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

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ABSTRACT

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) <60mL/min/1.73m^2) and anemia (hemoglobin <13g/dL in men and <12g/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 128 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 for the impact of early intervention for preventing CKD and anemia on those patients' prognosis were warranted.

背景: Cardio-renal-anemia syndrome (CRAS)は慢性心不全 (CHF)、慢性腎臓病 (CKD)、貧血が相互に影響しあい悪循環を形成することが知られている。しかしながら、無症

候性で心不全リスクを有するのみの患者における CKD、貧血の影響については依然不明である。

方法: 2005 年から 2012 年にかけて心血管疾患で当院に入院した患者の内、心不全既往が無い者を対象として後ろ向きに解析を行った。CKD(糸球体濾過量推定値 <60mL/min/1.73m2)と貧血(ヘモグロビン値　男性 <13g/dL、女性 <12g/dL)の合併例を RAS と定義し、その有無により患者を 2 群に割り付けを行った。主要評価項目は心血管死と心不全入院を含む主要心血管イベント (MACE)とした。

結果: 計 1801 例の患者が登録され、平均年齢は 69.6 ± 10.6 歳で 76%が男性であった。平均左室駆出率は 66.9 ± 12.3%で、stage A 心不全が全体の 73%を占めた。平均 4.6 年の追跡期間において、129 例で MACE 発生を認めた。Kaplan-Meier 分析では、RAS 群(n=217)は非 RAS 群(n=1584)と比し、有意差をもって予後は不良であった。Cox 比例ハザードモデルによる多変量解析では、年齢、性別、従来のリスク因子で調整を行った結果、RAS は MACE の発生率と有意な関連性を示した (HR 1.86; 95% CI 1.20-2.89, P = 0.005)。

結語: 心不全リスクを伴うのみの患者においても、RAS は将来的な心血管イベントを有意に増加させた。CKD、貧血への早期治療介入が、こうした患者の予後を改善し得るかに関しては更なる調査が必要である。

I Introduction

Currently, the rapid aging of society have caused rapid increase of the prevalence rate of CHF [1) 2)]. Though CHF in elderly have a poor prognosis because of frequent readmission cause to acute exacerbation[3)], the appropriate stage or method of intervention to prevent worsening of CHF is unclear. Anemia and/or CKD known as exacerbation factor 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, and the mechanism have been gradually elucidated. CKD and anemia activate the sympathetic system, the renin-angiotensin-aldosterone system (RAAS), and the antidiuretic hormone. Those neurohormonal actions and the consequent fluid retention cause the 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 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

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, Group 1-3 were combined into without renal-anemia syndrome (RAS) group. The primary endpoint was the composite of major adverse cardiovascular events (MACE), including cardio-vascular death (CVD) and heart failure requiring hospitalization. The secondary endpoints were cardio-vascular 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 (>55mm)[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 Cockcroft-Gault Equation 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 were less than 13 g/dL in male and 12 g/dL in female 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 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 Result

The baseline patient characteristics, classified by the presence of the CKD and/or anemia, were 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, were showed 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 dyslipidemia, serum hemoglobin, and eGFR were lower than MACE(-) group.

MACEs were observed in 129 patients (7%). CVD events were occurred in 78 patients and hospitalization for worsening HF in 62.-Incidence of MACEs were 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 were 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 significant 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 those 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 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, presence of anemia or CKD were 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 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 the adjustment for age, sex, and conventional risk factors (Table 3).

IV Discussion

The major findings in the present study were as 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 as 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 study reported that prevalence of CRAS ranged from 19 to 62% and mortality rates 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 cohort, only a few studies have thoroughly examined the impact of renal dysfunction and anemia (renal-anemia syndrome) on prognosis of patients at risk for HF.

In the present study, combination of renal dysfunction and anemia showed significant association with cardiovascular events in 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 factor of HF. Indeed, pathophysiological mechanism in patients with HF with preserved ejection fraction is assumed that those risk factors induces micro inflammation and oxidative stress that cause multi-organ failure in novice model[20]. Thus, renal protection and optimal hemoglobin concentration would be fundamental approach of 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]) caused 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 and remodeling via induction of fibrosis[22-24]. CKD also caused 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 activate sympathetic system and RAAS, and caused myocardial damage by similar mechanism[9)].

