Prognostic Significance of Insomnia in Heart Failure

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論　文　内　容　要　旨

学位論文題名	心不全患者における不眠症の検討

近年のメタ解析において、不眠症は、冠動脈心疾患や脳卒中の発症、さらには、心血管死亡と関連し、そのリスクを増加させることが報告されている。その背景として、睡眠不足や不眠症は肥満症や糖尿病、高血圧や脂質異常症を増加させ心血管疾患のリスクを上昇させると考えられている。しかし、不眠症と心不全の予後との関連はいまだ明らかではない。そこで、我々は、不眠症を合併した心不全患者の特徴と不眠症の予後への影響を明らかにするため検討を行った。2009 年から 2013 年に当院に入院し退院し得た心不全患者連続 1011 例を対象に前向き観察研究を行った。心不全に不眠（症状、既往）を伴う：不眠群 519 名と不眠を伴わない：非不眠群 492 名に分類し、2 群間における患者背景や退院時の血液検査、心臓超音波検査、運動耐容能の検査並びに心臓死および心不全増悪による再入院の心イベントについて比較検討を行った。研究結果は不眠症を合併した心不全患者の特徴として、高齢で女性が多く、心房細動や慢性腎臓病の合併率が高値であった。血液検査ではレニン活性、レニン濃度、アルドステロン濃度が高値であった。また、心臓超音波検査による心機能に差を認めないものの、運動耐容能が低値であり、心イベント発生率は高値だった。また、不眠症は心不全の予後予測因子であることがわかった。不眠症自体が心不全の予後に対し悪影響をおよぼしているのか、心不全の状態が悪いために不眠症になっているのか、眠剤の予後への影響などは今後の課題である。しかし、不眠が心不全に及ぼす影響は大きいと考えられるため不眠症を有する心不全患者に対して、引き続き積極的に介入していかなければならないと考えられた。

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Abstract

Background: Insomnia is associated with incident heart failure (HF). However, the clinical significance and impact of insomnia on HF remain unclear.

Methods and Results: Consecutive 1011 patients admitted for treatment of HF were divided into two groups according to the presence of insomnia: HF with insomnia (insomnia group, n=519) and HF without insomnia (non-insomnia group, n=492). We compared 1) cardiac event rates including cardiac death and worsening HF and 2) underlying clinical background including laboratory data, echocardiographic data, and cardio-pulmonary exercise test findings between the two groups. In the Kaplan-Meier analysis, cardiac event rates were significantly higher in the insomnia group than in the non-insomnia group (39.1 vs. 23.4%, P<0.001). The insomnia group, as compared to the non-insomnia group, had 1) higher levels of plasma renin activity (P=0.042), renin concentration (P=0.007), and aldosterone (P=0.047), 2) lower peak VO_2 (14.9 vs. 16.3 ml/kg/min, P=0.002) and higher VE/VCO_2 slope (36.0 vs. 33.5, P=0.001), and 3) similar levels of B-type natriuretic peptide and left ventricular ejection fraction. Importantly, in the multivariable Cox proportional hazard analyses after adjusting for potential confounding factors, insomnia was an independent predictor of cardiac events in HF patients (hazard ratio 1.899, P<0.001).

Conclusions: Insomnia was an independent predictor of cardiac events in HF patients. HF patients with insomnia exhibited activated renin-angiotensin-aldosterone system and lower exercise capacity.

Keywords heart failure, insomnia, sleep disorder, exercise capacity, renin-angiotensin-aldosterone system, prognosis

