01	1.01–1.02	<0.05
eGFR (per 10 ml min^{-1} per 1.73 m^2 decrease)	1.37	1.13–1.68	<0.01

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IABP, intraaortic balloon pumping; PCPS, percutaneous cardiopulmonary support.
Adjusted for demographic (age and sex), medical (body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, prior cardiovascular disease, Q wave myocardial infarction, peak creatine kinase and eGFR), angiographic (number of diseased vessles and killip classification ⩾II) and procedural (mechanical support, TIMI (thrombolysis in myocardial infarction) flow grade 0 at admission and TIMI flow grade 3 after treatment) variables.

more improved using the new Japanese equation rather than using the modification of diet in renal disease equation in Japanese populations. Therefore, the present study used the new Japanese equation to calculate the eGFR values.

Previous studies demonstrated that CKD is an independent risk factor for cardiovascular disease in the general population in Japan.[20,21] Anavekar *et al.*[11] showed that the prevalence of CKD patients suffering from AMI in Western countries was 33.5%, and Nakamura *et al.*[22] reported that it was 31.6% in Japanese patients with coronary artery disease. The prevalence of CKD in the present study was 42.4%, which is higher than the rates reported in previous studies.[11,22] These discrepancies may be partially explained by the differences in ethnicity and other risk factors such as age and obesity. More importantly, the registry used in this study enrolled all patients that were admitted to the hospital because of AMI and did not exclude those who had higher levels of serum creatinine or dialysis treatment. Thus, the patients in the present study had a high prevalence of renal dysfunction and were considered to be more reflective of current routine clinical practice.

The present study extended the previous studies and demonstrated the prognostic significance of reduced eGFR in patients with coronary artery disease.[3,10,20,21,23–28] The Atherosclerosis Risk in Communities (ARIC) study[23] and the Second National Health and Nutrition Examination Survey (NHANES II)[3] demonstrated that a mild reduction in eGFR was a significant risk factor for both coronary vascular disease and all-cause mortality. The present study confirmed the prior studies by Anavekar *et al.* in which reduced eGFR was independently associated with an increased risk of fatal and nonfatal adverse cardiovascular events after AMI.[11] However, in their study, the study patients were limited to have baseline serum creatinine levels <2.5 mg dl^{-1} and heart failure. In addition, only 20% of the patients were treated with percutaneous coronary intervention. Thus, the impact of CKD has not been elucidated in a representative cohort of patients receiving contemporary therapy for AMI. To examine the

Table 5 Subgroup analysis for all cause death according to eGFR levels

	Total patients, n	*All cause death,* n	*Odds ratio*	*95% CI*	P*-value*
Male	1632	39			
⩾60	997	6	1.00	Reference	
30–59	550	16	1.55	0.83–2.92	0.17
<30	85	17	4.60	1.81–11.70	<0.01
Female	634	71			
⩾60	307	24	1.00	Reference	
30–59	260	28	1.76	0.61–5.08	0.30
<30	67	19	10.23	3.43–34.52	<0.001
Age ⩾65 years	1327	91			
⩾60	597	23	1.00	Reference	
30–59	610	39	1.45	0.81–2.60	0.21
<30	120	29	4.13	1.68–10.14	<0.01
Age <65 years	939	19			
⩾60	707	7	1.00	Reference	
30–59	200	5	2.40	0.60–9.68	0.22
<30	32	7	27.12	6.70–78.28	<0.001
Hypertension	1010	70			
⩾60	471	14	1.00	Reference	
30–59	429	30	2.02	0.98–4.19	0.06
<30	110	26	7.33	2.56–21.05	<0.001
No hypertension	1256	40			
⩾60	833	16	1.00	Reference	
30–59	381	14	1.13	0.50–2.56	0.76
<30	42	10	2.69	1.12–6.58	<0.05
Diabetes mellitus	513	44			
⩾60	254	8	1.00	Reference	
30–59	193	18	1.25	0.67–2.35	0.49
<30	66	18	10.66	2.66–42.73	<0.01
No diabetes mellitus	1753	66			
⩾60	1050	22	1.00	Reference	
30–59	617	26	2.68	0.99–5.66	0.06
<30	86	18	3.38	1.17–9.83	<0.05

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.
Adjusted for demographic (age and sex), medical (body mass index, smoking, hypertension, diabetes mellitus, dyslipidemia, prior cardiovascular disease, Q wave myocardial infarction and peak creatine kinase), angiographic (number of diseased vessles and killip classification ⩾II) and procedural (mechanical support, TIMI (thrombolysis in myocardial infarction) flow grade 0 at admission and TIMI flow grade 3 after treatment) variables.

impact of eGFR in AMI and to determine whether it is independently associated with prognosis, we analyzed data from a prospective broad cohort of patients with AMI. The patients in the present study had baseline serum creatinine levels ranging from 0.3 to 12.6 mg dl^{-1}, and percutaneous coronary intervention was performed in 92.5% of the patients during the acute phase. We thus could extend the prognostic impact of CKD from selected patients in large-scale clinical trials to a diverse cohort of AMI patients in general. Kasai *et al.*[29] demonstrated that lower eGFR values were significant long-term predictors for all-cause and cardiac mortality in Japanese patients who underwent complete coronary revascularization using a 10-year cohort study. The present study also confirmed these findings. Although the present study included both patients that underwent complete and incomplete coronary revascularization, adjustments for this variable were included in the statistical analysis. As a result, the findings in this study might be more applicable to a general population.

The present study demonstrated that the significant risk factors differed depending on the outcomes such as all cause and cardiac death (Table 4). There are potential explanations for these findings. Cardiac death was defined as death due to heart failure, fatal arrhythmia, cardiac rupture and recurrent myocardial infarction. In contrast, all cause death included not only cardiac death but also other causes of death such as infection. Killip classification and prior cardiovascular disease were independent predictors for all cause death, suggesting that heart failure associated with AMI might induce systemic organ failure and other complications leading to death. Mechanical support was an independent predictor for cardiac death, indicating that severe circulatory shock associated with

AMI may result in cardiac death, including fatal arrhythmia and cardiac rupture.

There are several possible explanations by which CKD increases the in-hospital mortality in patients with AMI. CKD may be indicative of traditional risk factors such as older age, hypertension, dyslipidemia and diabetes mellitus, which have been established to be closely related to cardiovascular outcomes.[30] Therefore, CKD may reflect the presence of severe coronary artery disease. Even after adjustments for demographic, medical, angiographic and procedural variables, the eGFR remained a significant risk for in-hospital all-cause and cardiac mortality. The increase in mortality with a reduced eGFR can be partly explained by nontraditional factors associated with CKD, including increased inflammatory factor levels,[31] elevated homocysteine levels,[32] enhanced coagulability[31] and endothelial dysfunction,[33] which were not assessed in this study.

Study limitations

First, we only assessed the baseline eGFR and could not determine the effects of changes in eGFR on outcomes. Second, the present study did not collect data regarding the use of medication after hospitalization because it varies widely among patients according to their clinical status, especially during the acute phase of AMI. However, the use of medication may affect the outcomes of patients during the long-term follow-up. Third, information was not collected during the follow-up after discharge, and the impact of CKD on the long-term outcomes in AMI patients could not be assessed. Fourth, coronary catheterization was performed after the onset of AMI in all patients, but severe patients who could not undergo coronary catheterization were not included. Therefore, the present results cannot be applied to all patients with AMI in general.

