Prognostic Impact of Cardio-renal-anemia Syndrome in Patients at Risk for Heart Failure from the IMPACT-ABI study

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Background : Cardio-renal-anemia syndrome (CRAS) is known as a vicious circle, since chronic heart failure (CHF), chronic kidney disease (CKD), and anemia are exacerbated by each other. However, it remains unclear whether CKD and anemia would be associated with cardiovascular events in asymptomatic patients at risk for HF.

Methods : We retrospectively enrolled patients without prior HF history who were hospitalized for cardiovascular diseases between 2005 and 2012. Patients were divided into two groups with or without RAS defined as suffering from CKD (estimated Glomerular filtration rate (eGFR) ＜60 mL/min/1.73 m^2) and anemia (hemoglobin ＜13 g/dL in men and ＜12 g/dL in women). The primary endpoint was major adverse cardiovascular events (MACE), the composite of cardio-vascular death and HF hospitalization.

Results : A total of 1801 patients were enrolled. The mean age was 69.6 ± 10.6 years, and 76 % were men. The mean LV ejection fraction was 66.9 ± 12.3 %, and stage A HF was present in 73 % of the patients. Over a 4.6-year median follow-up, primary endpoint was observed in 129 patients. In Kaplan-Meier analysis, patients with RAS (n = 217) showed worse prognoses than those without RAS (n = 1584). In multivariable Cox proportional hazards analysis, after the adjustment for age, sex, and conventional risk factors, RAS showed significant association with the incidence of MACE (HR 1.86 ; 95 % CI 1.20-2.89, P = 0.005).

Conclusions : In patients at risk for HF, RAS was significantly associated with future cardiovascular events. Investigation of the impact of early intervention for preventing CKD and anemia on those patients' prognosis is warranted. *Shinshu Med J 68 : 139—147, 2020*

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Key words : cardio-renal-anemia syndrome, heart failure, chronic kidney disease, anemia

I Introduction

Currently, the rapid aging of society has caused a rapid increase in the prevalence of CHF[1)2)]. Though CHF in the elderly has a poor prognosis because of frequent readmission due to acute exacerbation[3)], the appropriate stage or method of intervention to prevent worsening of CHF is unclear. Anemia and/or CKD, known to be exacerbating factors of CHF, are often associated with that (35-57 % of patients with CHF have anemia[4)5)], and 47-57 % of them have stage 3 or greater CKD[6)7)]), and chronic heart failure (CHF), chronic kidney disease (CKD), and anemia are able to be caused and exacerbated by each other. This vicious cycle named as Cardio-renal-anemia (CRA) syndrome[8)] has begun to gather attention.

The interaction among CRA is complex, because each of these three conditions could be results and causes for each other, but the mechanism has been gradually elucidated. CKD and anemia activate the sympathetic system, the renin-angiotensin-aldo

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sterone system (RAAS), and the antidiuretic hormone. Those neurohormonal actions and the consequent fluid retention cause myocardial hypertrophy, necrosis, fibrosis and cardiomyopathy resulting in worsening of CHF[9]. Then, CRA syndrome was reported as an independent predictor of all-cause mortality in symptomatic HF[10)-12)]. However, it remains unclear whether CKD and anemia are associated with this vicious circle in patients at risk for asymptomatic HF. In this study, we sought to investigate the association of a combination of renal dysfunction and anemia with the incidence of adverse cardiovascular (CV) events, in asymptomatic patients at risk for HF.

Ⅱ Methods

A Study design

The current study was performed using integrated data from the impressive predictive value of ABI for clinical long-term outcomes in patients with cardiovascular disease examined by the ABI (IMPACT-ABI) study[13]. The IMPACT-ABI study was a retrospective cohort study that enrolled 3,131 consecutive patients who were admitted to Shinshu University for cardiovascular disease and examined by ABI between January 2005 and December 2012. Clinical, demographic, laboratory, and follow-up data were collated from hospital records or by contacting patients and their family. The present study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), as accepted by the International Committee of Medical Journal Editors (UMIN-ID ; 000020276). The study protocol was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Shinshu University School of Medicine. Because of the retrospective nature of the current study, informed written consent for participation was not obtained from patients and data were analyzed anonymously.