A Clinical Implications

Recently, "HF pandemic" strikes 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 part of the management of risk factor 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 the factors 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, etiology of renal dysfunction or anemia was unknown. Third, retrospective nature of this study, reason of 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 factors of future cardiovascular events among asymptomatic patients at risk for HF.

V Conclusions

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

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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 aneurythm	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 ㎡)	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
βBlocker	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 aneurythm	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/1.73m^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
βBlocker	435(27)	30(24)	0.404
Statin	819(51)	56(44)	0.137

Antiplatelet agents	1041(62)	76(59)	0.451

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 aneurythm	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		

Figure legends

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.

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

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.

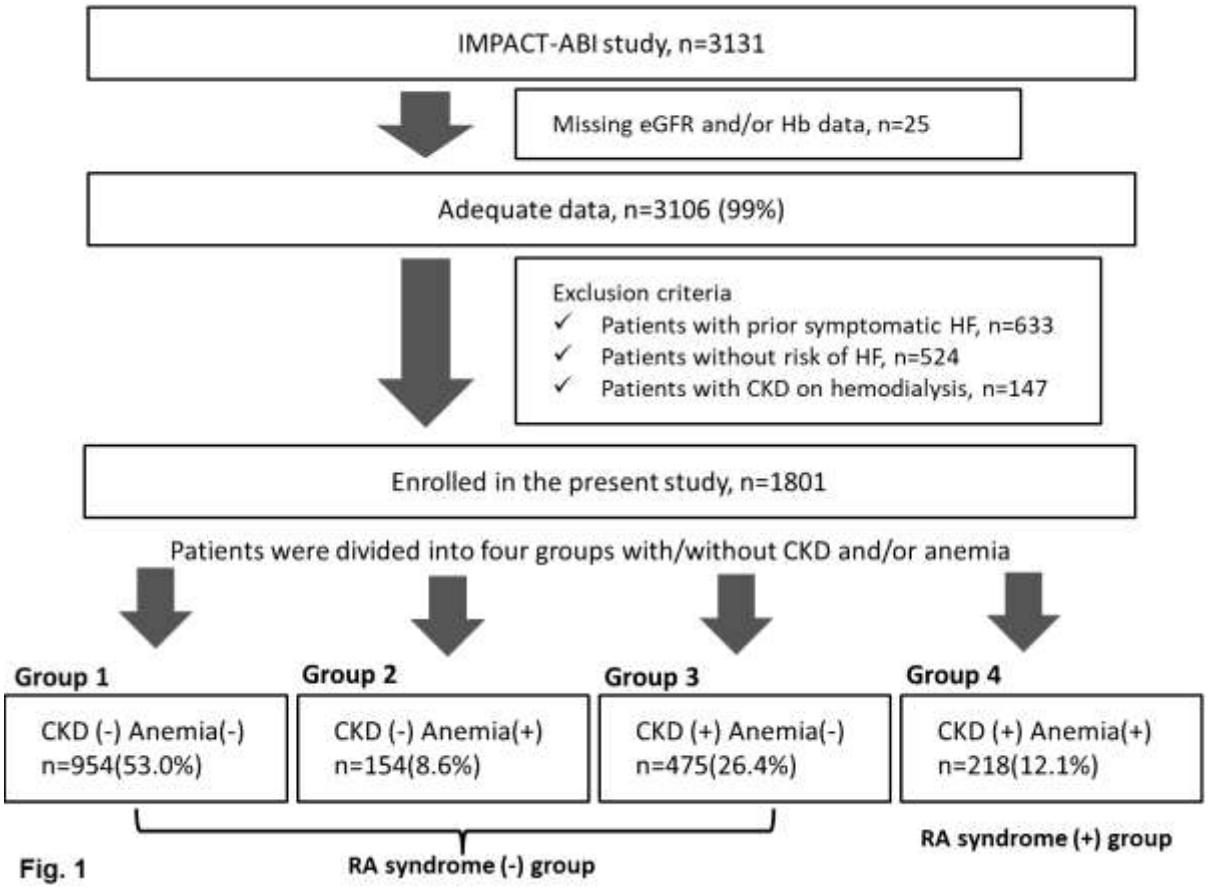
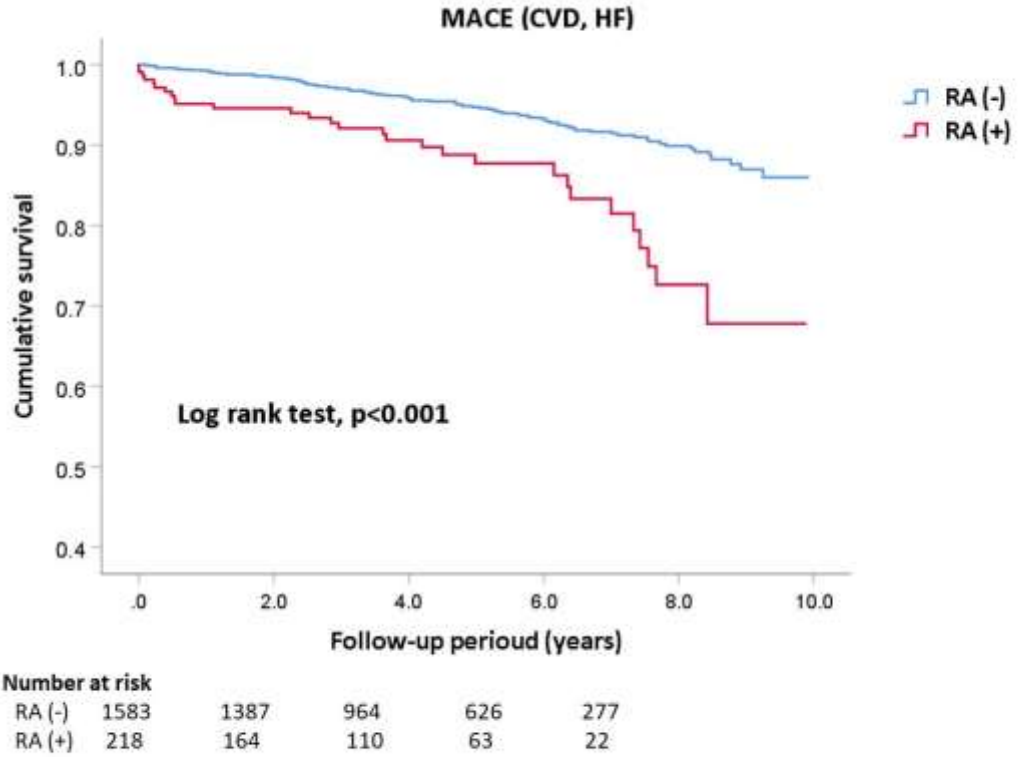