CONCLUSION

The reduced eGFR was a significant and independent risk for in-hospital all-cause and cardiac mortality in a broad cohort of Japanese patients hospitalized with AMI. Evaluation of renal function and effective management of these high-risk patients with AMI is important.

ACKNOWLEDGEMENTS

Participating hospitals and investigators for the Hokkaido Acute Myocardial Infarction Registry are as follows: Teisuke Anzai (Hokkaido Cardiovascular Center, National Hospital Organization Hakodate Hospital), Naoya Matsumura, Yasuhiro Makita (Hakodate Municipal Hospital), Hiroshi Asajima, Naotaka Saito (Hakodate Central General Hospital), Sigeru Takechi (Date Red Cross Hospital), Masaharu Machida (Tomakomai City Hospital), Takashi Shogase, Hitoshi Okada, Satoru Chiba (Nikko Memorial Hospital), Takefumi Ozaki (Chitose City Hospital), Junichi Teranishi (Nishi Sapporo National Hospital), Noriyoshi Kato, Yasumi Igarashi (Sapporo City General Hospital), Kouichi Kanda (Sapporo-Kosei General Hospital), Kazuo Tomita, Tetsuro Koya (NTT East Japan Sapporo Hospital), Toshiaki Nakagawa, Takehiro Yamashita, Toru Morita (Cardio-vascular Center Hokkaido Ohno Hospital), Masayuki Sakurai, Katsuhiko Sato, Yasushi Takagi (Hokko Memorial Hospital), Eiichiro Imamura (Ogasawara Clinic, Sapporo Hospital), Sigeo Kakinoki, Cika Takagi (Otaru Kyokai Hospital), Hisashi Matsuo (Keiwakai Ebetsu Hospital), Hideyuki Takano, Mitsunori Otsubo (Hokkaido Chuo Rosai Hospital), Isao Sato (Hokkaido Chuo Rosai Hospital Spinal Cord Injury Center), Takayuki Hirabayashi, Motoi Sasaki (Sunagawa City Medical Center), Yutaka Yamada (Asahikawa City Hospital), Yuta Nakagawa, Hiroyuki Iwano, Kagami Hirabayashi (Kitami Red Cross Hospital), Hidetsugu Sakai (Kushiro Rosai Hospital), Tomoharu Nakamura (Kushiroshi-Ishikai Hospital), Masashige Takahashi (Wakkanai City Hospital) and Ichiro Yoshida (Hokuto Medical Corporation Hokuto Hospital).

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ORIGINAL ARTICLE

Plasma adiponectin levels predict cardiovascular events in the observational Arita Cohort Study in Japan: the importance of the plasma adiponectin levels

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As the plasma level of adiponectin is related to metabolic syndrome and cardiovascular events, a low plasma adiponectin level may either cause or trigger cardiovascular disorders. The purpose of this study was to determine whether a low adiponectin level contributes to cardiovascular events, and to investigate the factors influencing adiponectin in the Japanese Arita-cho cohort study.We followed about 2000 subjects in Arita-cho, Saga, Japan as a cohort study, and we enrolled 637 subjects (205 men; 65.1 ± 8.3 years old) who participated in annual health checks from 2005 to 2008 and underwent measurement of the plasma adiponectin level and an oral glucose tolerance test. We monitored the incidence of cardiovascular or cerebrovascular events in these subjects until the end of 2010, discontinuing follow-up at 3 years after the start of enrollment. Subjects with low plasma adiponectin levels ($<10.5\,ng\,ml^{-1}$) had a higher incidence of newly diagnosed cardiovascular diseases such as acute heart failure or acute myocardial infarction than those with high plasma adiponectin levels ($\geqslant 10.5\,ng\,ml^{-1}$) over an average of 2.95 years of follow-up. Multivariate analysis showed that the adiponectin level was predicted by the following parameters in all subjects: age ($\beta = 0.16$), male gender ($\beta = -0.267$), homeostasis model assessment of insulin resistance ($\beta = -0.140$) and the plasma levels of high-density lipoprotein cholesterol ($\beta = 0.104$), uric acid ($\beta = -0.13$), triglycerides ($\beta = -0.169$) and brain natriuretic peptide ($\beta = 0.151$). The difference in plasma glucose before and 120 min after the intake of a 75-g glucose load did not influence the plasma adiponectin level. The plasma adiponectin level is useful for predicting cardiovascular events, and is a measure of the risk of lifestyle-related diseases.
Hypertension Research advance online publication, 5 April 2012; doi:10.1038/hr.2012.42

Keywords: adiponectin; myocardial infarction; stroke

INTRODUCTION

Adiponectin is a protein that is secreted exclusively by adipose tissue and contributes to the regulation of lipid and glucose metabolism. Adiponectin is also reported to have anti-inflammatory and anti-atherosclerogenic effects[1,2] in addition to its influence on insulin sensitivity and hepatic gluconeogenesis.[3,4] Such reports have led to the concept that a low plasma adiponectin level could predict the incidence of vascular events. However, there have been few prospective studies of plasma adiponectin levels and coronary artery disease (CAD) in healthy populations, and the results obtained have been inconclusive. The British Women's Heart and Health Study found no association between the plasma adiponectin level and new-onset CAD during 4 years of follow-up.[5] In older Dutch subjects, a high baseline plasma adiponectin level was associated with increased 15-year mortality.[6] In young survivors (<60 years of age) following a first myocardial infarction, however, a low plasma adiponectin level was associated with recurrent infarction.[7] Indeed, hypoadiponectinemia has usually been recognized as a risk factor for CAD[8-10] and the adiponectin level was linked to the severity of heart failure in our previous study.[11] Taken together, it seems that the plasma adiponectin level may influence cardiovascular or cerebrovascular events but not decisively, because the adiponectin level varies in relation to gender, race and the presence or absence of lifestyle-related disease.

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Received 22 December 2011; revised 24 January 2012; accepted 14 February 2012

Therefore, we investigated the predictive value of the plasma adiponectin level for cardiovascular or cerebrovascular disease, and explored factors that influence adiponectin in a cohort study performed in Arita-cho (Saga, Japan). As adiponectin is closely related to the pathophysiology of diabetes mellitus, we particularly investigated the influence of insulin resistance, and that of the glucose and insulin levels after the oral glucose tolerance test (OGTT), on the plasma adiponectin level.

METHODS

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of the National Cerebral and Cardiovascular Center and Arita-cho. Written informed consent was obtained from each subject before participation in the study.

Study population

The study population included participants in the health check program of Arita-cho (Saga, Japan) from 2005 to 2008 (the Arita-cho cohort Study). Participants who underwent an OGTT were included, but those who had cardiovascular and/or cerebrovascular disease at baseline were excluded from follow-up.

We enrolled 637 of the more than 2000 subjects who participated in the Arita-cho cohort study. The mean age, systolic/diastolic blood pressure (BP) and heart rate of the men ($n=205$) and women ($n=432$) was 66.4 ± 8.2 and 65.1 ± 8.4 years, 134.4 ± 18.0/82.6 ± 10.8 and 129.7 ± 20.0 mm Hg/78.8 ± 10.2 mm Hg and 63.3 ± 10.0 and 66.1 ± 10.1 per min, respectively.