Twenty-five patients with inadequate eGFR and/or Hb data were excluded. 633 patients with prior symptomatic HF (stage C or D HF), 524 patients without risk of HF defined in the 2013 ACCF/AHA HF guideline[14], and 147 patients with CKD on hemodialysis were also excluded. Then 1,801 patients diagnosed as stage A or B HF were subsequently enrolled and divided into four groups based on eGFR and Hb : with/without CKD and/or anemia **(Fig. 1)**. Furthermore, Groups 1-3 were combined without the renal-anemia syndrome (RAS) group. The primary endpoint was the composite of major adverse cardiovascular events (MACE), including cardiovascular death (CVD) and heart failure requiring hospitalization. The secondary endpoints were cardiovascular death and heart failure requiring hospitalization.

B Definitions

The ACC/AHA stages A and B of HF are defined as follows : Stage A, at risk for HF (i.e. hypertension, diabetes mellitus, obesity, atherosclerotic disease, metabolic syndrome, familial history of cardiomyopathy) but without structural heart disease or symptoms of HF ; Stage B, structural heart disease but without signs or symptoms of HF[15]. In the present study, structural heart disease was defined by clinical and echocardiographic findings as follows : prior myocardial infarction, cardiomyopathy, valvular heart disease, reduced left ventricular ejection fraction (LVEF, 40 %)[13], enlarged LV end-diastolic diameter >55 mm)[16], or LV mass index >115 g/m^2 in men or >95 g/m^2 in women[17]. Valvular heart disease was specifically defined as severe aortic or mitral valvular disease using echocardiography. Cardiovascular death was defined as mortality due to acute myocardial infarction, significant cardiac arrhythmia, congestive heart failure, stroke, or other cardiovascular causes. CKD was defined as eGFR calculated by the Cockcroft-Gault Equation of less than 60 ml/min/1.73 m^2 (classified as GFR categories G3a-G5 in Kidney Disease : Improving Global Outcomes guideline), and anemia was defined as Hb levels less than 13 g/dL in males and 12 g/dL in females according to World Health Organization criteria. Hypertension (HT) was defined as current systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or use of antihypertensive agents. Dyslipidemia was defined as total cholesterol >220 mg/dl, low-density lipoprotein cholesterol >140 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, triglycerides >150