Introduction

Heart failure (HF) is a major cause of death among the elderly in many countries.[1-4] It has recently been reported that insomnia, which is linked with incidence of HF in the general population (hazard ratio 4.53, 1.99–10.31)[5], is also associated with an increased risk of incident cardiovascular disease.[5-9] This hyperarousal disorder is accompanied by chronic activation of stress responses with increased activity in the hypothalamic-pituitary-adrenal axis and sympathetic nervous system leading to increased secretion of cortisol and up-regulation of the renin-angiotensin-aldosterone system (RAAS).[5, 10] Stress response caused by insomnia is also accompanied by increased heart rate, decreased heart rate variability, increased blood pressure, secretion of pro-inflammatory cytokines and catecholamines, and impaired exercise capacity and activity[1, 5], which are risk factors for the progression of HF and prognostic factors of HF. These risk factors may in turn contribute to endothelial dysfunction, atherosclerosis, renal dysfunction, and impaired cardiac function. Moreover, these abnormalities may represent a biologically plausible causal link between insomnia and HF. On the other hand, insomnia is highly prevalent in patients with chronic disease including HF and is a significant contributing factor to fatigue and poor quality of life.[11-17]

However, the prognostic impact of insomnia on HF patients remains unclear. We hypothesize

that HF patients with insomnia have poor prognosis accompanied with activated RAAS,[18] sympathetic nervous activity and inflammation, impaired cardiac function, and exercise capacity.

To address these issues, we aimed to investigate the impact of insomnia on prognosis of HF and compare the underlying clinical background in HF patients with or without insomnia (e.g. clinical features, echocardiographic parameters, exercise capacity, and neurohumoral and inflammatory factors such as plasma noradrenalin, renin activity, renin concentration, aldosterone, and C-reactive protein).

Methods

Subjects and study protocol

This was a prospective observational study that enrolled consecutive symptomatic HF patients (n = 1083) who were hospitalized to treat decompensated HF and were discharged from Fukushima Medical University between 2009 and 2013. The diagnosis of decompensated HF was made by several cardiologists based on the Framingham criteria.[19] Patients with acute coronary syndrome (n = 23), dialysis (n = 14) and already diagnosed depression[20] (n = 35) were excluded. Patients (n = 1011) were divided into two groups according to the presence of insomnia based on symptoms in normal daily life and/or at discharge, but not at hospitalization, by direct interview using a questionnaire taken by the attending physicians and medical staffs for patients or caregivers. Insomnia was defined by several physicians as the usual use of hypnotics 1) (‘Do you take hypnotics more than 3 times per week’ with the response options yes/ no) or 2) presence of either insomnia symptom of grade 3 or 4

accompanied by impairment of daytime function,[5, 21] specifically as follows: difficulty initiating sleep (‘Do you have difficulties falling asleep?’ with the response options 1. Never, 2. Occasionally, 3. Often, 4. Almost every night), difficulty maintaining sleep and/or early morning awakenings (‘Do you wake up in the early hours unable to get back to sleep?’ with the response options 1. Never, 2. Occasionally, 3. Often, 4. Almost every night), non-restorative sleep (‘How often do you suffer from poor sleep?’ with the response options 1. Never or a few times a year, 2. One to two times per month, 3. About once a week, 4. More than once a week), based on modified International Classification of Sleep Disorders-2 criteria[5, 21] supported by the American Academy of Sleep Medicine and the Japanese Society of Sleep Research, which are widely spread in Japanese clinical practice.

We performed examinations such as general laboratory tests, echocardiography, and cardio-pulmonary exercise tests at discharge, and compared parameters between the insomnia and non-insomnia groups. Co-morbidities were also assessed by several attending physicians. Hypertension was defined as the recent use of antihypertensive drugs, or systolic blood pressure > 140 mmHg, and/or diastolic blood pressure > 90 mmHg. Diabetes was defined as the recent use of insulin or antidiabetic drugs, a fasting blood glucose value of > 126 mg/dL, and/or a hemoglobin A1c value of > 6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of > 150 mg/dL, a low-density lipoprotein cholesterol value of > 140 mg/dL, and/or a high-density lipoprotein cholesterol value of < 40 mg/dL. The estimated glomerular filtration rate (GFR) was measured by the Modification of Diet in Renal Disease formula.[22] Chronic

kidney disease was defined as an estimated GFR < 60 ml/min/1.73 m^2.[22] Anemia was defined as hemoglobin of < 12.0 g/dl in females and < 13.0 g/dl in males.[1] Preserved left ventricular ejection fraction (LVEF) was defined as more than 50%.[2]