Laboratory tests

Blood was collected from each participant at least 10 h after the last food intake to measure the plasma levels of adiponectin, fasting plasma glucose, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and brain natriuretic peptide (BNP). The height, body weight and waist circumference of all participants were also measured. The OGTT was performed after a 10-h overnight fast. Each participant ingested a solution containing 75 g of dextrose, and venous blood samples were obtained at 0, 30, 60, 90 and 120 min for determination of the plasma glucose level, whereas plasma insulin levels were measured at 0 and 120 min. Then Δ insulin was calculated as the difference between the baseline and the 2-h insulin values, whereas ΔBG (Δ blood glucose) was calculated as the difference between the baseline and the 2-h plasma glucose values.

The plasma concentration of adiponectin was measured by an immunoradiometric assay and the plasma concentration of BNP was measured with a commercial kit immunoradiometric assay for human BNP (Shionoria; Shionogi, Osaka, Japan). The insulin resistance index was determined by the homeostasis model assessment of insulin resistance (HOMA-IR) method.

Cardiovascular and cerebrovascular events

Information on cardiovascular and cerebrovascular diseases was obtained from a standardized questionnaire at baseline and at the annual health checks. If a subject provided information that suggested the possibility of new-onset cardiovascular or cerebrovascular disease, we obtained confirmation from the clinic or hospital where the participant had consulted a cardiologist or neurologist. Diagnosis of new cardiovascular or cerebrovascular disease was defined as the study endpoint during follow-up. Cardiovascular events were defined as hospitalization or death due to heart failure or else the occurrence of acute myocardial infarction. Cerebrovascular events were defined as hospitalization or death due to stroke. For participants without cardiovascular or cerebrovascular events, the final date of follow-up was the date of last contact and follow-up was discontinued at 3 years after enrollment.

Statistical Analysis

Results are expressed as the mean ± s.d. or as percentages. Analysis of variance was employed for continuous variables and the χ^2-test was used for categorical data to compare differences between groups. Tukey's test was used for *post-hoc* analysis if analysis of variance revealed a statistically significant difference. For variables that did not show a normal distribution, including TG, HOMA-IR, BNP and adiponectin, the data were transformed into natural logarithmic values before statistical analysis. Multivariate analysis was performed to identify independent predictors. Gender-specific multivariate linear regression models were used to identify the associations that remained significant after adjustment for other variables. Cardiovascular and cerebrovascular event-free curves were drawn by the Kaplan–Meier method and then were compared by the log-rank test. All analyses were performed with SPSS software (SPSS version 12.0, Chicago, IL, USA), and $P<0.05$ was considered statistically significant.

RESULTS

Among 637 subjects, 384 participants without history of either cardiovascular or cerebrovascular disease enrolled in Arita-cho from 2005 to 2007 completed follow-up. These participants were divided into two groups based on the 50th percentile of plasma adiponectin (10.5 ng ml^{-1}). During the follow-up period, five participants from the low-adiponectin group (<10.5 ng ml^{-1}) suffered from cardiovascular disease (acute decompensated heart failure due to hypertension in three and acute myocardial infarction in two) and four participants developed cerebrovascular disease (cerebral hemorrhage in two and cerebral infarction in two). In the high-adiponectin group (⩾10.5 ng ml^{-1}), two participants suffered from cerebrovascular disease (both had cerebral infarction) and none of the participants developed cardiovascular disease. The cumulative cardiovascular and cerebrovascular event-free rate was lower in the low-adiponectin group (Figure 1). The cardiovascular event-free rate was markedly decreased in the low-adiponectin group (Figure 2), whereas the cerebrovascular event-free rate was similar in both groups (Figure 3).

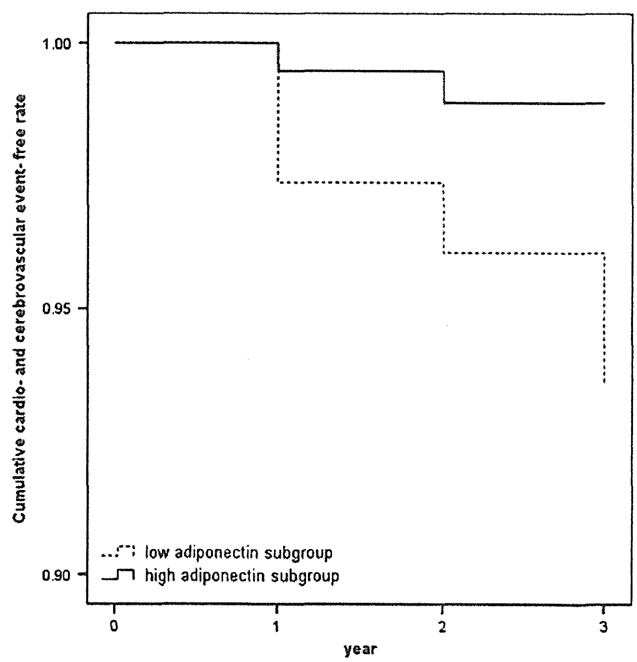

Figure 1 Cardiovascular and cerebrovascular event-free curves obtained with the Kaplan–Meier method in the respective groups divided by adiponectin levels. All participants were divided into two groups according to 50th percentile of adiponectin levels (10.5 ng ml^{-1}). Cumulative cardiovascular and cerebrovascular event-free rates in the low-adiponectin subgroup ($n=191$) and high-adiponectin subgroup ($n=193$) were 93.6% and 98.9%, respectively (log-rank test, $P=0.02$).

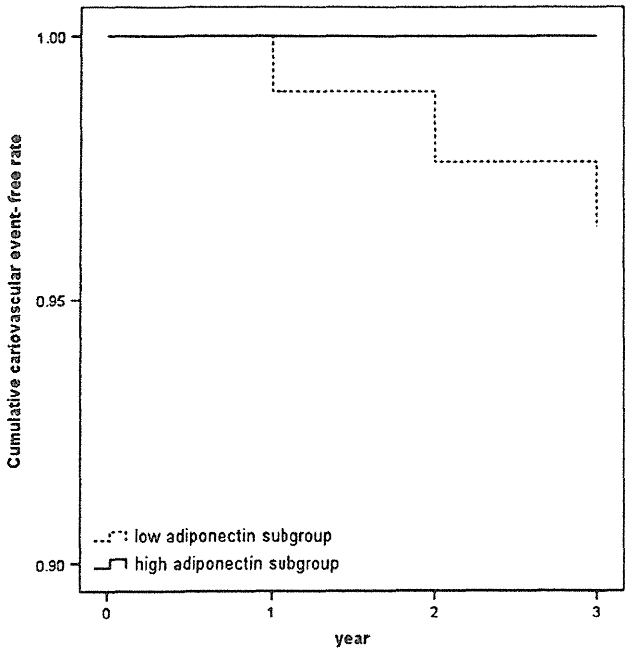

Figure 2 Cardiac event-free curves obtained with the Kaplan–Meier method in the respective groups divided by adiponectin levels. All participants were divided into two groups according to 50th percentile of adipoecntin levels (10.5 ng ml^{-1}). Cumulative cardiaovascular event-free rates in the low-adiponectin subgroup (n = 191) and high-adiponectin subgroup (n = 193) were 96.4% and 100%, respectively (log-rank test, P = 0.02).