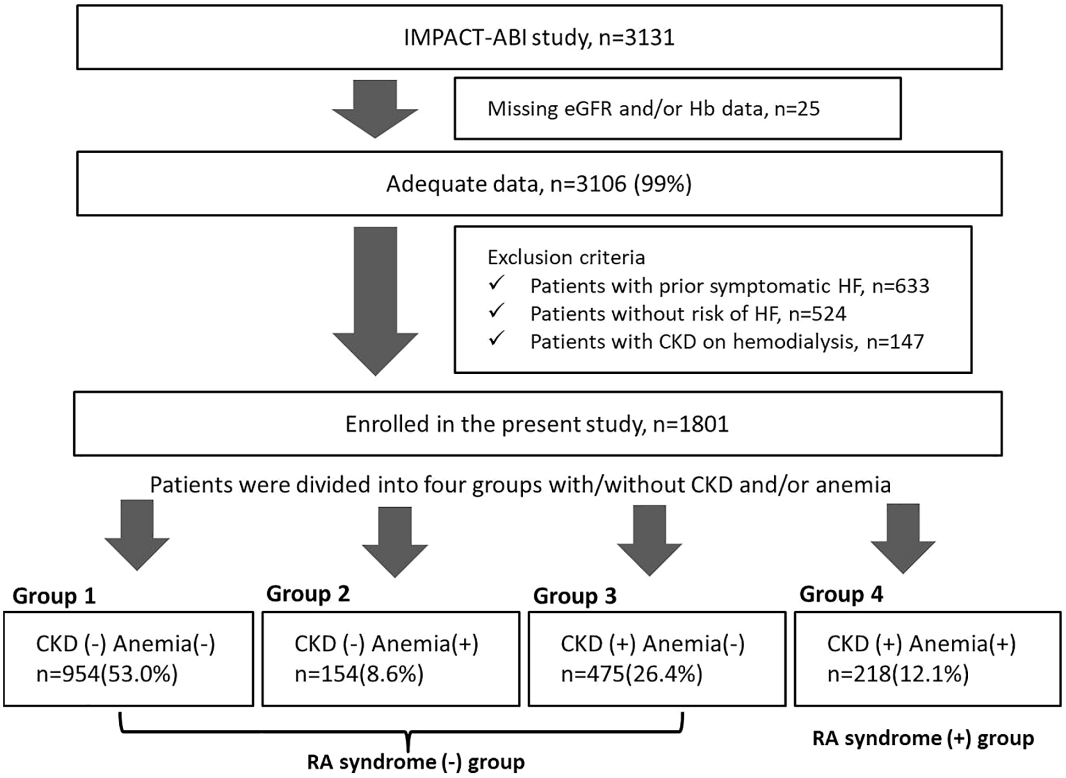


Fig. 1 Study design

IMPACT-ABI, impressive predictive value of ankle brachial index (ABI) for clinical long-term outcome in patients with cardiovascular disease examined using ABI ; eGFR, estimated glomerular filtration rate ; Hb, hemoglobin ; HF, heart failure ; CKD, chronic kidney disease ; RA syndrome, renal-anemia syndrome.

mg/dl, or use of cholesterol-lowering agents. Diabetes mellitus was defined as fasting blood glucose > 126 mg/dl and/or casual plasma glucose >200 mg/dl, HbA1c >6.5 % or use of hypoglycemic agents.

C Statistics

Data are reported as the mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Continuous variables were compared using variance analysis and categorical variables were compared using Chi-square test. The time to the first event of any one of the components of MACE was described with the use of Kaplan-Meier survival curves and we applied the log-rank test to compare the incidence of the endpoint between groups. We conducted a time-to-event analysis using Cox proportional hazards regression to determine the predictors of primary endpoint. All statistical analyses were performed using SPSS version 25 software (SPSS Ink., Chicago, IL, USA).

Ⅲ Results

The baseline patient characteristics, classified by the presence of the CKD and/or anemia, are presented in **Table 1**. A total of 1801 patients participated, with a median follow-up of 4.6 years. The mean age was 69.6±10.6 years, and 76 % were men. The mean LV ejection fraction was 66.9±12.3 %, and stage A HF was present in 73 % of the patients. Anemia was present in 21 % and CKD in 39 %. The patients with RAS (n=218) were significantly older. The ratio of stage A HF showed no significant difference between each group. The morbidity of dyslipidemia was lower, and that of hypertension and ACE-I/ARB use and diabetes mellitus were greater in the patients with RAS. The patient characteristics, classified by the incidence of MACE, are shown in **Table 2**. The patients in MACE (+) group were significantly older, had more ACE-I/ARB use, histories of prior cerebral infarction and atrial fibrillation. History of

Table 1　Comparison of baseline characteristics according to RA syndrome

	RAS (−) n = 1583	RAS (+) n = 218	p value
Age (y.o.)	68.8 ± 10.6	75.8 ± 8.1	< 0.001
Men	1215 (77)	162 (74)	0.426
Stage A HF	1136 (72)	168 (78)	0.074
Stage B HF	447 (28)	50 (22)	0.074
Hypertension	1212 (77)	185 (85)	0.006
Dyslipidemia	835 (53)	96 (44)	0.016
Diabetes mellitus	532 (34)	92 (42)	0.012
Ischemic heart disease	535 (34)	73 (34)	0.079
Prior myocardial infarction	321 (20)	36 (17)	0.190
Prior cerebral infarction	118 (7)	27 (12)	0.012
Abdominal aortic aneurysm	212 (13)	47 (22)	0.001
Atrial fibrillation	145 (9)	19 (9)	0.842
Serum creatinine (mg/dL)	0.86 ± 0.25	1.45 ± 0.70	< 0.001
eGFR (ml/min/1.73 m^2)	68.5 ± 17.9	40.2 ± 12.8	< 0.001
Hemoglobin (g/dL)	14.3 ± 1.5	11.4 ± 1.1	< 0.001
LV ejection fraction (%)	66.9 ± 12.2	66.9 ± 12.4	0.978
Medication n = 914			
ACE-Inhibitor or ARB	839 (53)	132 (65)	0.036
β-blocker	404 (26)	62 (30)	0.318
Statin	782 (49)	93 (46)	0.129
Antiplatelet agents	979 (62)	138 (63)	0.677