The patients were followed up until March 2015 for cardiac events, which were composite end points of cardiac death and/or worsening HF,[23, 24] were adjudicated by several independent cardiologists. Cardiac death was defined including worsening heart failure, which met the Framingham criteria[19], and ventricular fibrillation documented by electrocardiogram or implantable devices. Status and dates of deaths of all patients were obtained from the patients' medical records or cardiologists at the patient's referring hospital. Survival time was calculated from the date of hospitalization until the date of death or last follow-up. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University. The investigation conforms with the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.[25]

Echocardiography

Echocardiography was performed blindly by an experienced echocardiographer using the standard techniques.[26] The echocardiographic parameters investigated included LVEF, the ratio of early transmitral flow velocity to mitral annular velocity (mitral valve E/e'), inferior vena cava diameter,

right ventricular fractional area change (RV-FAC), and tissue Doppler-derived tricuspid lateral annular systolic velocity (tricuspid valve S').[27, 28] The LVEF was calculated using a modification of Simpson's method. Mitral valve E/E' was calculated by transmitral Doppler flow and tissue Doppler imaging. Tissue Doppler imaging was obtained from the average of the lateral and septal annulus velocities. The RV-FAC, defined as (end diastolic area − end systolic area) ÷ end diastolic area × 100, is a measure of right ventricular systolic function.[27, 28] All recordings were performed on ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA).

Cardiopulmonary exercise testing

The patients underwent incremental symptom-limited exercise testing using an upright cycle ergometer with a ramp protocol before discharge (Strength Ergo 8, Fukuda Denshi Co. Ltd., Tokyo, Japan). Breath-by-breath oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured during exercise using an AE-300S respiratory monitor (Minato Medical Science, Osaka, Japan). [28-30] Peak VO_2 was measured as an average of the last 30 s of exercise. Ventilatory response to exercise (expressed as a VE/VCO_2 slope) was calculated as the regression slope relating VE to CO_2 from the start of exercise until the respiratory compensation point (the time at which ventilation is stimulated by CO_2 output and end-tidal CO_2 tension begins to decrease).[28, 31] The ventilatory anaerobic threshold was calculated with the V-slope method.

Statistical analysis

Normally distributed data are presented as mean ± SD, and non-normally distributed data are presented as median (inter-quartile range). Categorical variables are expressed as numbers and percentages. The chi-square test was used for comparisons of categorical variables. Data of the two groups were compared using the independent Student's *t*-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. The Kaplan-Meier method was used for presenting the event-free rate, and the log-rank test was used for initial comparisons. Univariable and multivariable Cox proportional hazard analyses were used to analyze predictors of cardiac events with adjusting confounding factors. To prepare for potential confounding, we considered the following clinical factors, which are known to affect the risk of cardiac event in HF patients: age, gender, New York Heart Association functional class III or IV, body mass index, systolic blood pressure, heart rate, preserved LVEF, B-type natriuretic peptide, sodium, albumin, presence of hypertension, diabetes, dyslipidemia, atrial fibrillation, chronic kidney disease, anemia and insomnia, usage of RAAS inhibitors, β-blockers, diuretics, inotropics and device therapy (implantable cardioverter defibrillator and/or cardiac resynchronization therapy). Among these factors, those which were independent in predicting cardiac events with a value of $P < 0.05$ were included in the final adjusted model. A value of $P < 0.05$ was considered significant for all comparisons. These

analyses were performed using a statistical software package (SPSS ver. 21.0, IBM, Armonk, NY, USA).

Results

Of all the HF patients, 519 (51.3%) were categorized into the insomnia group as shown in **Table 1**. During the follow-up period (mean 801 days, median 748 days), there were 236 worsening HF cases (163 and 73 in the insomnia group and non-insomnia groups, respectively) and 151 cardiac deaths (85 and 66 in the insomnia and non-insomnia groups, respectively). As shown in **Figure 1**, the insomnia group experienced more cardiac events than the non-insomnia group ($P < 0.001$).

