Disclosures

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Consciousness Level and Off–Hour Admission Affect Discharge Outcome of Acute Stroke Patients: A J–ASPECT Study

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Hemoglobin A1c predicts heart failure hospitalization independent of baseline cardiac function or B-type natriuretic peptide level

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ABSTRACT

Aims: Diabetes is a major risk factor for heart failure (HF). We examined whether baseline HbA_{1c} level predicts HF incidence independent of other HF risk factors, including baseline cardiac structural and functional abnormalities.

Methods: In patients with type 2 diabetes, multivariable Cox regression models were constructed to examine the independent association between baseline HbA_{1c} and future HF hospitalization.

Results: In 608 subjects (mean age, 66.5 years; men, 68%; mean HbA_{1c}, 9.1% (76 mmol/mol)), 92 were hospitalized for HF during a median follow-up of 6 years. For a 1% (11 mmol/mol) increase in baseline HbA_{1c}, the hazard ratio for HF was 1.23 (95% confidence interval, 1.1–1.7, $p < 0.001$) with adjustment for age, sex, body mass index, blood pressure and plasma B-type natriuretic peptide (BNP) level. The effect of HbA_{1c} on HF was independent of baseline left ventricular (LV) ejection fraction, the ratio of peak early to late diastolic filling velocity, and prevalent/incident coronary heart disease (CHD), and was more evident in patients with enlarged LV, decreased systolic function, prevalent CHD, or prevalent HF.

Conclusion: In patients with type 2 diabetes, HbA_{1c} significantly predicts future HF hospitalization independent of baseline BNP level or echocardiographic parameters.

1. Introduction

Diabetes is considered one of the major risk factors for heart failure (HF) [1]. The presence of diabetes markedly increases the likelihood of HF occurring, and results in a worse outcome for patients with HF [2–4]. In addition, an association between HbA_{1c} and HF incidence has been reported in patients with diabetes [2,5–7]. The result of a meta-analysis suggests that the relative risk for HF associated with a 1% (11 mmol/mol) increase in HbA_{1c} level among patients with type 2 diabetes is

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1.11 (95% confidence interval (CI), 1.05–1.18) [8]. Since diabetes is often associated with hypertension, coronary heart disease (CHD), chronic kidney disease (CKD), or prevalent/preclinical HF, all of which are major risk factors for HF incidence [1], and since, conversely, HF prevalence is an independent risk factor for developing or worsening diabetes [9], the association between diabetes and HF could be confounded by the HF- or diabetes-associated factors. Therefore, there is no clear proof of whether a high HbA_{1c} level predicts the incidence of HF beyond these co-morbidities.

In addition, since previous epidemiological studies have lacked the cardiac function or imaging data to detect subclinical myocardial dysfunction [2,5–7], it has not been fully addressed whether the association between HbA_{1c} and incidence of HF is independent of baseline cardiac dysfunction. In fact, since the progression to clinical HF may take a few years, it is likely that, in the cohorts studied previously, some patients with diabetes had preclinical HF at baseline [5].

Therefore, we sought to determine the association between HbA_{1c} and HF hospitalization with adjustment for blood pressure, CHD prevalence, estimated glomerular filtration rate (eGFR), and cardiac function evaluated by plasma B-type natriuretic peptide (BNP) or echocardiography at baseline, in order to examine the independent effect of baseline HbA_{1c} level on future incidence of HF in patients with type 2 diabetes.

2. Methods

2.1. Subjects

The study population was selected from patients who were referred to the Department of Endocrinology and Metabolism, National Cerebral and Cardiovascular Center, Osaka, Japan, between 1 January 2000 and 31 December 2007. A total of 1345 patients were referred to the center, of which 826 who had a diagnosis of type 2 diabetes were selected for the study. We analyzed results obtained from 608 of these patients who were asymptomatic for HF (class 1 of the New York Heart Association (NYHA) functional classification) at baseline, and who underwent screening echocardiography for silent cardiac dysfunction. Reasons for eligibility and non-participation at each stage of the study are given in Supplemental Fig. S1.

2.2. Determination of clinical variables and diagnosis of diseases

Age, sex, BMI, eGFR, cigarette smoking status, and alcohol consumption status were obtained at baseline. Echocardiographic parameters such as LV dimension, ejection fraction (EF), the ratio of peak early LV filling velocity to late diastolic atrial filling velocity (E/A ratio), and deceleration time were obtained by trained sonographers and reviewed by experienced cardiologists.

Diabetes was diagnosed by measuring fasting or non-fasting glucose levels, diagnosis of diabetes by a physician, or medical treatment for diabetes at baseline. Prevalent and incident HF were determined by expert cardiologists and defined either as death from HF (2.2% of total events) or as the first HF hospitalization during follow-up. Prevalent CHD was defined as a history of cardiologist-diagnosed myocardial infarction (MI) with elevated cardiac enzymes, or angina pectoris with coronary stenosis, documented myocardial ischemia, or a prior coronary reperfusion procedure at baseline. The incident coronary event was defined as the first hospitalization because of cardiologist-diagnosed acute coronary syndrome, including MI with elevated cardiac enzymes, unstable angina with documented coronary lesions, a coronary reperfusion procedure, or coronary arterial bypass operation during follow-up.

