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Risk of de-novo heart failure and competing risk in asymptomatic patients with structural heart diseases

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ABSTRACT

Aims: Asymptomatic patients with structural heart diseases are classified as a population at high risk for heart failure (HF) in Stage B. However, limited data are available regarding incidence and related factors of de-novo HF (DNHF) considering competing risk in this population.

Methods and results: In 3362 Stage B patients (mean age 68 yrs, male 76%) from the CHART-2 Study (N = 10,219), we examined incidence of death and DNHF, defined as the first episode of either HF hospitalization or HF death, and factors related to DNHF.

Results: During the median 6.0-year follow-up, 627 deaths (31/1000 person-years) and 293 DNHF (15/1000 person-years) occurred. Among the 627 deaths, 212 (34%) and 325 (52%) were specified as cardiovascular and non-cardiovascular deaths, respectively. During the follow-up of 271 DNHF hospitalizations, we observed 124 deaths, including 65 (52%) cardiovascular and 47 (40%) non-cardiovascular deaths. The competing risk model showed that age, diabetes mellitus, stroke, atrial fibrillation, diastolic blood pressure, hemoglobin levels, estimated glomerular filtration ratio and left ventricular ejection fraction was significantly associated with DNHF. Bayesian structural equation modeling showed that many of these cardiac and non-cardiac variables contribute to DNHF by affecting each other, while diabetes mellitus was independently associated with DNHF.

Conclusions: Stage B patients had a high incidence of DNHF as well as that of death due to both cardiovascular and non-cardiovascular causes. Thus, management of Stage B patients should include multidisciplinary approaches considering both cardiac and non-cardiac factors, in order to prevent DNHF as well as non-HF death as a competing risk.

Trial registration: clinicaltrials.gov identifier: NCT00418041.

1. Introduction

The prevalence of heart failure (HF) is approximately 1–2% in developed countries and the burden of HF has been emerging as a worldwide health issue [1–3]. HF is a clinical syndrome characterized by overt symptoms based on lower output and/or higher pressure of end diastolic phase, caused by a structural heart disease (SHD) and other factors [4]. Before clinical symptoms appeared, patients must have asymptomatic structural or functional cardiac abnormalities as precursors of HF. The American Heart Association (AHA)/American College of Cardiology (ACC) have broadened the concept of HF in order to emphasize the importance of primary and secondary prevention of the disorder, proposing 4 stages depending on the development of HF syndrome as Stages A to D [5]. The European Society of Cardiology (ESC) also states importance of recognition about these precursors and recommends starting treatment at the precursor stage [6]. However, the real clinical course of asymptomatic patients as Stage B is still unclear. Furthermore, the strategies proposed to prevent de novo HF (DNHF) in asymptomatic patients with precursor of HF have been largely unchanged because evidence is still limited regarding the mechanisms and predictors for the transition from asymptomatic SHD to symptomatic HF. Indeed, the evidence regarding development of DNHF has been mainly obtained from community-based cohort studies, particularly from general population including Stage A patients [7–9]. It

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is still unclear a rate of transition to HF or non-HF death in patient with Stage B. Furthermore, although left ventricular (LV) hypertrophy, hypertensive cardiomyopathy (HHD), ischemic cardiomyopathy (IHD) and valvular heart disease (VHD) have been recognized as major risk factors for DNHF development, patients with these factors also had high risk of death due to both cardiovascular and non-cardiovascular causes. To date, however, no comprehensive analyses considering these competing risks have been made to stratify the risk for DNHF in patients with SHD [9–11]. Thus, the clinical course and risk factors for DNHF in Stage B patients need to be better understood.

In 2006, we started the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART)-2 Study (N = 10,219), a prospective, observational study, which was characterized by inclusion of asymptomatic SHD patients (N = 4188) in addition to patients with a current or past history of HF (N = 5163) and those with coronary artery disease (CAD) (N = 868) in Japan [12–15]. One of the main purposes of the CHART-2 Study was to elucidate the factors predicting the transition from Stage B to symptomatic HF [12]. Our aim in this study is to examine the outcomes of patients with Stage B heart failure in relation to their risk factors based on the CHART-2 patient cohort.