Table 2　Comparison of baseline characteristics according to MACE

	MACE (−) n = 1672	MACE (+) n = 129	p value
Age (y.o.)	69.4 ± 10.6	73.1 ± 9.0	< 0.001
Men	1272 (76)	105 (81)	0.170
Stage A HF	1219 (73)	86 (67)	0.126
Hypertension	1303 (78)	94 (73)	0.184
Dyslipidemia	881 (53)	50 (39)	0.002
Diabetes mellitus	583 (35)	41 (32)	0.478
Ischemic heart disease	560 (34)	48 (37)	0.390
Prior myocardial infarction	323 (19)	34 (26)	0.054
Prior cerebral infarction	124 (7)	21 (16)	< 0.001
Abdominal aortic aneurysm	233 (14)	26 (20)	0.053
Atrial fibrillation	143 (9)	21 (16)	0.003
Serum creatinine (mg/dL)	0.91 ± 0.36	1.13 ± 0.69	0.001
eGFR (ml/min/1.73 m^2)	65.8 ± 19.5	56.4 ± 19.7	< 0.001
Hemoglobin (g/dL)	14.0 ± 1.7	13.3 ± 1.8	< 0.001
LV ejection fraction (%)	67.1 ± 12.1	64.3 ± 13.9	0.013
Medication n = 914			
ACE-Inhibitor or ARB	885 (53)	86 (67)	0.003
β-blocker	435 (27)	30 (24)	0.404
Statin	819 (51)	56 (44)	0.137
Antiplatelet agents	1041 (62)	76 (59)	0.451