2.3. Statistical analysis

Baseline anthropometric characteristics according to HbA_{1c} tertiles (<8.4% (68 mmol/mol), 8.4% $\leq HbA_{1c} <$ 9.6% (81 mmol/mol), ≥9.6%) were compared using one-way ANOVA, Kruskal–Wallis test, or Pearson's chi-square test, as applicable. The proportion of individuals remaining free of incident HF at any time during follow-up was calculated using the Kaplan–Meier method. Risk of HF was analyzed by obtaining hazard ratios using Cox proportional hazard models. We compared models with adjustment for major HF risk factors using likelihood ratio tests. Models with HbA_{1c} as a continuous variable were used to determine the reduction in risk associated with a 1% (11 mmol/mol) reduction in the level of HbA_{1c}, while, in models with HbA_{1c} as a categorical variable, we compared hazard ratios according to HbA_{1c} category. The relative risk for new HF hospitalization was computed for the middle HbA_{1c} category (8.4% (68 mmol/mol) $\leq HbA_{1c} <$ 9.6% (81 mmol/mol)) and the highest HbA_{1c} category (≥9.6% (81 mmol/mol)) in comparison with the lowest HbA_{1c} category (<8.4% (68 mmol/mol)) as a reference, in the model adjusted for age, sex, BMI, systolic blood pressure, and eGFR (model 1), in the model adjusted for age, sex, BMI, systolic blood pressure, eGFR, and ln[BNP (pg/mL)] (model 2), and in the model adjusted for age, sex, BMI, systolic blood pressure, eGFR, EF, and E/A ratio (model 3).

In the subgroup analysis, the study population was divided by the median values of echocardiographic parameters, presence/absence of baseline co-morbidities, or duration of follow-up, and the hazard ratio for 1% (11 mmol/mol) increase in HbA_{1c} as a continuous variable for HF hospitalization was determined in each category after adjustment of factors in model 2. The entire study group was also divided into nine groups according to tertiles of HbA_{1c} (the cut-off points were 8.4% (68 mmol/mol) and 9.6% (81 mmol/mol)) stratified by three categories of BNP (the cut-off points were 39 pg/mL (median of ln[BNP(pg/mL)]) and 90 pg/mL (3rd quartile of ln[BNP(pg/mL)])) and risk of HF was calculated across these categories using Cox proportional hazard models as compared with the lowest HbA_{1c} and the lowest BNP group after adjustment of factors in model 1. We also determined the adjusted hazard ratios of HF according to the different HbA_{1c} categories (the cut-off points were 7% (53 mmol/mol), 8% (64 mmol/mol), 9% (75 mmol/mol) and 10% (86 mmol/mol)) compared with the risk for the 7% (53 mmol/mol) $\leq HbA_{1c} <$ 8% (64 mmol/mol) group as the reference.

Since coronary events such as MI often lead to cardiac dysfunction and subsequent HF, the association between glucose control and HF could be confounded by a CHD event during follow-up. Assuming that CHD and HF act as competing

events, the sensitivity analysis was performed by censoring all patients who developed CHD prior to HF at the time of the CHD event, where the incident HF occurred in individuals who had no clinical CHD event during follow-up at the time of first hospitalization for HF [7].

We further performed the correlation analysis with hazard ratios per each % step in HbA1c (from below 7.0% (53 mmol/mol) to above 10% (86 mmol/mol)) stratifying with the presence or the absence of prevalent MI at baseline. Age, gender, body mass index, systolic blood pressure, eGFR and ln[BNP(pg/mL)]-adjusted hazard ratios according to baseline HbA1c category were calculated in first HF hospitalization or censoring coronary event analyses, where the lowest category (HbA1c < 7.0% (53 mmol/mol)) was considered as the referent. Curve-fittings were performed by second-order polynomial regression analysis.

All analyses were conducted using JMP version 10.0.0 (SAS Institute, Cary, NC, USA) statistical software. All p values were two-tailed, and values less than 0.05 were considered statistically significant. All CIs were calculated at the 95% level.

3. Results

3.1. Baseline characteristics

The baseline characteristics of all subjects and according to three categories of HbA_{1c} are presented in Supplemental Table S1. The mean age of the subjects was 66.3 years and 68% were male. Mean BMI, fasting plasma glucose, HbA_{1c} level, and eGFR were 25.3, 151 mg/dL, 9.1% (76 mmol/mL) and 65 mL/min/1.73 m^2, respectively. Comparing the three HbA_{1c} categories, no significant differences were observed for the baseline characteristics except for age, alcohol consumption, triglyceride concentration, fasting blood glucose, and HbA_{1c} level. A higher HbA_{1c} was significantly associated with younger age, higher triglyceride level, and lower alcohol consumption. In the group of subjects as a whole, most had hypertension (82%) and dyslipidemia (82%), while more than half had prevalent CHD (54%) at baseline. Among the categories of increasing HbA_{1c} level, there were no significant trends in the proportions of these comorbidities. However, although they did not reach statistical significance, increased prevalence for lower baseline EF, thinner ventricular walls, and CHD was observed in the group with the highest level of HbA_{1c} (Supplemental Table S1).