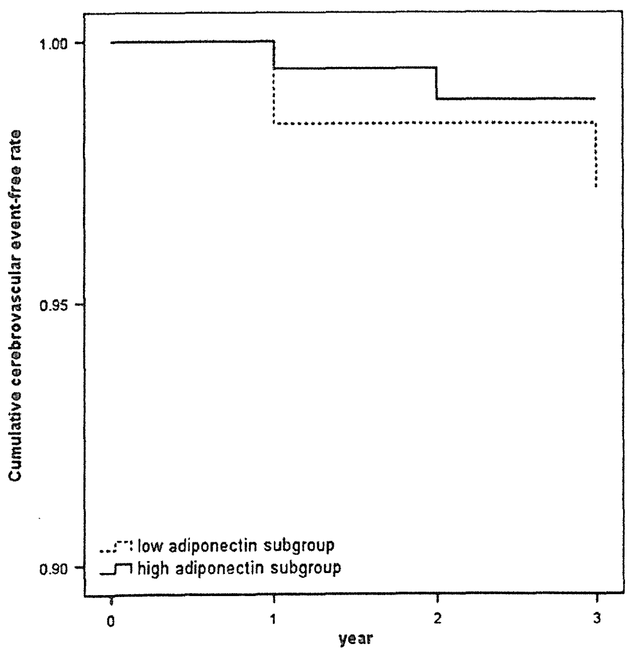

Figure 3 Cerebrovascular event-free curves obtained with the Kaplan–Meier method in the respective groups divided by adiponectin levels. All participants were divided into two groups according to 50th percentile of adipoecntin levels (10.5 ng ml^{-1}). Cumulative cerebrovascular event-free rates in the low-adiponectin subgroup (n = 191) and high-adiponectin subgroup (n = 193) were 97.2% and 98.9%, respectively (log-rank test, P = 0.37).

Adiponectin level may be related to BP, and we found that four men in the low-adiponectin group developed hypertension, whereas none of the subjects in the high-adiponectin group developed hypertension, hinting that adiponectin is related to hypertension. However, systolic BP in the low- and high-adiponectin groups were 130.0 ± 18.6 and 131.0 ± 19.1 mm Hg, respectively (P = 0.40); diastolic BPs in the low- and high-adiponectin group were 79.5 ± 9.5 and 78.2 ± 10.6 mm Hg, respectively (P = 0.26). Furthermore, the systolic and diastolic BP during the annual check-up in three subjects who developed heart failure due to hypertension was 130.2 ± 20.0 and 81.2 ± 8.3 mm Hg, respectively, at examination. The two subjects with a low adiponectin level who had myocardial infarction had no experience of smoking, and did not have diabetes mellitus, but both had hypertension and one of them had dyslipidemia. Our data set did not include data for anticoagulants and anti-hypertensive therapy.

We then investigated factors that influenced the plasma adiponectin level. Table 1 shows the clinical characteristics of all 637 participants from 2005 to 2008 categorized by plasma adiponectin quartiles (first quartile, <6.66 ng ml^{-1}; second quartile, ⩾6.66 ng ml^{-1} and <9.80 ng ml^{-1}; third quartile, ⩾9.80 ng ml^{-1} and <14.28 ng ml^{-1}; fourth quartile: ⩾14.28 ng ml^{-1}). There were no significant differences of HbA_{1c} among the four quartiles. The fourth quartile was older than the other three quartiles, and plasma levels of HDL-C and BNP were significantly higher in the fourth quartile than in the other three. The fourth quartile had lower BMI, waist circumference, plasma uric acid, plasma TG, Δ insulin, Δ BG, HOMA-IR and percentage of men than the other three quartiles. The first quartile had higher fasting BG levels and a higher prevalence of diabetes mellitus than the other three quartiles. In addition, the mean BMI of the four quartiles was below 25. The plasma adiponectin level (Ln adiponectin) was higher in women than in men (2.42 ± 0.51 *vs.* 1.99 ± 0.99; P < 0.0001). The plasma adiponectin level was negatively associated with HOMA-IR in women, men and all subjects (Figure 4).

To further clarify the factors that influenced the plasma adiponectin level, multivariate linear regression analysis was performed with plasma adiponectin as the dependent variable. As a result, the age (β = 0.16), HOMA-IR (β = −0.140), male gender (β = −0.267) and plasma levels of HDL-C (β = 0.104), uric acid (β = −0.13), TG (β = −0.169) and BNP (β = 0.151) were significant predictors of the plasma adiponectin level in all participants (Table 2). Because women have higher plasma adiponectin levels than men, we separately investigated the determinants of adiponectin in men and women. We found that the age (β = 0.153), HOMA-IR (β = −0.208) and plasma BNP(β = 0.149) were independently associated with the plasma adiponectin level in men, whereas the age (β = 0.194), Δ insulin (β = −0.152), HOMA-IR (β = −0.131) and plasma levels of HDL-C (β = 0.129), uric acid (β = −0.119), TG (β = −0.179) and BNP (β = 0.161) were independently associated with adiponectin in women. Thus, the present study demonstrated that HOMA-IR, but not Δ BG, is associated with a decrease of the plasma adiponectin level.

DISCUSSION

In the present study, we found that subjects with low plasma adiponectin levels had a higher incidence of cardiovascular diseases, such as heart failure and myocardial infarction, than subjects with high plasma adiponectin levels. On the other hand, we found that age, insulin resistance and the plasma levels of HDL-C, uric acid, TG and BNP were independent predictors of the plasma adiponectin level.

Table 1 Comparison of characteristics by quartiles of serum adiponectin levels in all subjects