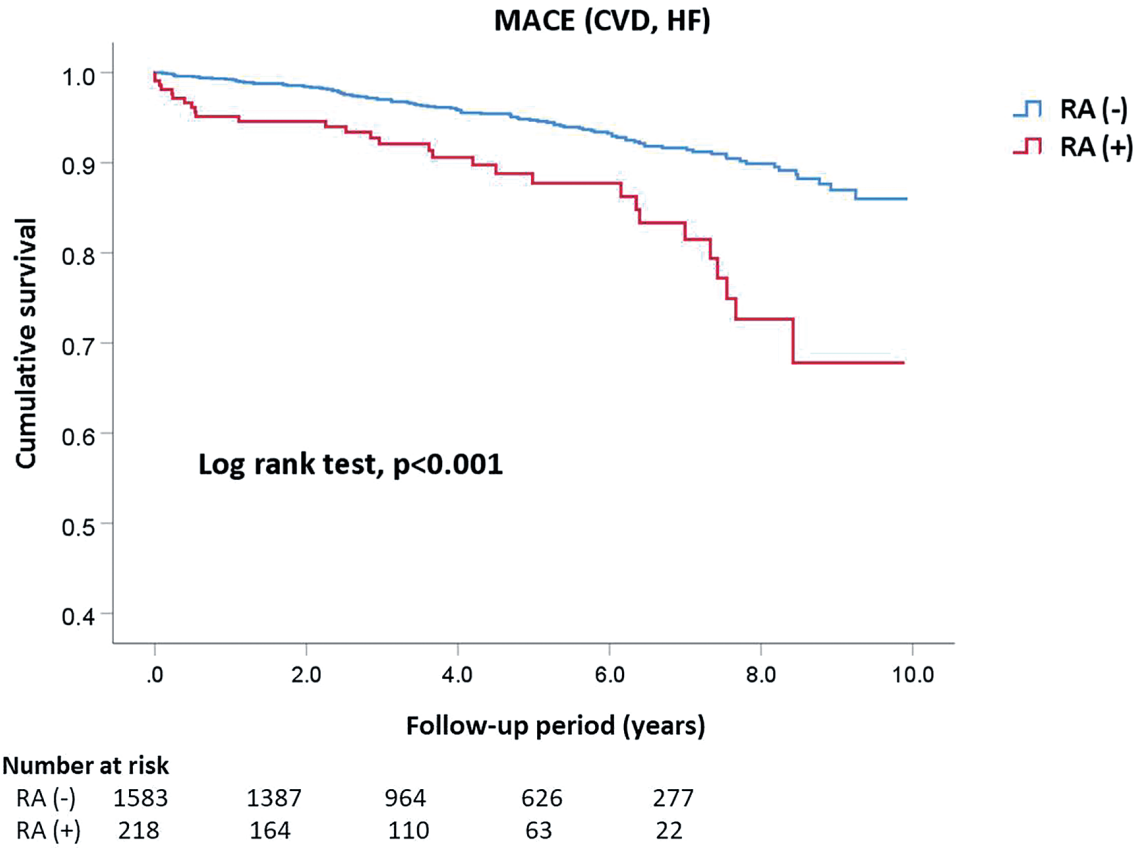


Fig. 2A Kaplan-Meier curves for MACE (including cardiovascular death and hospitalization for heart failure) according to RA syndrome
MACE, major adverse cardiac events ; CVD, cardiovascular death ; HF, heart failure ; RA, renal-anemia

dyslipidemia, serum hemoglobin, and eGFR were lower than the MACE (−) group.

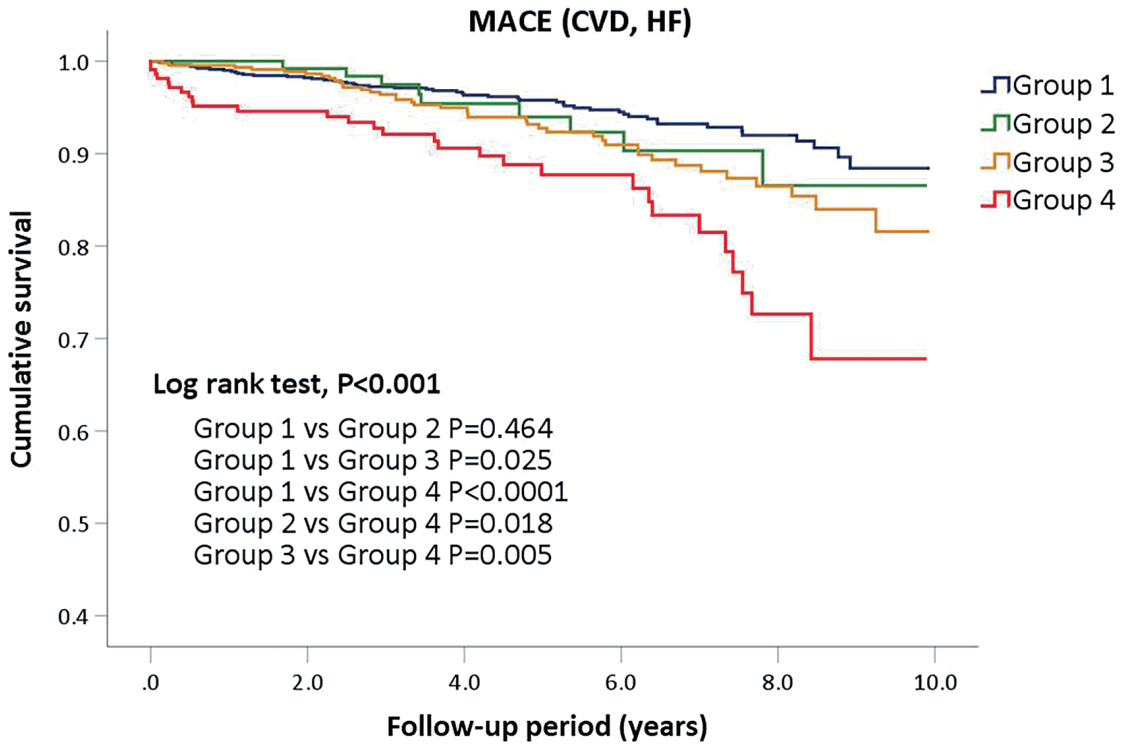
MACEs were observed in 129 patients (7 %). CVD events occurred in 78 patients and hospitalization for worsening HF in 62. Incidence of MACEs was significantly greater in the patients with RAS (29 patients, 13 % and 100 patients, 6 %, P<0.001). Considering the components of MACE, hospitalization for worsening HF occurred more frequently in the patients with RAS (19 patients, 9 % and 43 patients, 3 %, P<0.001), but CVD events were equivalent between the 2 groups (12 patients, 6 % and 69 patients, 4 %, P=0.364).