2. Methods

2.1. Study design

The details of the CHART-2 Study and the design of the present study are described in the Supplementary text. Briefly, the CHART-2 Study is a prospective observational multicenter cohort study for HF in the Tohoku district, Japan (NCT00418041) [12–15]. A total of 24 institutions, located in the Tohoku district, participated in the CHART-2 Study. Consecutive stable patients were eligible for enrollment at any institution of the CHART-2 Study if they were aged ≥ 20 years with coronary artery disease or were in Stage B, C or D defined according to the Guidelines for the Diagnosis and Management of Heart Failure in Adults by the American Heart Association (AHA)/American College of Cardiology Foundation (ACCF). In the present study, we defined Stage B as patients with HHD or IHD without prior HF. HHD was defined by presence of left ventricular hypertrophy (LVH; interventricular septal thickness at end-diastole + posterior wall diameter ≥ 22 cm) or low left ventricle ejection fraction (LVEF) with hypertension. IHD was defined by the presence of a history of previous myocardial infarction or coronary artery disease. We examined the clinical characteristics and outcomes of the 3362 consecutive patients with Stage B in the CHART-2 Study. Furthermore, we elucidated the factors associated with transition from Stage B to symptomatic HF and using these factors, we performed network modeling for DNHF, and elucidated high risk strata to DNHF.

2.2. Outcomes

The endpoints of this study were death and DNHF. Cause of death was determined by the committee consisting of experienced cardiologists based on the information obtained through the chart review, interviews or a death certificate. DNHF was defined as the first episode of either acute death due to HF or HF requiring hospitalization with use of 2 or more diuretics or cardiotonics, and with 2 or more symptoms [12].

2.3. Statistical analysis and the DNHF score development

We performed the Cox proportional hazard models to predict all-cause death and performed competing risk model for DNHF using the Fine and Gray model with the cmprsk package for R considering all-cause death as the competing risk in the derivation cohort [16]. We performed variable selection by optimizing the Akaike's information criterion (AIC), and missing data were handled using a multiple imputation procedure with 20 resampling replications [17,18]. Age, sex and IHD/HHD were forced into any models. The survival classification and regression trees (survival CART) analysis was performed to elucidate the discriminating values of prognostic factors in the risk models for the onset of DNHF [19]. Among the variables in the model, network analyses with censored data of time-to-event were conducted using Bayesian structural equation modeling (Bayesian SEM) in Amos 24 and SPSS 24 (IBM Corp.) in the overall cohort. The strengths of association between two covariates are indicated as mean covariance, and association between covariates and time-to-event are expressed as mean coefficients using an arrow path. Finally, using these categorical variables together with the binary variables, we elucidate high risk strata to DNHF. All statistical analyses were performed using R software, version 3.5.1 [19]. All reported *P* values were 2-tailed, with a *P* value of <0.05 indicating statistical significance.

3. Results

3.1. Baseline characteristics

Median follow-up period was 6.0 years (IQR 5.1–7.5) and follow-up rate was 98.7%. Mean age was 68.6 ± 11 years old and males represented 76% of the study population (Table 1). Mean left ventricular ejection fraction (LVEF) was 63.7%. The prevalence of hypertension (HT),

Table 1
Baseline clinical characteristics of the patients.

Clinical characteristics		Medical history	
Male	2544 (76%)	Stroke	633 (19%)
Age (year)	68.6 ± 11	Cancer	442 (13%)
BMI	24.6 ± 3.4	Hypertension	3163 (94%)
Smoking	593 (19%)	Diabetes mellitus	1295 (39%)
Systolic BP (mmHg)	131.3 ± 17.5	Dyslipidemia	2859 (85%)
Diastolic BP (mmHg)	75.5 ± 11.5	Laboratory data	
Heart rate (bpm)	70 ± 13.4	Hb (g/dl)	13.6 ± 1.7
LVEF	63.7 ± 11.6	LDL cholesterol (mg/dl)	105.7 ± 29.2
Baseline cardiovascular disease		HbA1c (%)	6.3 ± 0.9
Ischemic heart disease	2280 (68%)	eGFR (ml/min/1.73 m^2)	66 ± 19.3
Hypertensive heart disease	1082 (32%)	BNP (pg/ml, median, (IQR))	49.4 (22−113)
Atrial fibrillation	409 (12%)	Medications	
		Beta blockers	1148 (34%)
		RAS inhibitors	2169 (65%)
		Diuretics	366 (11%)
		Statins	1638 (49%)