3.2. Hospitalization for HF

The median follow-up time was 6 years for the 608 individuals who had diabetes and were available for analysis. Over the course of the follow-up, 92 patients were hospitalized for HF (15.1% of the total study population). The cumulative hospitalization rates for HF according to category of HbA_{1c} are shown in Supplemental Fig. S2. When the patients were divided into three groups according to HbA_{1c} tertile (<8.4% (68 mmol/mol), 8.4% $\leq HbA_{1c} <$ 9.6% (81 mmol/mol), and ≥9.6%), the Kaplan–Meier analysis showed that the slope of the curve for the high HbA_{1c} tertile (≥9.6% (81 mmol/mol)) was steeper, indicating an increased rate of HF development compared with that for the group with lowest level of HbA_{1c} group (<8.4% (68 mmol/mol); Supplemental Fig. S2a). In the censoring of a new CHD event analysis, which included only HF hospitalizations occurring in the absence of a prior coronary event during follow-up, the differences between the cumulative incidence curves for the three HbA_{1c} tertiles were more clearly visible and achieved statistical significance (log-rank $p = 0.0053$) (Supplemental Fig. S2b).

3.3. Cox proportional hazards model

Cox proportional hazard analysis with three different models was used to obtain hazard ratios for HF hospitalization with HbA_{1c} as a continuous (Table 1, top) and a categorical (Table 1, bottom) variable. The basic model including age, sex, BMI, systolic blood pressure, eGFR and HbA_{1c} as a continuous variable, produced a crude hazard ratio of 1.17 (95% CI, 1.05–1.30) for HF for each 1% increase in HbA_{1c} (model 1 in Table 1, left). The association between HbA_{1c} and incident HF was more consistent after adjustment for age, sex, BMI, systolic blood pressure, eGFR, and ln[BNP (pg/mL)], with a hazard ratio of 1.23 (95% CI 1.1–1.37) (model 2). The association was also independent of baseline LV, EF, or E/A ratio (model 3). Following censoring of the coronary event during follow-up, increased hazard ratios for the association were observed in all models (Table 1, right (Censoring coronary event)).

HbA_{1c} was also modeled as a categorical variable with cut-off points of 8.4% (68 mmol/mol) and 9.6% (81 mmol/mol) (Table 1, bottom). In all three models, the difference between risk in the lowest HbA_{1c} category and the highest category was significant. There was a nonsignificant trend toward an increased risk of HF hospitalization across other categories of HbA_{1c}, which became significant when follow-ups were censored at the first coronary event (Table 1, right). In the censoring coronary event analysis, a 1% (11 mmol/mol) increase in the HbA_{1c} level resulted in approximately a 30% increase in risk for HF, and patients with HbA_{1c} more than 9.6% (81 mmol/mol) were found to have a three to four times greater chance of developing HF compared with those with an HbA_{1c} level less than 8.4% (68 mmol/mol).

3.4. Sensitivity analysis

The effects of HbA_{1c} were next examined with respect to the choice of HbA_{1c} cut-off point and the choice of the echocardiographic variables analyzed after adjustment for HF risk factors. Supplemental Fig. S3 shows the results of regression analyses, which were based on the HbA_{1c} cut-off points of 7% (53 mmol/mol), 8% (64 mmol/mol), 9% (75 mmol/mol), and 10% (86 mmol/mol). When the HbA_{1c} 7–7.9% (53–63 mmol/mol) group was considered as a reference, the HbA_{1c}-associated risk of HF tended to increase linearly in patients whose HbA1c was more than 7% (53 mmol/mol), achieving statistical significance at HbA_{1c} 9% (75 mmol/mol). In addition, multivariate analysis with echocardiographic parameters, rather than BNP, indicated that HbA_{1c} predicts HF hospitalization independently of baseline EF (Table 1, model 3), E/A ratio (Table 1, model 3), LV diastolic dimension (LVDd; data not shown), or deceleration time (data not

Table 1 – Cox proportional hazard analysis with three different models.