	First quartile (n = 159)	*Second quartile (n = 159)*	*Third quartile (n = 160)*	*Fourth quartile (n = 159)*	P-*value*
Age (years)	64.0 ± 9.3	64.5 ± 9.2	66.1 ± 7.2	67.4 ± 7.1[c,e]	0.001
BMI (kg m^{-2})	23.4 ± 2.6	23.6 ± 3.1	22.5 ± 2.8[b,d]	21.4 ± 3.1[c,e,f]	<0.0001
Waist circumference (cm)	85.6 ± 6.9	86.2 ± 8.8	83.7 ± 8.9	79.3 ± 9.8[c,e,f]	<0.0001
HbA1c (%)	5.3 ± 0.4	5.4 ± 0.6	5.3 ± 0.3	5.3 ± 0.4	0.43
HDL-C (mg dl^{-1})	55.1 ± 13.6	58.8 ± 14.0	60.5 ± 14.1[b]	68.3 ± 15.7[c,e,f]	<0.0001
Uric acid (mg dl^{-1})	5.8 ± 1.4	5.1 ± 1.2[a]	4.6 ± 1.2[b,d]	4.5 ± 1.1[c,e]	<0.0001
Ln TG (mg dl^{-1})	4.8 ± 0.5	4.6 ± 0.4[a]	4.6 ± 0.5[b]	4.3 ± 0.4[c,e,f]	<0.0001
Ln adiponectin (ng ml^{-1})	1.6 ± 0.2	2.1 ± 0.1[a]	2.5 ± 0.1[b,d]	3.0 ± 0.2[c,e,f]	<0.0001
Δ insulin (μU ml^{-1})	50.7 ± 39.8	58.7 ± 53.6	40.1 ± 30.3[d]	30.9 ± 23.8[c,e]	<0.0001
Δ BG (mg dl^{-1})	48.9 ± 43.7	47.5 ± 44.1	36.0 ± 36.8[b]	33.4 ± 45.1[c,e]	0.001
Fasting glucose (mg dl^{-1})	97.1 ± 11.4	96.2 ± 10.4	92.8 ± 8.2[b,d]	93.1 ± [c,e]	<0.0001
Fasting insulin (μU ml^{-1})	5.8 ± 4.6	5.7 ± 4.1	4.4 ± 2.3[b,d]	3.6 ± 1.9[c,e]	<0.0001
Ln HOMA-IR	0.13 ± 0.66	0.11 ± 0.64	−0.11 ± 0.55[b,d]	−0.35 ± 0.60[c,e,f]	<0.0001
Ln BNP (pg ml^{-1})	2.7 ± 0.7	2.9 ± 0.8	3.1 ± 0.7[b]	3.4 ± 0.8[c,e,f]	<0.0001
Gender (men)	95 (59.7%)	55 (34.6%)[a]	36 (22.5%)[b,d]	19 (11.9%)[c,e,f]	<0.0001
Diagnosed DM	25 (15.7%)	14 (8.8%)	10 (6.3%)[b]	12 (7.5%)[c]	0.02

Abbreviations: BG, blood glucose; BMI, body mass index; BNP, brain natriuretic peptide; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglyceride.
Adiponectin: First quartile, <6.66; second quartile, ⩾6.66 and <9.80; third quartile, ⩾9.80 and <14.28; fourth quartile: ⩾14.28.
[a]First *vs.* second quartile.
[b]First *vs.* third quartile.
[c]First *vs.* fourth quartile.
[d]Second *vs.* third quartile.
[e]Second *vs.* fourth quartile.
[f]Third *vs.* fourth quartile.

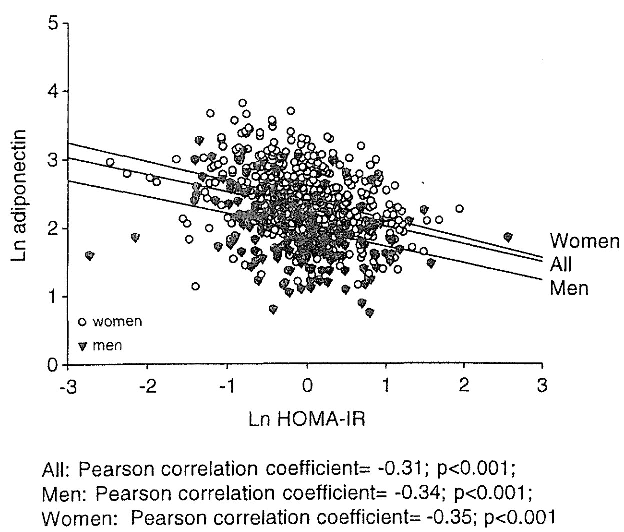

Figure 4 Scatter plot of the association between natural log-transformed plasma adiponectin levels and homeostasis model assessment-insulin resistance (HOMA-IR) in healthy subjects. Lines indicate the regression lines.

Furthermore, we showed that the glucose spike during the OGTT was not related to the plasma adiponectin level.

What is the role of adiponectin in cardiovascular and cerebrovascular events? First, a low adiponectin level was not associated with cerebral hemorrhage or infarction after adjusting for other cardiovascular risk factors in the JMS cohort study that was performed in 12 rural districts in Japan,[12] and that the finding corresponds with the present result that the plasma adiponectin level is not related to cerebrovascular events. Second, Persson *et al.*[7] reported that low plasma adiponectin levels are associated with myocardial infarction in individuals below the age of 60 years, and Nakamura *et al.*[10] found that hypoadiponectinemia may increase the risk of acute coronary syndrome. Furthermore, in a study of Japanese men with CAD, patients with acute coronary syndrome had lower adiponectin levels than stable CAD patients, whereas patients with multiple complex lesions had significantly lower adiponectin levels than those with solitary complex lesions.[13] Thus, low adiponectin levels may be related to vulnerability to coronary atherosclerosis, which was also confirmed by the results of the present study. An important new finding of the present study is that adiponectin levels were monitored in a cohort and cardiovascular events were assessed prospectively.In our study, the low adiponectin level predicted cardiovascular events but not cerebrovascular events. The vascular or endothelial response to adiponectin may differ between the coronary and cerebral artery; however, the precise molecular mechanism underlying this difference remained unclear. Further basic and epidemiological studies are needed to elucidate the lack of a protective effect of adiponectin against stroke.

With regard to the vulnerability of coronary plaques, hypertension is believed to be one of the most important factors. Iwashima *et al.*[14] reported that the plasma adiponectin levels were lower in hypertensive subjects in a hospital-based study. In addition, two prospective Asian studies have shown that hypoadiponectinemia is associated with incident hypertension. Chow *et al.*[15] conducted a 5-year prospective study to examine the association between adiponectin and hypertension in a nondiabetic Chinese cohort. From health insurance data, 391 healthy Japanese men were followed for a period of 6 years in another study, during which 45 of them developed hypertension.[16] Our results were partially consistent with those of these studies, because four men in the low-adiponectin group developed hypertension, whereas none of the subjects in the high-adiponectin group developed hypertension. However, BP was not linked to the adiponectin levels, although in the present study we did

Table 2 Multivariate linear regression analysis of independent determinants of Ln adiponectin

	All (n = 637)		*Men (n = 205)*		*Women (n = 432)*	
	β	P-*value*	β	P-*value*	β	P-*value*
Age (years)	0.160	<0.001	0.153	0.03	0.194	<0.001
BMI (kg m^{-2})	0.018	0.75	0.007	0.96	0.034	0.63
Waist circumference (cm)	−0.092	0.11	−0.134	0.30	−0.093	0.19
HbA1c (%)	−0.015	0.66	0.088	0.21	−0.067	0.12
HDL-C (mg dl^{-1})	0.104	0.005	0.100	0.16	0.129	0.007
Uric acid (mg dl^{-1})	−0.130	0.001	−0.126	0.06	−0.119	0.006
Ln TG (mg dl^{-1})	−0.169	<0.001	−0.151	0.05	−0.179	<0.001
Δ BG (mg dl^{-1})	0.014	0.77	−0.118	0.27	0.068	0.25
Δ insulin (μU ml^{-1})	−0.062	0.12	0.127	0.10	−0.152	0.004
Ln HOMA-IR	−0.140	0.001	−0.208	0.009	−0.131	0.02
Ln BNP (pg ml^{-1})	0.151	<0.001	0.149	0.03	0.161	<0.001
Diagnosed DM	−0.052	0.25	−0.001	0.99	−0.067	0.22
Gender (men)	−0.267	<0.001				

Abbreviations: BG, blood glucose; BMI, body mass index; BNP, brain natriuretic peptide; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglyceride.
All: adjusted R^2:0.38; Men: adjusted R^2:0.26; Women: adjusted R^2:0.30; *β*: standardized regression coefficient.

not have information about the anti-hypertensive drugs used. Indeed, in the Copenhagen City Heart Study, the plasma adiponectin level was not an independent predictor of new-onset hypertension,[17] so there may be a racial difference with regard to the influence of adiponectin on hypertension. The linkage between hypertension and the plasma adiponectin level is not conclusive in the present study.