The clinical features of the study subjects are summarized in **Table 1**. The insomnia group patients were of a higher age, had a higher prevalence of female gender, and had higher usage of diuretics and inotropics. Comparisons of the laboratory data between the two groups are shown in **Table 2**. The insomnia group had lower levels of estimated GFR, and higher levels of plasma renin activity, renin concentration, and aldosterone. In contrast, BNP, C-reactive protein, albumin, sodium, glucose and lipid parameters, and plasma noradrenaline did not differ between the two groups. The parameters of echocardiography and the cardio-pulmonary exercise test are summarized in **Table 3**. Although left and right ventricular systolic function did not differ between the two groups, peak VO_2, end-tidal CO_2 at respiratory compensation point, anaerobic threshold, and $\Delta VO_2/\Delta$work rate were significantly lower in the insomnia group than in the non-insomnia group. The minimum VE-VCO_2 and VE/VCO_2 slopes were higher in the insomnia group than in the non-insomnia group. Taken

together, these data suggest that worse prognosis of HF patients with insomnia may not be related to cardiac function but to activated RAAS and impaired exercise capacity.

The Cox proportional hazard model was used to examine the prognostic impact of insomnia on patients with HF (**Table 4**). We confirmed that the Cox models supported the assumption of proportional odds. In the multivariable analysis, insomnia was an independent predictor of cardiac events (HR 1.899, 95% CI 1.333–2.705, $P < 0.001$).

Then, we focused on the relationship between RAAS and cardiac event rates in HF patients with or without insomnia. In the Cox proportional hazard analysis, plasma renin activity and renin concentration were predictors of cardiac events only in HF patients with insomnia (plasma renin activity, HR 1.018, 95% CI 1.003-1.034, P = 0.020; renin concentration, HR 1.001, 95% CI 1.001-1.002, P <0.001), but not in HF patients without insomnia. Aldosterone was not a predictor of cardiac event in both groups.

Discussion

To the best of our knowledge, the present study is the first to show that HF patients with insomnia experienced more cardiac events, but their worse prognosis was related to rather activated RAAS and impaired exercise capacity than cardiac function.

In our study, insomnia was an independent predictor of cardiac events in HF patients after adjusting for multiple known confounding factors. Thus, our data suggest that insomnia itself may

be associated with adverse outcomes in HF patients, or that insomnia as a symptom can be a potential marker in risk-stratification of HF patients. In addition, the insomnia group exhibited activated RAAS, impaired renal function, and lower exercise capacity. These mechanisms may in part explain the poor prognosis of HF patients with insomnia. In contrast, plasma noradrenalin, C-reactive protein, and echocardiographic parameters did not differ between the two groups. Although we did not investigate the reason for these results, HF itself and HF treatment may strongly affect sympathetic activity, inflammation, and cardiac function.

Restorative functions occur during different stage of sleep, with physical restoration occurring primarily during non-rapid eye movement (NREM) sleep and brain restoration occurring primarily in rapid eye movement (REM) sleep. Sleep and exercise influence each other through complex and bilateral interactions that involve multiple physiological and psychological pathways.[32] Insomnia causes inhibition of restorative functions and fatigue, and these are resulting in impairment of psychomotor and physical performance[1] and activity,[5, 17] which are risk factors for poor prognosis in HF.

With regard to inflammation, proinflammatory cytokines, interleukin-6, and tumor necrosis factor α are fatigue-inducing cytokines that negatively influence quality of sleep. Mean 24 h secretions of these cytokines did not differ between insomnia patients and normal sleepers; however, there was a significant increase of interleukin-6 from mid-afternoon to evening.[10, 33] In addition, the characteristic circadian secretion of tumor necrosis factor α with a peak close to sleep offset was

observed in the normal sleepers, but not in the insomnia patients.[33] The hypersecretion and/or circadian alteration of the cytokine secretion associated with a hypothalamic-pituitary-adrenal axis activation may explain the fatigue and poor sleep associated with insomnia.[10] Another study reported elevated C-reactive protein levels in insomnia patients.[34] In contrast, erythrocyte sedimentation rate is not associated with incidence of HF in insomnia patients.[9] Thus, the associations between insomnia and inflammation are complex and not fully addressed especially in HF patients.