	First HF hospitalization			Censoring coronary event		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
HbA_{1c} (continuous)						
Model 1	1.17	1.05–1.30	0.0065*	1.21	1.08–1.35	0.0011*
Model 2	1.23	1.1–1.37	0.0004*	1.28	1.14–1.44	0.0001*
Model 3	1.19	1.02–1.39	0.0272*	1.30	1.10–1.52	0.0023*
HbA_{1c} (categorical)						
Model 1						
Tertile 1 (<8.4%)	Referent			Referent		
Tertile 2 (8.4–9.5%)	1.41	0.82–2.45	0.2142	1.79	0.98–3.40	0.0597
Tertile 3 (9.6%≤)	1.96	1.18–3.35	0.0095*	2.72	1.54–5.03	0.0005*
Model 2						
Tertile 1 (<8.4%)	Referent			Referent		
Tertile 2 (8.4–9.5%)	1.54	0.90–2.71	0.118	2.01	1.10–3.82	0.0247*
Tertile 3 (9.6%≤)	2.24	1.33–3.87	0.0023*	3.10	1.75–5.78	0.0001*
Model 3						
Tertile 1 (<8.4%)	Referent			Referent		
Tertile 2 (8.4–9.5%)	1.85	0.88–4.05	0.1030	3.41	1.32–10.50	0.0101*
Tertile 3 (9.6%≤)	2.10	1.01–4.59	0.0458*	4.34	1.73–13.21	0.0013*

(Above) Hazard ratios of HF for each 1% increase in HbA_{1c}. (Below) Hazard ratios of HF for increasing category of HbA_{1c} as compared to the referent (HbA_{1c} < 8.4% (68 mmol/mol)). HbA_{1c} was modeled as a categorical variable with cut points of 8.4% (68 mmol/mol) and 9.6% (81 mmol/mol). Model 1; adjusted by age, sex, body mass index, systolic blood pressure and eGFR. Model 2; adjusted by factors in model 1 and BNP. Model 3; adjusted by factors in model 1, left ventricular ejection fraction and the E/A ratio.

* $P < 0.05$.

shown), either with or without censoring patients at the first coronary event.

3.5. *Effects of HbA_{1c} on HF hospitalization in BNP categories*

When Kaplan–Meier estimation of HF-free survival according to HbA_{1c} category was stratified by BNP category (<39 pg/mL, 39 ≤ BNP < 90 pg/mL, and ≥90 pg/mL), a clear difference was demonstrated between HbA_{1c} categories in the two higher BNP categories, whereas the difference was not observed in the lowest BNP category (Fig. 1a–c). Similarly, when censoring patients at the time of first coronary event during follow-up, there was a significant trend toward lower HF-free survival in the higher HbA_{1c} category, in the intermediate and in the highest BNP categories but not in the lowest BNP category (Fig. 1d–f).

We then evaluated the additive roles of HbA_{1c} and BNP as predictors of the risk of future HF events with adjustment of confounding factors, where the study patients were divided into nine groups according to low (<8.4%), intermediate (8.4–9.5%), and high (≥9.6%) levels of HbA_{1c}, and low (<39 pg/mL), intermediate (38–89.9 pg/mL), and high (≥90 pg/mL) levels of BNP. Adjusted HF-free survival rates (95% CI) for each group (Fig. 2a) suggested a combined effect of BNP and HbA_{1c}; that is, for example, in the intermediate BNP category, HF-free survival was lower as the HbA_{1c} level increased. The risk of HF hospitalization was the lowest among patients with the lowest levels of HbA_{1c} and the lowest BNP levels, while it was the highest among patients with the highest HbA_{1c} and highest BNP levels (Fig. 2a). The censoring coronary event analysis produced similar results (Fig. 2b). As shown in Fig. 2c and d, among patients with intermediate and high BNP levels, the risk of HF was significantly several-fold higher in those in the highest HbA_{1c} category compared with those in the lowest HbA_{1c} category.

3.6. *Subgroup analysis*

When the total number of patients was divided into two groups according to the median or the presence/absence of cardiac morbidity at baseline, an association between HbA_{1c} and HF hospitalization was demonstrated in the groups with enlarged LVDd, decreased EF, prevalent CHD, and prevalent CHF (Fig. 3). When the analysis using the fully adjusted model (model 2) was restricted to the subgroup of patients with diabetes and small LVDd, preserved EF, and without prevalent CHD or CHF, the association between HbA_{1c} and HF was no longer demonstrated (Fig. 3). Interestingly, censoring patients with incident CHD at the time of a coronary event restored the significant association between HbA_{1c} and HF hospitalization in patients without prevalent CHD or CHF (Fig. 3).

3.7. *Effects of HbA_{1c} category on HF hospitalization in patients with or without MI at baseline*

Cox proportional hazard analyses stratified by the presence or the absence of prevalent MI were next performed with the lowest HbA1c category as the referent, in the first HF hospitalization and the censoring coronary event analyses. As shown in Fig. 4, curve-fitting by second-order polynomial regression analysis demonstrated an apparent J-shaped relationship between baseline HbA1c category and HF hospitalization during follow-up in patients with prevalent MI, while hazard ratios tended to increase linearly in patients without MI. P-values against the HbA1c < 7.0% (53 mmol/mol) or 7–7.9% (63 mmol/mol) category were shown in Supplemental Table S2.