In Kaplan-Meier analysis for the incidence of primary endpoints, the patients with RAS showed significantly worse prognoses than the patients without RAS (the rate of MACE was 14 % in RAS (−) group and 32 % in RAS (+), respectively) (**Fig. 2A**). In addition, MACE incidence in the patients with RAS was greater than in the patients with only anemia or CKD (the rate of MACE was 12 % in Group 1, 14 % in Group 2, 19 % in Group 3, 32 % in Group 4, respectively) (**Fig. 2B**). Although CVD incidence did not significantly differ in each group (P=0.364), hospitalization for HF was significantly greater in the RAS (+) group (7 % in Group 1, 2 % in Group 2, 10 % in Group 3, 26 % in Group 4, respectively, P<0.0001).

In univariable Cox proportional hazards analysis, the presence of anemia or CKD was significantly associated with the incidence of MACE (HR 1.96 ; 95 % CI 1.34-2.87, P=0.001, and HR 1.94 ; 95 % CI 1.38-2.75, P<0.001), and the presence of RAS was a stronger predictor than presence of only anemia or CKD (HR 2.59 ; 95 % CI 1.72-3.92, P<0.001). In multivariable Cox proportional hazards analysis, RAS was an independent predictor of MACE (HR 1.86 ; 95 % CI 1.20-2.89, P=0.005) after adjustment for age, sex, and conventional risk factors (**Table 3**).

Ⅳ Discussion

The major findings in the present study were as



Number at risk

Group 1	954	847	598	397	170
Group 2	154	123	79	48	18
Group 3	475	417	287	18	89
Group 4	218	164	110	64	23

Fig. 2B Kaplan-Meier curves for MACE (including cardiovascular death and hospitalization for heart failure) for patients divided into 4 groups with or without anemia and/or CKD
MACE, major adverse cardiac events ; CVD, cardiovascular death ; HF, heart failure ; CKD, chronic kidney disease.

Table 3 Cox proportional hazard analysis for MACE

	Univariate HR (95 % CI)	p value	Multivariate HR (95 % CI)	p value
Female Sex	0.72 (0.46-1.12)	0.147	0.79 (0.50-1.24)	0.3
Age per decade	1.66 (1.35-2.02)	<0.001	1.55 (1.25-1.92)	<0.001
Hypertension	0.78 (0.53-1.15)	0.208	0.77 (0.52-1.16)	0.216
Dyslipidemia	0.56 (0.39-0.80)	0.001	0.62 (0.43-0.90)	0.011
Diabetes mellitus	0.88 (0.60-1.27)	0.485	0.90 (0.61-1.33)	0.596
Prior myocardial infarction	1.43 (0.97-2.12)	0.720	1.30 (0.85-1.98)	0.224
Prior cerebral infarction	2.24 (1.40-3.57)	0.001	2.03 (1.27-3.27)	0.003
Abdominal aortic aneurysm	1.73 (1.12-2.66)	0.013	1.26 (0.80-2.00)	0.324
Atrial fibrillation	1.83 (1.15-2.92)	0.011	1.60 (1.00-2.58)	0.052
LV ejection fraction	0.98 (0.96-0.99)	0.004	0.98 (0.97-1.00)	0.009
CRAS	2.59 (1.72-3.92)	<0.001	1.86 (1.20-2.89)	0.005
Anemia	1.96 (1.34-2.87)	0.001		
CKD	1.94 (1.38-2.75)	<0.001		

follows. 1) The prevalence of RAS in asymptomatic patients at HF (12 %) was lower than that in symptomatic HF in the present study (21 %). 2) RAS was an independent predictor of MACE in those patients.