Furthermore, symptoms of HF itself, including coughing, orthopnea, paroxysmal nocturnal dyspnea, and nocturia, often lead to insomnia,[13, 35] and insomnia itself may reflect the severity of HF. In addition, insomnia is also an indicator of depression, which is associated with adverse prognosis of HF.[20] These in turn are associated with poor prognosis of HF patients. On the other hand, insomnia increases with both the number of chronic illnesses the patient has and the number of medications taken.[13, 36-38] Insomnia could also be partially caused by medications used in the treatment of HF.[1, 2] Melatonin production may be affected by β-blockers, diuretics cause nocturia, and inotropics affect agitation, all of which result in poor sleep quality.[13]

In future, functional imaging may be useful to determine the association between HF and insomnia. Functional neuroimaging studies have shown that transition from wakefulness to sleep is associated with a decrease of brain activity in specific regions, such as the brain stem, thalamus, and prefrontal cortex.[39] Cerebral abnormalities detected by magnetic resonance imaging and cognitive

performance in HF patients have been reported.[40] For instance, medial temporal lobe atrophy was related to cognitive dysfunction, involving memory impairment and executive dysfunction, whereas total white matter hyperintensities were related to depression resulting in insomnia.[40]

To date, there are no data evaluating effective treatment for insomnia in HF patients. General behavioral measures for improved sleep hygiene, such as minimal use of caffeine, cigarettes and alcohol, maintaining a regular sleep schedule, going to bed only when sleepy, regular exercise, and avoiding daytime naps, should be explained to the patients.[10] It has been recently reported that exercise training improves sleep quality in HF patients.[41] Since HF patients with insomnia had impaired exercise capacity in present data, cardiac rehabilitation may be more strongly recommended.[1, 41]

Study limitations

There are several limitations in the present study. Firstly, the number of subjects was relatively small as the study was performed in a single institution. Further studies with a larger population are needed. However, diagnosis of cardiac events was accurately made by our experienced cardiologists. Secondly, we diagnosed insomnia based on patient's symptoms assessed by interview or medical history, hence we could not completely exclude the effect of psychiatric disorders, depression and cognitivty. In addition, we did not consider any changes in any parameters, and baseline data at admission were used for the analyses. Furthermore, we did not use polysomnography or actigraphy,

which are objective tests of sleep disorders. However, these are not routinely performed in patients with HF and/or insomnia. Thirdly, levels of plasma renin activity and concentrations of renin, aldosterone, and noradrenaline might be affected by administration of RAAS inhibitors and β-blockers. Fourthly, although we have conducted multivariable analyses to evaluate associations between insomnia and prognosis in HF patients, confounding factors cannot be entirely eliminated. Our results do not establish a cause-effect relationship between the presence of insomnia and increased cardiac events. Finally, further studies are required to examine the impact of hypnotics on prognosis of HF patients with insomnia.

Conclusions

Insomnia was a common and independent predictor of cardiac events in HF patients. HF patients with insomnia exhibited activated RAAS and impaired exercise capacity, and insomnia may be a potential marker of adverse prognosis in HF patients. Further studies are required to determine whether controlling insomnia improves the prognosis of such patients.

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Disclosures, Conflict of interest

None.

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FIGURE LEGENDS

Figure 1. Comparison of cardiac events between the insomnia and non-insomnia groups.

Kaplan-Meier analysis for cardiac events (Insomnia vs. Non-insomnia group) in all HF patients (n = 1011).