The next issue is the mechanisms by which a low adiponectin level can be linked to cardiovascular disease. Ouchi *et al.*[18] reported that hypoadiponectinemia is associated with impaired endothelium-dependent vasorelaxation, and endothelial dysfunction is an important feature of the early stages of atherosclerosis and hypertension.[19] In Apo E-deficient mice, an increase in the plasma adiponectin level suppressed the progression of atherosclerotic lesions by attenuating endothelial inflammation and transformation of macrophages to foam cells *in vivo*.[20,21] Furthermore, a low adiponectin level and/or impaired endothelial dysfunction are associated with the onset of pressure-overload heart failure.[22] whereas impaired endothelial dysfunction is related to hypertension and diastolic dysfunction,[23] which may explain the high incidence of acute heart failure in patients who have hypertension as well as those with acute coronary syndrome. Therefore, a low plasma adiponectin level may provoke coronary and myocardial changes that culminate in cardiovascular disease.

Because a low adiponectin level was associated with an increased incidence of cardiovascular disease, we investigated the determinants of adiponectin among participants who underwent the OGTT, because we hypothesized that the glucose spike during this test would be related to the plasma adiponectin level. We found that the age, gender, insulin resistance and plasma levels of TG, HDL-C, BNP and uric acid influenced the adiponectin level in all participants, which agreed with previous reports.[5,24,25] However, we found that the glucose spike during the OGTT did not affect the plasma adiponectin level, although HOMR-IR (which represents insulin resistance) had an influence on adiponectin. The present results suggest that adiponectin may have a regulatory role in insulin secretion. However, this relationship between insulin secretion and the plasma adiponectin level was found in women, but not in men, in the present study. Therefore, the plasma adiponectin level may be influenced by the pattern of abnormal glucose metabolism, with the most important factor being the level of insulin resistance rather than the glucose spike or the amount of insulin secretion. Thus, impaired signal transduction following insulin receptor activation may be linked to the plasma adiponectin level.

Overall, the results of our study were consistent with those of other population-based studies. The plasma adiponectin level was inversely associated with insulin resistance, plasma TG and plasma uric acid, whereas it was positively correlated with HDL-C and BNP levels.[4,5,24,26] The adiponectin levels increase in patients with myocardial dysfunction in our study, although adiponectin is protective against heart failure because adiponectin attenuates cardiac hypertrophy.[22,27] The plasma adiponectin level may be upregulated to compensate for cardiovascular damage because BNP can modulate adiponectin signaling via a cyclic guanosine 5′-monophosphate-mediated pathway in human adipocytes.[28] That may be one of the explanations for the positive correlation between the plasma adiponectin and BNP.

However, several limitations of the present study should be considered. The study population was only of moderate size and the percentage of men was relatively low. This cohort study focused on rural residents, who may differ in various ways from urban residents. Moreover, the follow-up period was relatively short. Nevertheless, we demonstrated that the plasma adiponectin level is tightly related to cardiovascular events, suggesting that adiponectin is a potential biomarker for predicting cardiovascular events, although further studies are required for confirmation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by Grants-in-aids from the Japanese Ministry of Health, Labor and Welfare, and the Japanese Ministry of Education, Culture, Sports, Science and Technology and by Grants from the Japan Heart Foundation, and the Japan Cardiovascular Research Foundation.

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Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Landiolol, an Ultra-Short-Acting β_1-Blocker, More Effectively Terminates Atrial Fibrillation Than Diltiazem After Open Heart Surgery

– Prospective, Multicenter, Randomized, Open-Label Study (JL-KNIGHT Study) –

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Background: Recent studies have suggested that esmolol is the first choice for rate control in patients with postoperative atrial fibrillation (AF) after coronary artery bypass surgery, but side-effects of esmolol such as hypotension are problematic. To overcome this problem, landiolol, an ultra-short-acting β_1-blocker with a less negative inotropic effect than esmolol, has been developed. The aim of the present study was to investigate whether landiolol was effective for both rate control and conversion to normal sinus rhythm (NSR).

Methods and Results: A prospective, randomized, open-label comparison between i.v. landiolol and diltiazem in patients with postoperative AF was undertaken between January 2008 and June 2009 in Japan. Of 335 patients included in the analysis, 71 patients went into AF. Among these 71 patients, conversion to NSR within 8 h after onset of AF occurred in 19 of 35 patients (54.3%) in the landiolol group vs. 11 of 36 patients (30.6%) in the diltiazem group ($P<0.05$). The incidence of hypotension was lower in the landiolol group (4/35, 11.4%) compared with the diltiazem group (11/36, 30.6%; $P<0.05$). The incidence of bradycardia was also lower in the landiolol group (0%) compared with the diltiazem group (4/36, 11.1%; $P<0.05$).

Conclusions: Landiolol is more effective and safer than diltiazem for patients with postoperative AF after open heart surgery. (*Circ J* 2012; **76:** 1097–1101)

Key Words: Atrial fibrillation; Beta-blocker; Cardiovascular surgery; Landiolol

Supraventricular tachyarrhythmias, especially atrial fibrillation (AF), are common after open heart surgery.[1–3] In many cases, postoperative AF is transient and spontaneously reverts to sinus rhythm, but tachycardia due to prolonged AF may impair left ventricular function and cause congestive heart failure.[4] Previous studies reported that postoperative AF increases the incidence of postoperative pneumonia, myocardial infarction, and/or heart failure, followed by an increase in mortality.[5] It is also associated with increased low cardiac output syndrome and costs. Thus, heart rate and/or rhythm control are necessary to prevent cardiovascular events in patients with postoperative AF. Common therapeutic approaches to achieve rate and/or rhythm control include digoxin, β-blockers, calcium antagonists, and pharmacological or electrical cardioversion.[6] Recent studies suggest that, among these modalities, esmolol is the first-choice drug for patients with postoperative AF after coronary artery bypass grafting (CABG), but side-effects of esmolol such as hypotension are a concern.[7,8] To overcome such problems, an ultra-short-acting β_1-blocker, landiolol, has been developed by Ono Pharmaceutical in Japan. At low doses, landiolol can exert a clinically relevant negative chronotropic action without any negative inotropic effects, so that it is less

Received November 18, 2011; revised manuscript received January 5, 2012; accepted January 12, 2012; released online February 23, 2012 Time for primary review: 13 days

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Clinical Trial Registration Information: UMIN Clinical Trial Registry ID: UMIN000000957 [http://www.umin.ac.jp/ctr/index-j.htm].

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ISSN-1346-9843 doi:10.1253/circj.CJ-11-1332

likely to have negative inotropic effects compared with esmolol.[9,10] Although there have been several studies that support the efficacy of landiolol,[11–13] a large-scale multicenter randomized clinical trial has not been performed to assess the efficacy of landiolol for patients with postoperative AF after open heart surgery.