3) Hypertension and diabetes mellitus known to be components of stage A HF were not associated with adverse events. 4) History of atherosclerotic diseases such as prior cerebral infarction, prior myocardial infarction and abdominal aortic aneurysm were independent predictors of adverse events.

Previous studies reported that the prevalence of CRAS ranged from 19 to 62 % and mortality rates were up to 51 % in patients with HF[10)11)18)19)]. The interactive links between the CRAS triad are complex and multi-factorial with high potential for increased morbidity, mortality, complexity and cost of care. Thus, early detection and optimal treatment of CKD, CVD, and anemia are important to prevent the prevalence and progression of CRAS. Nowadays, anemia is a main therapeutic target in CRAS ; however, overall its intensity, duration, and optimal hemoglobin concentration are not well established. Moreover, although both renal dysfunction and anemia have been extensively studied in HF cohorts, only a few studies have thoroughly examined the impact of renal dysfunction and anemia (renal-anemia syndrome) on the prognosis of patients at risk for HF.

In the present study, a combination of renal dysfunction and anemia showed a significant association with cardiovascular events in the earlier stage of HF. This result indicates that CRAS might be an advanced disease which consists of hypertension, diabetes mellitus, dyslipidemia, and chronic inflammatory disorders, i.e. risk factors for HF. Indeed, the pathophysiological mechanism in patients with HF with preserved ejection fraction is assumed to involve those risk factors inducing micro-inflammation and oxidative stress that cause multi-organ failure in the novice model[20)]. Thus, renal protection and optimal hemoglobin concentration would be the fundamental approach toward asymptomatic patients with RAS and HF risk factors.

The mechanism by which renal failure and anemia cause heart failure is as follows. Chronic low-grade inflammation due to various factors in CKD (i.e. visceral edema, oxidative stress, uremic toxins and so on[21)]) cause renin-angiotensin-aldosterone system (RAAS) and sympathetic nerve activity. Sodium and water retention due to these hormonal responses also exacerbate inflammation by production of proinflammatory cytokines and cardiac hypertrophy leading to necrosis and/or fibrosis of myocardial cells[9)]. In addition, angiotensin II, aldosterone and macrophage-derived galectin-3 stimulated by them directly promote cardiac remodeling via induction of fibrosis[22)-24)]. CKD also causes hyperphosphatemia, decreasing circulating levels of vitamin D metabolites, and increasing parathyroid hormone and fibroblast growth factor 23[25)]. These mineral and bone disorder are associated with cardiovascular toxicity, left ventricular hypertrophy[26)27)] and catabolism[28)]. Anemia leading to tissue hypoxia also activates the sympathetic system and RAAS, and causes myocardial damage by a similar mechanism[9)].

A Clinical implications

Recently, an "HF pandemic" has been striking our aging society. The prevalence of HF with multimorbidity also increases with age[29)]. Thus, effective interventions for HF management are necessary for elderly patients, including treatment of concurrent decompensated chronic conditions, reduction of polypharmacy, monitoring of patient exercise capacities, and prescription of physical exercise and nutritional supplementation[30)31)]. Prevention would be one of the leading parts of the management of risk factors for HF. Our findings corroborate the potential benefit of offering early intervention to asymptomatic patients with risk factors. This study also showed a positive impact of risk stratification of HF classification (i.e. stage A/B) for future cardiovascular events. Thus, recognition of those risk factors and early intervention for them would be effective strategies to stop the rot of "HF pandemic" in Japan.

B Limitations

Several limitations need to be noted in this study. First, the follow-up period of this retrospective investigation was short. Second, the etiology of renal dysfunction or anemia was unknown. Third, the retrospective nature of this study, reasons for admission, and therapeutic strategy after discharge were unknown. Finally, the impact of early intervention for preventing CKD and anemia on those patients'

prognosis needs to be investigated in other trials hopefully in a prospective manner. Despite these limitations, RAS proved to be a significant risk factor of future cardiovascular events among asymptomatic patients at risk for HF.

V Conclusions

In patients at risk for HF, CKD and anemia were significantly associated with future cardiovascular events. Investigation of the impact of early intervention for preventing CKD and anemia on those patients' prognosis is warranted.

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