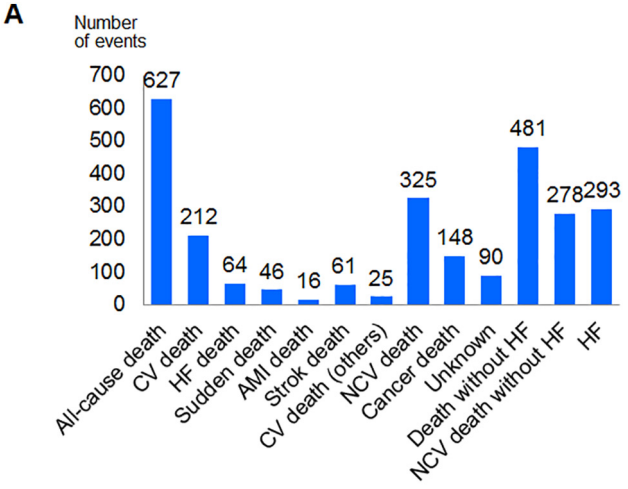
BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; eGFR, estimated glomerular filtration ratio; Hb, hemoglobin; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RAS, renin angiotensin system.

diabetes mellitus (DM) and dyslipidemia (DL) was 94, 39 and 85%, respectively, while IHD and HHD accounted for 68, 32%, respectively, as an etiology of structural heart disease. Atrial fibrillation (AF) was noted in 12% of the study subjects. Median serum BNP level was 49.4 pg/ml (IQR 22–113). Beta-blockers, renin-angiotensin-aldosterone system (RAS) inhibitors and statins were prescribed in 34, 65 and 49%, respectively (Table 1).

3.2. Incidence of death and DNHF in Stage B

During the follow-up period, 627 deaths (31/1000 person-years) and 293 DNHF (15/1000 person-years) were noted (Supplementary Fig. 1). Among the 627 deaths, 212 (33%) and 325 (52%) were specified as those due to cardiovascular and non-cardiovascular causes, respectively, while the causes of the remaining 90 (14%) were not specified (Fig. 1A). Among the 212 cardiovascular deaths, 64, 61, 46 and 16 were HF death, stroke death, sudden death and AMI death, respectively (Fig. 1A).

DNHF, defined as the first episode of either HF death or HF hospitalization, consisted of 22 deaths and 271 hospitalization. Among the 271 patients who experienced HF hospitalization, 124 died during the follow-up, of whom 65 (52%) and 47 (38%) died of cardiovascular causes and non-cardiovascular causes, respectively, and 42 (34%) died of HF (Fig. 1B). Median duration from HF hospitalization to death was 313 days (IQR 144–878). Among the comorbidities of HT, DM and DL, DM was associated with the highest mortality and incidence of DNHF, followed by HT (Supplementary Fig. 2). Among the etiologies of LV dysfunction, AF had the highest mortality and incidence of DNHF, followed by IHD and HHD (Supplementary Fig. 2).



B

	Event	rate (%)
All-cause death	124	100
Cardiovascular death	65	52
HF death	42	34
Sudden death	10	8
AMI death	2	2
Stroke death	7	6
Non-cardiovascular death	47	38
Cancer death	13	10
Unknown	12	10

Fig. 1. Cause of death in overall patients (A) and cause of death of patients with HF hospitalization without HF death (B). CV, cardio vascular; HF, heart failure; AMI, acute myocardial infarction; NCV, non-cardiovascular.

Table 2A
Cox hazard model for all-cause death.

Factors	Hazard ratio	95%CI	*P* value
Age	1.07	1.06–1.09	<0.001
Sex	0.58	0.47–0.71	<0.001
DM	1.36	1.16–1.60	<0.001
HD	2.61	1.34–5.06	0.005
MI	0.79	0.65–0.95	0.015
IHD	1.09	0.88–1.36	0.416
Smoking	1.40	1.14–1.72	0.001
AF	1.49	1.20–1.86	<0.001
Cancer	1.34	1.10–1.62	0.003
BMI	0.96	0.94–0.99	0.003
Heart rate	1.01	1.00–1.02	<0.001
Hb	0.83	0.79–0.87	<0.001
eGFR	0.99	0.99–1.00	0.001
LVEF	0.99	0.98–0.99	<0.001
BNP	1.02	1.00–1.04	0.036

AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration ratio; Hb, hemoglobin; HD, hemodialysis; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction.

3.3. Predictors for death and DNHF

The variables selected for the Cox proportional hazard models for all-cause death and the competing model for DNH are shown in Tables 2A and 2B. The numbers of missing data in variables are shown in Supplementary Table 1. Among the variables selected, statistically significant predictors for mortality included age, male sex, DM, hemodialysis, myocardial infarction (MI), smoking, AF, cancer, BMI, heart rate, Hb, eGFR, LVEF and BNP, while those for DNHF were age, DM, AF, diastolic blood pressure (DBP), Hb, eGFR and LVEF.