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The aim of the present prospective, randomized, open-label trial in patients with AF or atrial flutter (AFl) after open heart surgery was therefore to compare the efficacy and safety of landiolol to diltiazem for postoperative AF or AFl.

Methods

Study Design and Subjects

A prospective, multicenter, randomized, open-label study of i.v. landiolol vs. i.v. diltiazem in patients with postoperative AF or AFl (Japan Landiolol kick-off of novel investigation for gold standard heart study [JL-KNIGHT study]) was undertaken at 36 hospitals in Japan between January 2008 and June 2009. Patients between 20 and 85 years of age who were undergoing elective open heart surgery were eligible for inclusion. The steering committee initially planned to enroll 400 patients in the study, based on the following considerations. If the frequency of conversion to sinus rhythm after 8h of treatment with landiolol or diltiazem is 60% and 25%, respectively, the number of subjects required would be 30 for each group based on the Mooss et al data.[8] Considering dropout and withdrawal during the study, 40 patients would be needed for each group. Consequently, we estimated that the total number of subjects should be 400, assuming that the frequency of AF after open heart surgery is 20%. Exclusion criteria were acute myocardial infarction within 3 days; history of supraventricular arrhythmia that had required treatment; sinus node disease; permanent pacemaker; severe heart failure (New York Heart Association III/IV or ejection fraction <35%); atrioventricular block (AV block; ≥second degree); contraindications to either β-blocker or calcium channel blocker therapy; AF with a known secondary cause (eg, electrolyte imbalance, Wolff-Parkinson-White syndrome, or hyperthyroidism); hypotension (<90/60mmHg); and perioperative use of an anti-arrhythmic agent other than digitalis.

All patients provided written informed consent to this study after admission to hospital. The study protocol was approved by the institutional review boards and ethics committees of all participating hospitals, and the study was performed in accordance with the Declaration of Helsinki.

Study Protocol

When patients were enrolled in this study, one of the 2 study drugs was randomly assigned at the participating institution using the envelope method. Patients were continuously monitored on telemetry for up to 1 week after surgery. A study drug was given if postoperative AF/AFl occurred with a ventricular rate ≥100beats/min for 5min. Landiolol was given as a continuous infusion at an initial rate of $0.5–2\mu g \cdot kg^{-1} \cdot min^{-1}$ that was titrated to a maximum rate of $40\mu g \cdot kg^{-1} \cdot min^{-1}$ (reassessed every 10min) based on hemodynamic or electrocardiographic responses. Diltiazem was given as a bolus dose of 0.25mg/kg over 2min, followed by an initial rate of 3mg/h that was titrated to a maximum rate of 15mg/h (reassessed at approximately 1-h intervals) based on hemodynamic or electrocardiographic responses at the investigator's discretion. The maintenance infusion of either drug was titrated upward to control the ventricular rate at <90beats/min. Patients all received the study drugs following the onset of AF/AFl and had a treatment duration of 24h. If hypotension (systolic blood pressure <90mmHg) or bradycardia (heart rate <50beats/min) occurred, the dose was down-titrated or infusion of the drug was discontinued until symptoms resolved.

The primary endpoint was frequency of conversion to sinus rhythm after 8h of treatment. The secondary endpoints were (1) frequency of conversion to sinus rhythm after 24h of treatment and (2) achievement of rate control (<90beats/min).

Accordingly, the total number of treated patients who were converted to sinus rhythm or who achieved the target heart rate after 8h and 24h of study drug infusion was determined, and blood pressure and heart rate data were collected every 1h following initiation of therapy. Patients were assessed for adverse reactions including AV block, bronchospasm, asystole, bradycardia, and hypotension. When AF/AFl was converted to sinus rhythm, the patient was monitored on telemetry for 3 days after the discontinuation of the drug to detect the recurrence of arrhythmia.

Statistical Analysis

Continuous variables are expressed as mean±SD. Clinical characteristics of the 2 groups were compared using an independent t-test for continuous variables and with either Fisher's exact test or a chi-square test for categorical variables. Differences of conversion rates, the percentage of patients achieving rate control, and adverse events were analyzed with Fisher's exact test or the chi-square test as appropriate. In all analyses, P<0.05 was considered statistically significant.

Results

A total of 420 patients from 36 hospitals participated in the study. Among them, 82 patients (19.5%) developed postoperative AF and received one of the study drugs. In all patients, AFl was not observed perioperatively. Eighty-five patients were excluded because of missing data or lack of adherence to the study protocol, therefore 335 patients were included in the final analysis. Among them, 71 patients (21.2%) developed postoperative AF and received either landiolol (n=35) or diltiazem (n=36; **Figure**). The clinical characteristics of the 2 study groups were similar (**Table 1**).

A higher conversion rate to sinus rhythm after 8h of treatment was obtained in the landiolol group (54.3%) than the diltiazem group (30.6%; P<0.05; **Table 2**). In contrast, there was no difference between the landiolol and diltiazem groups with regard to conversion to sinus rhythm after 24h (74.3% vs. 61.1%, P=NS). When the efficacy of heart rate control (<90beats/min) was analyzed, there was no difference between the 2 groups after 8h and 24h of treatment. Only one of 35 patients in the landiolol group, however, had failure of heart rate control within 72h of starting treatment, while 8 of 36 patients in the diltiazem group did not achieve heart rate control (P<0.05).

With respect to side-effects, the incidence of hypotension (systolic blood pressure <90mmHg) was significantly lower in the landiolol group (11.4%; P<0.05) compared with the diltiazem group (30.6%; **Table 3**). In addition, 4 patients receiving diltiazem experienced bradycardia that required treatment, vs. no patients from the landiolol group (P<0.05). The length of intensive care unit stay, however, did not differ between the 2 groups (landiolol, 3.9±2.1 days; diltiazem, 3.4±1.2 days; NS).

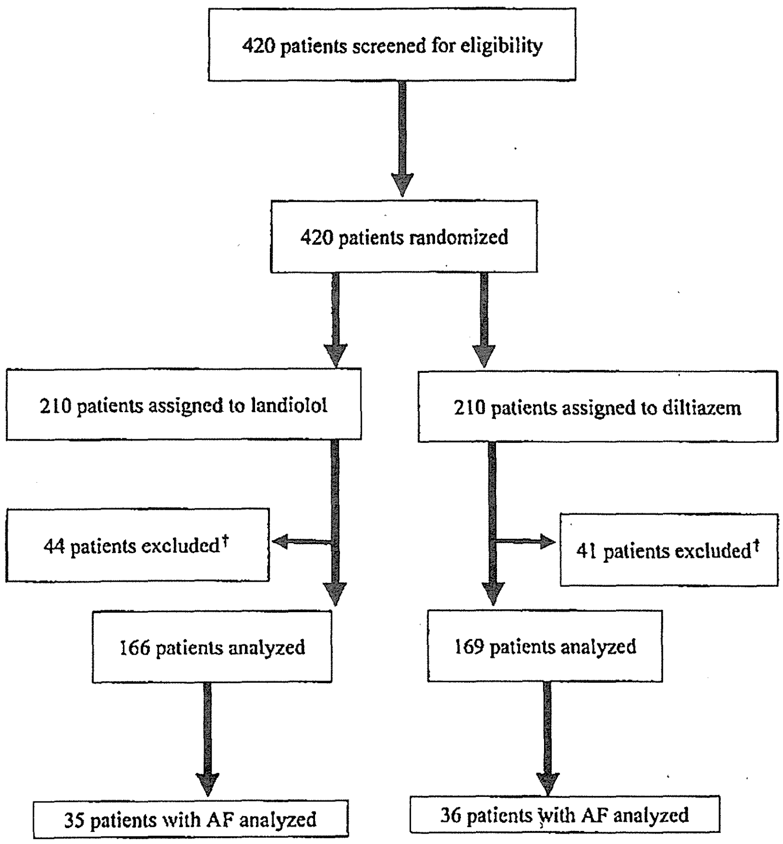

Figure. Trial profile. †Missing data or lack of adherence to the study protocol. AF, atrial fibrillation.