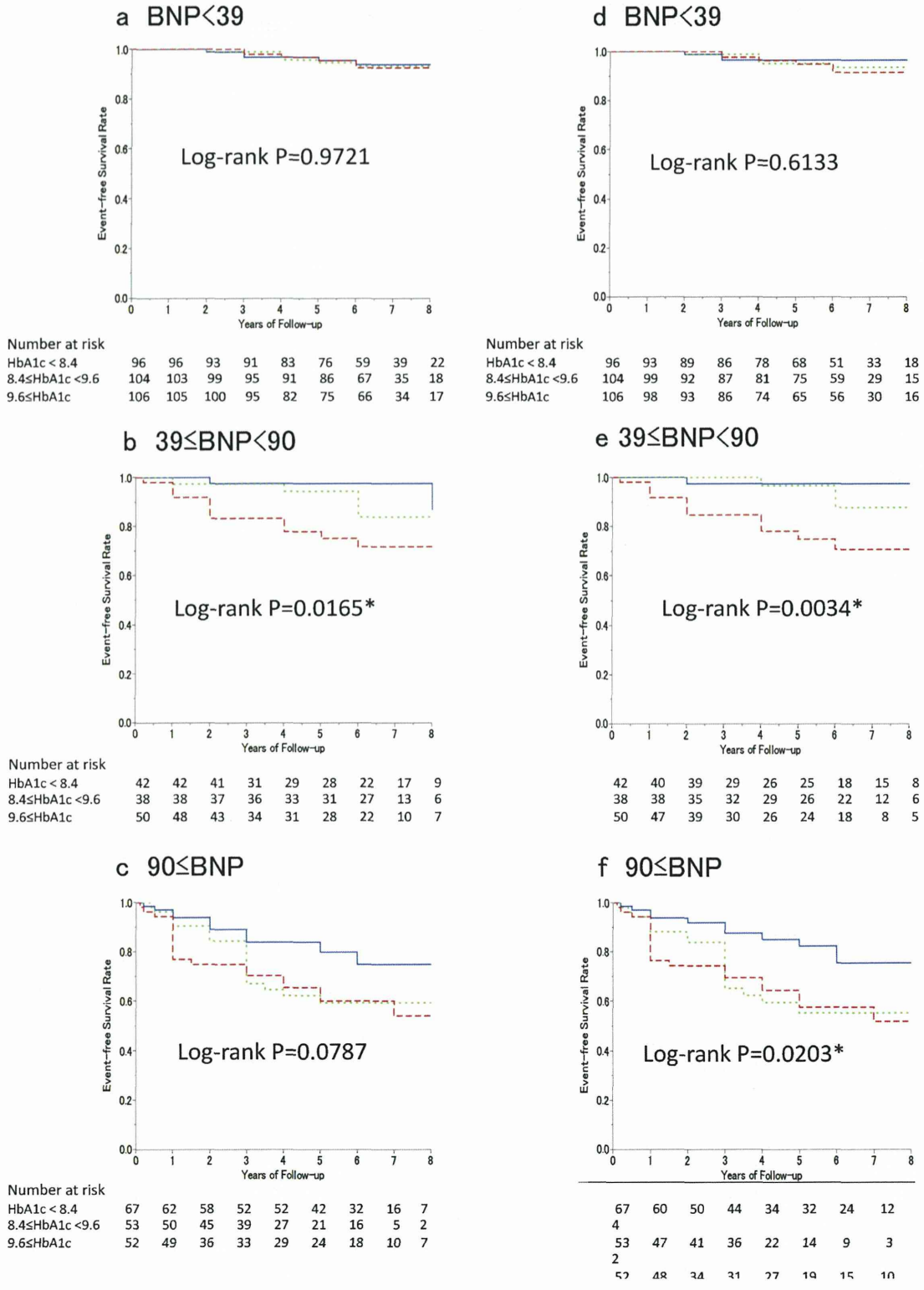
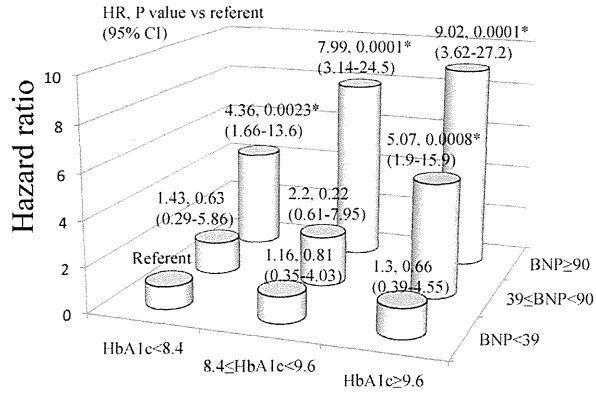
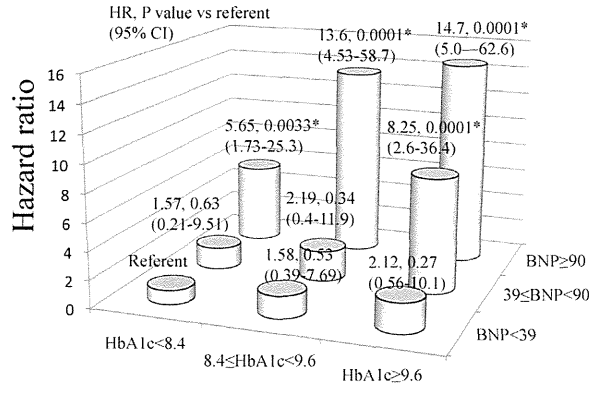