Among the variables for DNHF, continuous variables (age, DBP, LVEF, Hb and eGFR) were replaced with binary variables using the cut-off points of age ≥ 75 years, DBP < 60 mmHg, LVEF < 45%, Hb < 11 g/dl and eGFR<50 ml/min/1.73 m^2, based on the optimal cut-off points derived from the CART (Supplementary Fig. 3). Incidence of DNHF was increased along with the number of these factors the study subjects had at baseline, in both IHD and HHD patients (Fig. 2A–D).

Bayesian structural equation modeling showed that these factors, particularly AF and DM, significantly associated with DNHF development, and that many of these variables contribute to DNHF by affecting each other; in particular, age contributed DNHF in significant associations with AF, low DBP, low Hb and low eGFR, while DM contributed to DNHF independently of other factors and LVEF did only in association with AF in this model (Fig. 2E, Supplementary Table 2).

Table 2B
Competing model for DNHF.

Factors	Hazard ratio	95%CI	*P* value
Age	1.06	1.04–1.07	<0.001
Sex	1.06	0.81–1.38	0.683
DM	1.42	1.12–1.80	0.004
IHD	0.94	0.71–1.26	0.690
AF	1.77	1.27–2.46	0.001
Systolic BP	1.01	1.00–1.02	0.072
Diastolic BP	0.98	0.97–1.00	0.035
Hb	0.85	0.78–0.92	<0.001
eGFR	0.98	0.98–0.99	<0.001
LVEF	0.97	0.96–0.98	<0.001
BNP	1.03	1.00–1.06	0.087

AF, atrial fibrillation; BNP, brain natriuretic peptide; BP, blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration ratio; Hb, hemoglobin; IHD, Ischemic heart disease; LVEF, left ventricular ejection fraction.