Table 1. Clinical Characteristics: Treated Patients

	Landiolol (n=35)	Diltiazem (n=36)
Age (years)	70.2±10.6	69.3±8.4
Sex (F/M)	11/24	12/24
Complications		
Hypertension	22	22
Diabetes	10	9
Preoperative oral β-blocker use	6	8
Surgery		
CABG	17	8
VR	10	15
CABG+VR	3	6
Others	5	7
Pre-infusion HR (beats/min)	129±20	131±20
Pre-infusion BP (mmHg)	116±26/62±14	112±17/62±13

Data given as mean±SD or n.
CABG, coronary artery bypass grafting; VR, valve replacement; HR, heart rate; BP, blood pressure.

Discussion

There were 2 main findings of this study. First, landiolol was more effective compared with diltiazem for conversion of AF to sinus rhythm within 8 h of starting treatment. Second, landiolol treatment for postoperative AF was associated with a lower incidence of side-effects such as hypotension or bra-

Table 2. Treatment Effects

	Landiolol (n=35)	Diltiazem (n=36)
Conversion to sinus rhythm		
<8h	19 (54.3)*	11 (30.6)
<16h	21 (60.0)	17 (47.2)
<24h	26 (74.3)	22 (61.1)
HR controlled, but not converted		
<8h	22 (62.9)	18 (50.0)
<24h	29 (82.9)	27 (75.0)
<72h	34 (97.1)*	28 (77.8)
Recurrence of AF	3/26 (11.5)	6/22 (27.2)

Data given as n (%). *P<0.05 vs. diltiazem (χ^2-test).
HR, heart rate; AF, atrial fibrillation.

Table 3. Adverse Effects and Duration of ICU Stay

	Landiolol (n=35)	Diltiazem (n=36)
Hypotension	4 (11.4)*	11 (30.6)
Bradycardia	0 (0)*	4 (11.1)
Ischemic ECG	0 (0)	2 (5.6)
AV block	0 (0)	0 (0)
Bronchospasm	0 (0)	0 (0)
ICU stay (days)	3.9±2.1	3.4±1.2

Data given as mean±SD or n (%). *P<0.05 vs. diltiazem (χ^2-test).
ICU, intensive care unit; ECG, electrocardiogram; AV, atrioventricular.

dycardia compared with diltiazem.

Although it is still not clear whether the same mechanisms leading to AF in the general population are responsible for the onset of postoperative AF, current evidence suggests that its pathogenesis is multifactorial. The inflammatory response and oxidative stress associated with cardiopulmonary bypass, cardiotomy, and ischemia-reperfusion injury can induce further myocardial damage and are arrhythmogenic, which may lead to the onset of AF in patients with a susceptible anatomical substrate. Moreover, excessive sympathetic activity or suppression of parasympathetic activity can promote the onset and persistence of AF.[14] It is well known that sympathetic hyperactivity and high circulating catecholamine levels occur after cardiac surgery. Increased sympathetic activation provokes ectopic impulses, inflammation, increased vascular permeability, and altered atrial refractoriness, contributing to the creation of an arrhythmogenic substrate.[15] In the present study, landiolol was more effective for achieving conversion to sinus rhythm than diltiazem, which suggests that controlling excessive sympathetic activity may be important in the treatment of postoperative AF.

The present results for landiolol seem to be similar to those for esmolol at first assessment, but are not. Regarding the effect of esmolol vs. calcium antagonists (verapamil or diltiazem) for postoperative AF: (1) esmolol was superior to calcium antagonists in the conversion rate[8,16] and did not inhibit spontaneous conversion;[17] (2) there was no difference of heart rate control or the incidence of side-effects between esmolol and calcium antagonists;[7,8] and (3) intraoperative use of esmolol for heart rate control may worsen cardiac performance, as indicated by an increase of pulmonary arterial pressure or pulmonary vascular resistance.[18] In contrast, the present study showed that landiolol treatment led to a significantly higher rate of conversion than diltiazem treatment during the initial 8 h of therapy and that only one of 35 patients in the landiolol group had inadequate heart rate control during the 72-h observation period following the start of treatment. Landiolol, however, caused a lower incidence of side-effects such as bradycardia and hypotension compared with diltiazem, so these results differed from the data obtained for esmolol and calcium antagonists.[7,8] One explanation for the disparity between esmolol and landiolol is that landiolol is a potent short-acting and more β_1-selective blocker than esmolol. Another is that landiolol exerts a clinically relevant negative chronotropic action without any associated negative inotropic action, thus having fewer negative inotropic side-effects compared with esmolol.[9,10] Therefore, landiolol may be superior to esmolol with respect to the suppression of cardiovascular events, although we did not compare these drugs in the present study. We used low-dose infusion of landiolol at a similar level as in other studies to minimize the incidence of side-effects. Fujiwara et al reported that low-dose infusion (1.5–2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) of landiolol for 2 days after CABG is effective and sufficient for preventing AF without suppressing cardiac function.[13] Sezai et al reported that infusion of landiolol at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ from the time of central anastomosis during CABG and for 2 days subsequently was more effective for preventing AF than placebo and was associated with a lower incidence of major complications.[19] The incidence of side-effect in these studies was similar to that in the present study.

In the present study, infusion of the ultra-short-acting β_1-blocker landiolol ($t_{1/2}$=4min) for only 24h maintained heart rate control for 48 h after the cessation of treatment, and 24-h infusion of landiolol had a similar suppressant effect to diltiazem on the recurrence of AF. It is possible that control of sympathetic activity at the time close to the onset of AF may be important for treating tachycardiac AF, but the mechanism involved is still unclear. Also, the optimum timing and duration of landiolol infusion need to be determined in the future.

In addition to treatment of AF, it is also important to prevent postoperative AF.[6] Several drugs, such as amiodarone and sotalol, have shown efficacy in preventing postoperative AF, but these agents need to be started several days before surgery and have the potential to cause significant adverse effects that include hypotension, bradycardia, and severe ventricular arrhythmias. Because landiolol may be able to prevent the postoperative onset of AF, we plan to start the JL-KNIGHT study II to test the preventive effects of landiolol.

Conclusion

This study showed that landiolol is more effective and safer than diltiazem for patients with postoperative AF after open heart surgery.

Acknowledgments

We would like to express our gratitude to Associate Professor Mitsuyoshi Urashima, Jikei University, for his contribution to the study and to Professor Tatsuyuki Kakuma, Kurume University School of Medicine, for his contribution to statistical analysis.

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