Fig. 1 – Cumulative event-free survival rates for heart failure (HF) according to HbA_{1c} category (cut-off points: 8.4% (68 mmol/mol) and 9.6% (81 mmol/mol)) stratified by BNP category (cut-off points: 39 and 90 pg/mL) for all (a–c) or in the analysis that canceled the follow-up at the time of the first coronary event (d–f). Straight lines (blue), HbA_{1c} < 8.4% (68 mmol/mol); dotted lines (green), 8.4 ≤ HbA_{1c} < 9.6% (81 mmol/mol); dashed lines (red), HbA_{1c} ≥ 9.6%. (For interpretation of the references to color in this legend, the reader is referred to the web version of the article.)

a First HF hospitalization



b Censoring coronary event



c First HF hospitalization

BNP category	HbA1c category	Hazard ratio	95%CI	P value
BNP<39	HbA1c<8.4	Referent		
	8.4≤HbA1c<9.6	1.16	0.35-4.03	0.8071
	HbA1c≥9.6	1.3	0.39-4.55	0.6637
39≤BNP<90	HbA1c<8.4	Referent		
	8.4≤HbA1c<9.6	1.53	0.37-7.48	0.5553
	HbA1c≥9.6	3.54	1.13-15.5	0.0286 *
BNP≥90	HbA1c<8.4	Referent		
	8.4≤HbA1c<9.6	1.83	0.93-3.67	0.0787
	HbA1c≥9.6	2.07	1.06-4.14	0.0343 *

d Censoring coronary event

BNP category	HbA1c category	Hazard ratio	95%CI	P value
BNP<39	HbA1c<8.4	Referent		
	8.4≤HbA1c<9.6	1.58	0.39-7.69	0.5281
	HbA1c≥9.6	2.12	0.56-10.1	0.2745
39≤BNP<90	HbA1c<8.4	Referent		
	8.4≤HbA1c<9.6	1.4	0.23-10.6	0.7132
	HbA1c≥9.6	5.25	1.41-33.9	0.0108 *
BNP≥90	HbA1c<8.4	Referent		
	8.4≤HbA1c<9.6	2.41	1.16-5.25	0.018 *
	HbA1c≥9.6	2.6	1.26-5.66	0.0097 *

Fig. 2 – (a) Hazard ratios for heart failure (HF) incidence according to HbA_{1c} and B-type natriuretic peptide (BNP) categories. Hazard ratios were adjusted by age, sex, body mass index, systolic blood pressure, and estimated glomerular filtration rate (eGFR). Labels above each column are hazard ratios (95% confidence interval) and *p* values as compared with subjects in the reference category (HbA_{1c} < 8.4% (68 mmol/mol) and BNP < 39 pg/mL). (b) Hazard ratios for HF incidence according to HbA_{1c} and BNP categories in the censoring coronary event analysis. Patients who developed a coronary event prior to HF during follow-up were censored at the date of the event. Hazard ratios were adjusted by age, sex, BMI, systolic blood pressure, and eGFR. Labels above each column are hazard ratios (95% confidence interval) and *p* values as compared with subjects in the reference category (HbA_{1c} < 8.4% (68 mmol/mol) and BNP < 39 pg/mL). (c) Hazard ratios for HF incidence according to HbA_{1c} category stratified by BNP category. Hazard ratios, corresponding 95% confidence interval, and *p* values were calculated using Cox proportional hazards models adjusted for age, sex, body mass index, systolic blood pressure, and eGFR. The lowest HbA_{1c} (<8.4% (68 mmol/mol)) group was considered as a reference group. (d) Hazard ratios for HF incidence according to HbA_{1c} category stratified by BNP category in the censoring coronary event analysis. Patients who developed a coronary event prior to HF during follow-up were censored at the date of the event. Hazard ratios, corresponding 95% confidence interval, and *p* values were calculated using Cox proportional hazards models adjusted for age, sex, body mass index, systolic blood pressure, and eGFR. The lowest HbA_{1c} (<8.4% (68 mmol/mol)) group was considered as a reference group.

4. Discussion

In the present study we examined the effect of baseline HbA_{1c} levels on future HF hospitalization of patients with type 2 diabetes and multiple coronary and HF risk factors. HbA_{1c} levels significantly predicted HF hospitalization in these patients and the association between HbA_{1c} and HF persisted after adjusting for parameters of cardiac and renal functions. Moreover, HbA_{1c} was an independent risk factor for HF regardless of the presence of coronary risk factors, or of the development of CHD during follow-up.