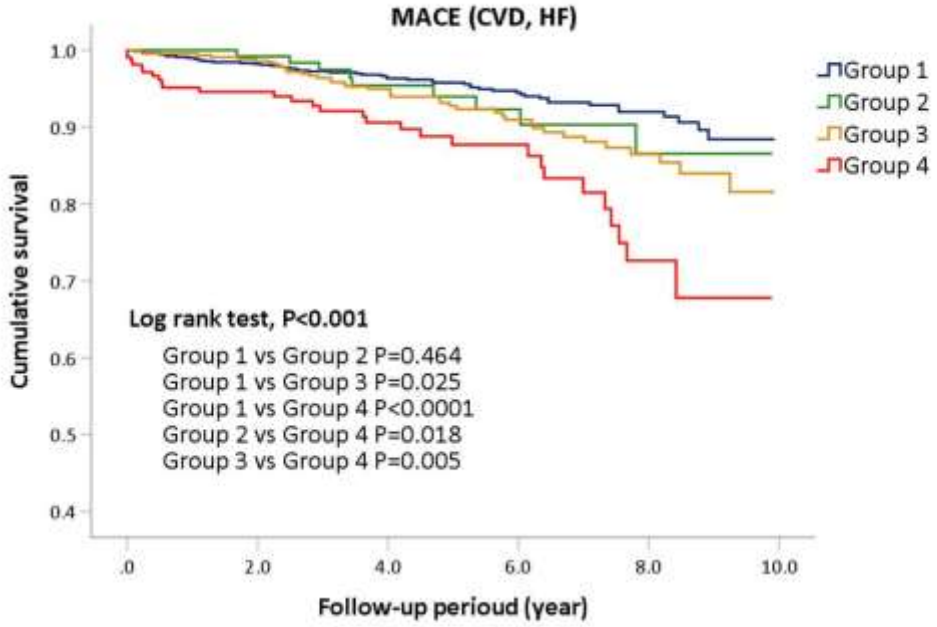
Fig. 1



Number at risk

RA (-)	1583	1387	964	626	277
RA (+)	218	164	110	63	22

Fig. 2A



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