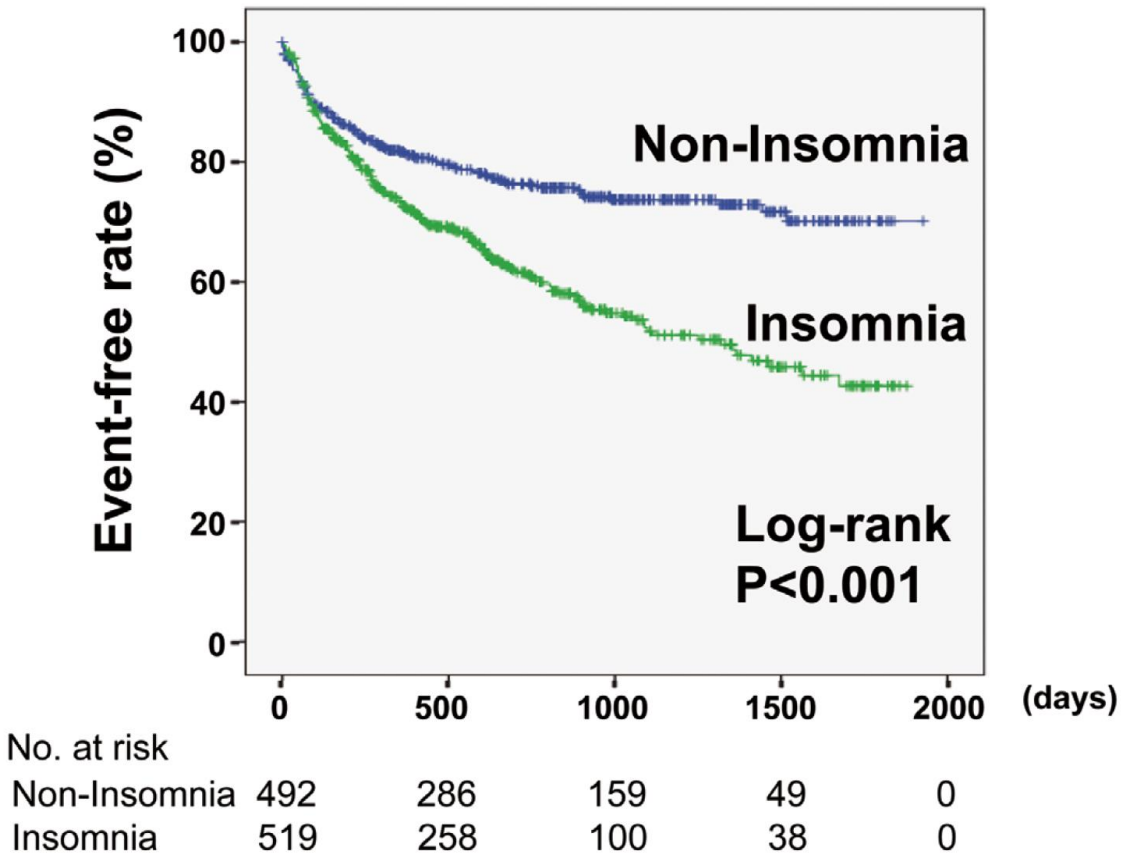

Table 1 Comparisons of clinical features

	Non-Insomnia (n=492)	**Insomnia (n=519)**	***P*-value**
Age (years)	66.2 ± 15.8	68.5 ± 13.6	0.012
Male gender (*n*, %)	313 (63.6)	298 (57.4)	0.044
Body mass index (kg/cm^2)	23.2 ± 4.0	22.7 ± 4.1	0.114
Systolic BP (mmHg)	129.7 ± 31.5	126.9 ± 35.1	0.184
Diastolic BP (mmHg)	73.6 ± 20.2	72.3 ± 22.6	0.308
Heart rate (bpm)	82.9 ± 24.9	83.9 ± 26.8	0.518
NYHA class III or IV	88 (17.9)	111 (21.4)	0.162
Ischemic etiology (*n*, %)	121 (24.6)	134 (25.8)	0.654
Preserved EF (*n*, %)	224 (45.5)	227 (43.7)	0.567
Co-morbidity			
Hypertension (*n*, %)	369 (75.0)	389 (75.0)	0.986
Diabetes (*n*, %)	205 (41.7)	213 (41.0)	0.840
Dyslipidemia (*n*, %)	372 (75.6)	411 (79.2)	0.173
Atrial fibrillation (*n*, %)	169 (34.3)	218 (42.0)	0.012
Chronic kidney disease (*n*, %)	272 (55.3)	334 (64.4)	0.003
Anemia (*n*, %)	272 (55.3)	322 (62.0)	0.029
Medications			
RAAS inhibitors (*n*, %)	371 (75.4)	399 (76.9)	0.583
β-blockers (*n*, %)	368 (74.8)	408 (78.6)	0.151
Diuretics (*n*, %)	305 (62.0)	369 (71.1)	0.002
Inotropics (*n*, %)	46 (9.3)	84 (16.2)	0.001
ICD or CRT device (*n*, %)	76 (15.4)	111 (21.4)	0.015

RAAS, renin-angiotensin-aldosterone system; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.