Although a few epidemiological studies have established a significant association between HbA_{1c} and HF [2,5–7], those studies lacked measures to detect subclinical cardiac dysfunction and it is likely that some patients with diabetes may have had subclinical HF at enrollment in the study. In fact, patients with diabetes and no symptoms of cardiovascular disease were shown to have reduced LV systolic and diastolic function when compared with healthy subjects [10]. In addition, it has been reported that 30–40% of patients with diabetes and no history of CVD exhibited abnormal LV function on subsequent echocardiography [11,12]. Since cardiac dysfunction is often associated with insulin resistance and with sedentary lifestyles, which could worsen their glucose control and thereby HbA_{1c} levels, the reported relationship between HbA1c levels and HF incidence could be confounded by prior cardiac dysfunction.

In the present study, in patients with type 2 diabetes and cardiovascular complications or multiple risk factors, HbA_{1c}

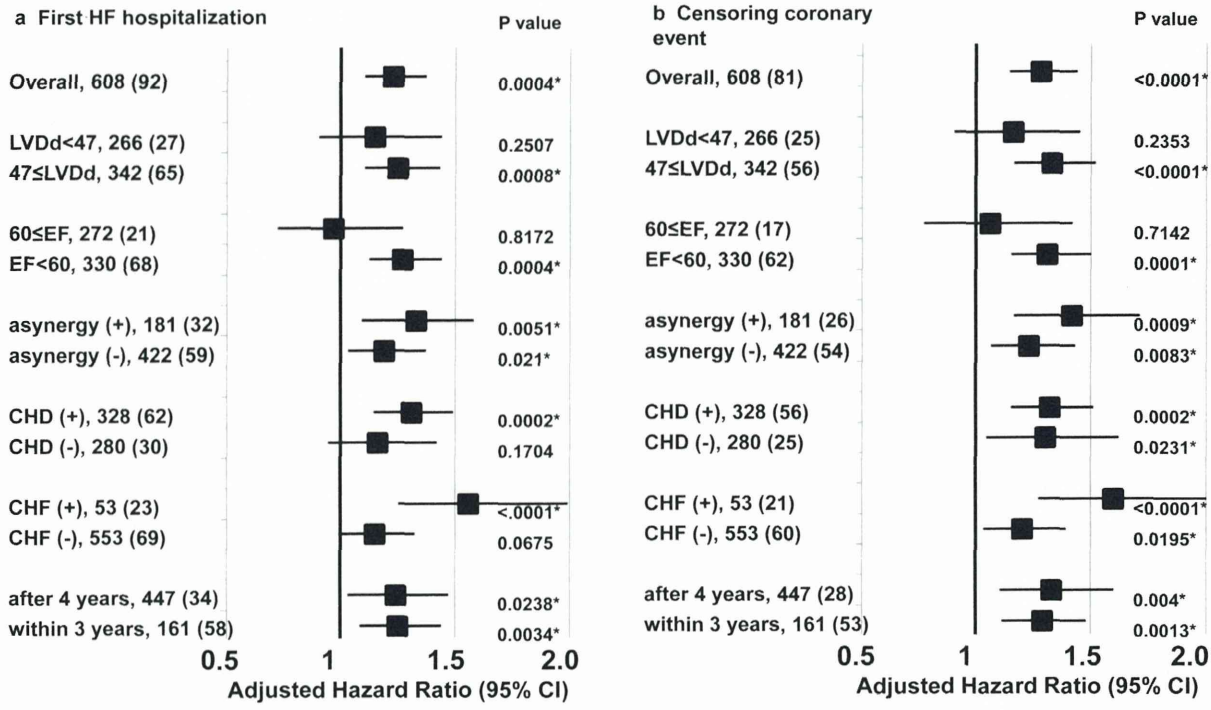


Fig. 3 – (a) Adjusted hazard ratios and 95% confidence intervals for a 1% (11 mmol/ml) increase in HbA_{1c} for the first heart failure (HF) hospitalization according to baseline left ventricular dimension, systolic function, and asynergy, the presence or absence of prevalent CHD or CHF, and the duration of follow-up. (b) Censoring coronary event analysis illustrating the hazard ratios of a 1% increase in HbA_{1c} for the first HF hospitalization occurring prior to any CHD event during follow-up. LVDd, left ventricular diastolic dimension; EF, ejection fraction; CHD, coronary heart disease; CHF, congestive heart failure. Numbers of patients (and events in parenthesis) in each category are shown.