Table 2 Laboratory data

	Non-Insomnia (n=492)	**Insomnia (n=519)**	***P*-value**
White blood cell (/ul)	7.20 ± 3.09	7.45 ± 3.46	0.246
Hemoglobin (g/dl)	12.5 ± 2.5	12.2 ± 2.2	0.061
BNP (pg/ml) §	318.8 (597)	375.0 (660)	0.501
eGFR (ml/min/1.73 cm^2)	57.3 ± 26.1	53.1 ± 23.6	0.034
C-reactive protein (mg/dl)	0.26 (0.35)	0.39 (0.46)	0.345
Total protein (g/dl)	6.9 ± 0.8	7.0 ± 0.8	0.263
Albumin (g/dl)	3.6 ± 0.6	3.6 ± 0.6	0.633
Sodium (mEq/l)	138.8 ± 4.0	138.7 ± 4.1	0.693
Glucose (mg/dl)	126.8 ± 55.5	133.1 ± 59.7	0.137
Insulin (μU/ml)	11.2 ± 1.2	11.8 ± 2.0	0.727
Hemoglobin A1c (%)	5.7 ± 0.9	5.9 ± 1.1	0.185
Total cholesterol (mg/dl)	179.1 ± 44.4	177.5 ± 40.4	0.688
High-density lipoprotein cholesterol (mg/dl)	47.7 ± 16.6	50.1 ± 21.6	0.126
Low-density lipoprotein cholesterol (mg/dl)	106.5 ± 34.9	103.6 ± 38.6	0.326
Triglyceride (mg/dl)	115.0 ± 72.7	116.2 ± 76.3	0.832
Plasma renin activity (ng/ml/h) §	6.2 (3.5)	9.0 (6.5)	0.041
Renin concentration (pg/ml) §	61.5 (36)	120.4 (98)	0.007
Aldosterone (pg/ml) §	126.8 (91)	147.0 (116)	0.039
Noradrenaline (pg/ml)	811.2 ± 542.7	806.2 ± 453.5	0.960

BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration.

§ Data are presented as median (interquartile range).

Table 3 Echocardiography and Cardiopulmonary exercise test data

Echocardiography	**Non-Insomnia (n=490)**	**Insomnia (n=512)**	***P*-value**
LVEF (%)	48.7 ± 16.0	47.5 ± 16.5	0.264
Mitral valve E/E'	15.4 ± 8.2	16.2 ± 9.0	0.213
Inferior vena cava diameter (mm)	15.2 ± 5.6	15.5 ± 5.2	0.387
SPAP (mmHg)	30.5 ± 14.7	31.2 ± 16.8	0.570
RV-FAC (%)	42.0 ± 15.6	42.4 ± 15.2	0.779
Tricuspid valve S' (cm/sec)	9.3 ± 3.9	9.5 ± 4.6	0.731
Tricuspid valve E/E'	5.7 ± 4.4	6.4 ± 5.5	0.296
Cardiopulmonary exercise test	**Non-Insomnia (n=224)**	**Insomnia (n=213)**	***P*-value**
Peak VO_2 (ml/kg/min)	16.3 ± 5.2	14.9 ± 4.4	0.002
End-tidal CO_2 at respiratory compensation point (mmHg)	36.2 ± 5.0	34.9 ± 5.2	0.008
Anaerobic threshold (ml/kg/min)	11.5 ± 2.7	10.8 ± 2.2	0.010
minimum VE-VCO_2	35.0 ± 6.3	37.0 ± 7.0	0.003
VE/VCO_2 slope	33.5 ± 7.7	36.0 ± 8.4	0.001
Δ VO_2/Δ work rate (ml/min/watts)	8.4 ± 3.5	7.7 ± 2.2	0.013

LVEF, left ventricular ejection fraction; Mitral valve E/E', ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole; SPAP, systolic pulmonary artery pressure; RV-FAC, right ventricular fractional area change; Tricuspid valve S', Doppler-derived tricuspid lateral annular systolic velocity; Tricuspid valve E/E', ratio of the peak transtricuspid velocity during early diastole to the peak tricuspid valve annular velocity during early diastole; VO_2, oxygen consumption; VCO_2, carbon dioxide production; VE, minute ventilation; Peak VO_2, peak oxygen uptake; minimumVE-VCO_2, and rate of minute ventilation to carbon dioxide production; VE/VCO_2 slope, rate of increase in ventilation per unit increase in carbon dioxide; Δ VO_2/Δ work rate, rate of increase in VO_2 to increase in work rate.

Table 4 Cox proportional hazard models of cardiac events in HF (318 events/ n = 1011)

Risk factor	Univariate			Multivariate		
	HR	95% Cl	*P*-value	HR	95% Cl	*P*-value
Age	1.019	1.011-1.028	<0.001	1.011	0.996-1.025	0.150
Male	0.977	0.780-1.224	0.842			
NYHA III or IV	3.777	2.983-4.783	<0.001	2.284	1.497-3.424	<0.001
Body mass index	0.955	0.925-0.987	0.006	0.997	0.953-1.043	0.891
Systolic blood pressure	0.993	0.989-0.997	<0.001	0.996	0.989-1.002	0.195
Heart rate	1.003	0.999-1.007	0.109			
Preserved LVEF	0.471	0.371-0.596	<0.001	0.722	0.477-0.994	0.042
Log BNP	2.389	1.866-3.058	<0.001	1.075	0.730-1.582	0.714
Sodium	0.926	0.901-0.952	<0.001	0.965	0.925-1.007	0.097
Albumin	0.622	0.511-0.756	<0.001	0.970	0.701-1.343	0.856
Ischemic etiology	1.295	1.013-1.654	0.039	1.083	0.706-1.661	0.715
Hypertension	0.985	0.763-1.272	0.909			
Diabetes	1.507	1.210-1.878	<0.001	1.002	0.701-1.432	0.993
Dyslipidemia	1.151	0.875-1.514	0.315			
Atrial fibrillation	1.398	1.121-1.743	0.003	1.187	0.845-1.667	0.323
Chronic kidney disease	2.848	2.189-3.707	<0.001	1.786	1.194-2.671	0.005
Anemia	2.162	1.692-2.763	<0.001	1.301	0.875-1.934	0.194
RAAS inhibitors	0.774	0.602-0.994	0.045	1.005	0.656-1.540	0.980
β-blockers	0.879	0.680-1.136	0.324			
Diuretics	1.601	1.242-2.063	<0.001	1.174	0.772-1.784	0.454
Inotropics	2.919	2.265-3.762	<0.001	1.458	0.914-2.325	0.113
ICD or CRT device	1.659	1.293-2.129	<0.001	1.202	0.772-1.872	0.414
Insomnia	1.864	1.482-2.344	<0.001	1.899	1.333-2.705	<0.001

CI, confidence interval; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.