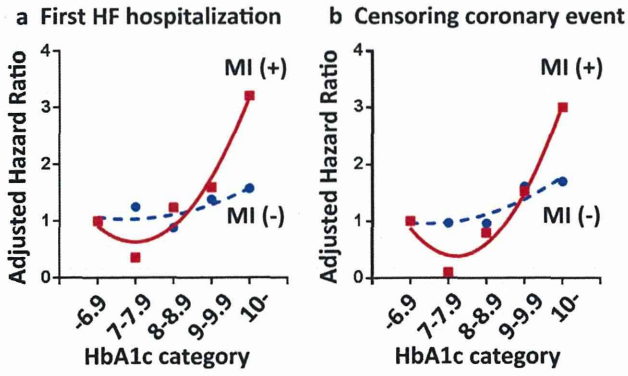


Fig. 4 – Cox proportional hazard analysis stratified by the presence or the absence of prevalent myocardial infarction (MI). Adjusted hazard ratios for heart failure (HF) incidence per each % step in HbA1c were calculated in the first HF hospitalization (a) and censoring coronary event (b) analyses. Hazard ratios were adjusted by age, gender, body mass index, systolic blood pressure, eGFR and ln[BNP (pg/mL)] as in model 2. The lowest category (HbA1c < 7.0% (53 mmol/mol)) was considered as the referent in these figures. Curve-fittings were performed by second-order polynomial regression analysis and shown in patients with history of MI (solid line and square, red) and in patients without MI (dashed line and circle, blue). (For interpretation of the references to color in this legend, the reader is referred to the web version of the article.)

remained an independent risk marker for increased hospitalization for HF, after adjustment for age, sex, systolic blood pressure, renal function, and markers of cardiac dysfunction, including BNP or echocardiographic parameters for LV systolic/diastolic function at baseline. BNP is a member of the natriuretic peptide family that exerts various cardiovascular actions through its unique signaling system [13–16] and it is an independent predictor of high LV end-diastolic pressure [17]. Since measurement of plasma BNP level is an excellent test to prescreen patients for LV dysfunction or myocardial ischemia [18–20], the result of the present study indicates that the association between baseline HbA_{1c} and future HF hospitalization is independent of baseline cardiac abnormality. In addition, to exclude the confounding impact of associated CHD and its myocardial dysfunction sequelae [21], the relationship between glycemic control and HF was examined in the absence of CHD during follow-up by censoring patients at the time of the first CHD event. Given that HbA_{1c} significantly predicts hospitalization for HF in patients with diabetes and no CHD at baseline or during follow-up (Fig. 3), these results suggest that HbA_{1c} predicts future incidence of HF independent of baseline cardiac abnormalities or CHD development during follow-up.

The guidelines for HF highlight the need to identify persons at high risk of developing HF for preventive measures and for early diagnosis, where it is recommended that healthcare providers should make every effort to control hyperglycemia [1]. However, optimal treatment strategies and targets remain

controversial. In fact, no significant reduction in cardiovascular outcomes including HF incidence was found in the ACCORD [22] and ADVANCE [23] trials, which targeted $HbA_{1c} < 6.5\%$ (48 mmol/mol) in their tight glucose control arms. In addition, in type 2 diabetes with cardiovascular risk factors or with CVD, the patients with mean HbA_{1c} levels of 7.0–8.0% (53–64 mmol/mol) were found to have the lowest risk for a composite of CVD hospitalization and all-cause mortality [24–26], that agrees well with our results shown in Fig. 4 MI (+). In contrast, in the patients without history of MI, the risk of HF hospitalization tends to increase linearly from the lowest HbA1c category (Fig. 4 MI (–)). It is reported that, in young patients with type 1 diabetes, incidence of HF hospitalization increased monotonically from the lowest category ($HbA_{1c} < 6.5\%$ (47.5 mmol/mol)) [27], while, in relatively low-risk patients with type 2 diabetes, the hazard ratio for HF for patients with HbA_{1c} 6.0 to <7.0% (42 to <53 mmol/mol) was the lowest [28]. Furthermore, in patients with naïve diabetes, the average HbA1c of which was 7.7% (61 mmol/mol), a graded positive association of HbA1c has recently been shown in a prospective manner, where HbA1c < 6.0% (42 mmol/mol) group had the lowest hazard [29]. Therefore, the point for controlling glycemia optimal for HF in type 2 diabetes [30] may vary depending on the condition of the patient, in concordance with the current recommendation that the management of diabetes should be individualized depending on condition of the patient [31,32].

In summary, HbA_{1c} is a predictor of HF hospitalization independent of baseline BNP or cardiac function parameters in patients with type 2 diabetes at high risk for HF. The results suggest that screening and preventive measures for HF need to be carried out in patients with poor glucose control, even in those without clinically overt symptoms of HF.

Ethics

This observational study followed the World Medical Association's Declaration of Helsinki and was approved by the Institutional Review Board.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

Contributions of each author

IK, design, data collection, analysis, and preparation of the manuscript. HM, collection of clinical data regarding renal function. YO, collection of clinical data regarding glucose control. TT, collection of clinical data regarding diabetes complications. MT, collection of clinical data regarding obesity. AK, statistical analysis as a statistician. MI, advice as a coronary interventionist. TA, advise as a heart failure specialist. WS, advice as an expert on arrhythmia. SY, advice as an expert on coronary heart diseases HO, supervision of the whole work. IK takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2014.02.009.

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