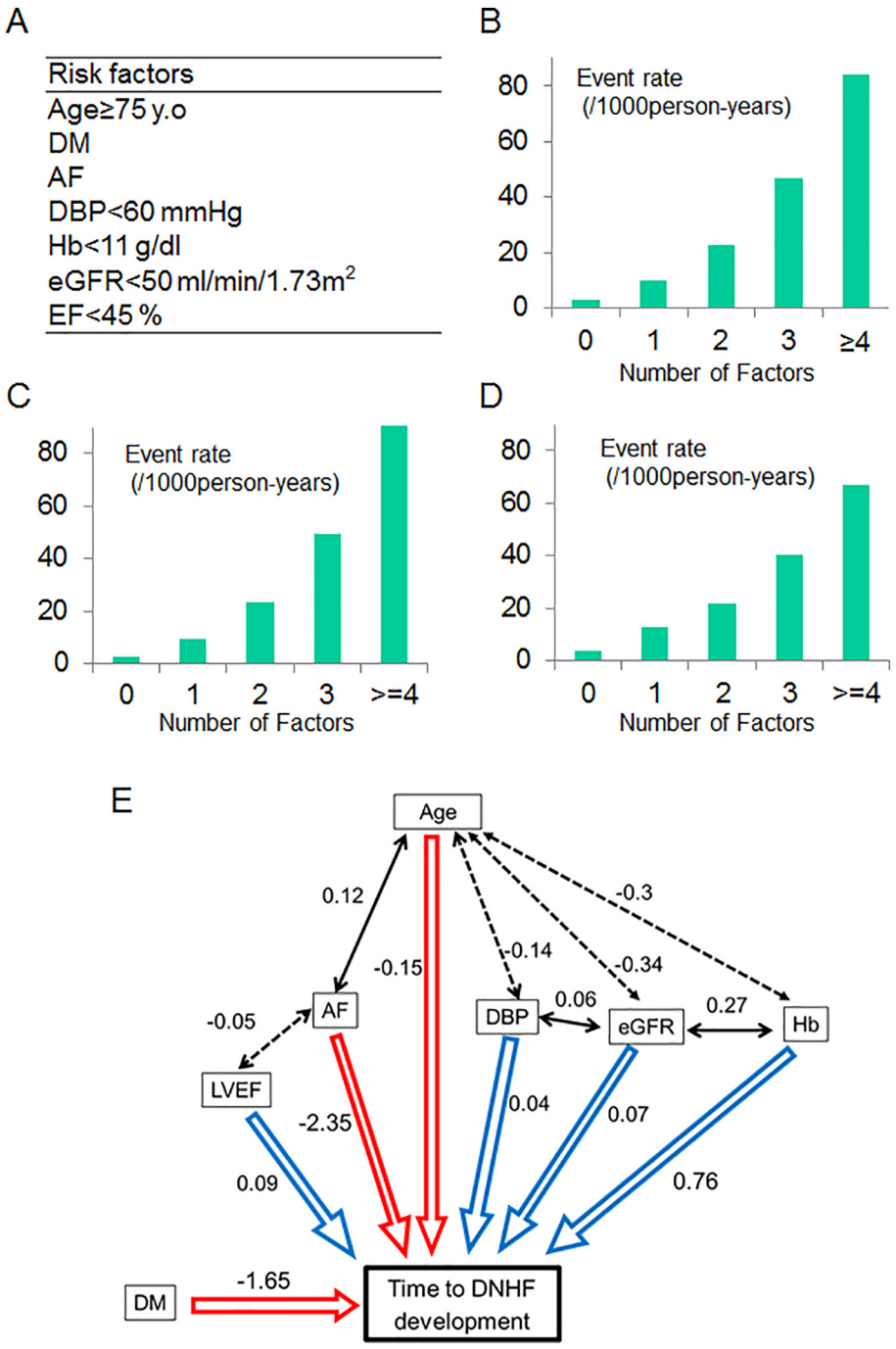


Fig. 2. An association between number of factors and incidence rate. (A) Risk factors, (B) incidence of DNHF by risk factors in overall patients, (C) incidence of DNHF by risk factors in patients with IHD, and (D) incidence of DNHF by risk factors in patients with HHD, (E) path diagram of Bayesian structural equation modeling for the span of heart failure and the risk factors. Double headed arrows indicate associations between two covariates with correlation coefficient, where solid and dashed lines indicate positive and negative correlations, respectively. Single headed arrows indicate associations between covariates and time-to-event with mean coefficient (E). AF, atrial fibrillation; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; DM, diabetes mellitus; DNHF, de-novo heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration ratio; Hb, hemoglobin.

4. Discussion

The CHART-2 Study is a multicenter observational clinical study with a pre-specified purpose to elucidate the factors predicting DNHF in Stage B patients. The present study identified that significant predictors for DNHF in Stage B patients were age, DM, AF, low DBP, low Hb, low eGFR and low LVEF. Network modeling indicates that all variables but DM interact. To the best of our knowledge, this is the first study of Stage B HF patients that demonstrates associations between risk factors and progression to clinical HF.

4.1. Stage B patients from the CHART-2 Study

During the median follow-up period of 6.6 years, we observed 293 DNHF (15/1000 person-years) in the present study, indicating that Stage B is a population at actually high risk for DNHF. This finding provides a significant importance, since 1) although the predictors for DNHF in general population were reported in the past studies, evidence in high-risk patients has been limited [7,9], and 2) this observation was obtained in a prospective fashion according to one of the prespecified purposes of the CHART-2 Study to elucidate the factors associated

with DNHF development [12]. It is also noteworthy that the present study provided included both IHD and HHD asymptomatic patients since previous studies mainly examined the risk of DNHF in asymptomatic CAD patients with diastolic dysfunction [20], asymptomatic CAD patients with LV dysfunction [21] and those in the general population [22]. In the Framingham Heart Study, it was reported that age-adjusted incidence of congestive heart failure during 1980s among men and women aged ≥45 years was 7.2 and 4.7 cases/1000 person-year, respectively [22]. Thus, the incidence of DNHF in our cohort was higher than that in the general population, which was expected as an asymptomatic SHD population. Furthermore, it is reasonable to consider that the present patient cohort represented those at high risk for DNHF without past or current history of HF, since median BNP level was 49.4 pg/ml in the present study, which was almost normal or slightly increased level when considering the median age (69 years). Taken together, the present patient cohort is considered to be appropriate to examine the clinical profiles and long-term prognosis of asymptomatic patients with precursors of HF.

4.2. Competing risk against DNHF in Stage B patients

The present study also revealed that Stage B patients had more than twice higher risk of death as compared with DNHF risk and higher incidence of non-cardiovascular death than that of cardiovascular death. Furthermore, among the 271 patients who experienced HF hospitalization, 124 died during the follow-up, of whom 47 (38%) died of non-cardiovascular causes. These observations clearly underline the significant involvement of non-cardiovascular factors in Stage B patients. We have recently reported that 3-year incidence of non-cardiovascular death has significantly increased, while those of all-cause death and cardiovascular death has decreased in Japan [15]. These lines of observations indicate an importance to consider non-cardiovascular factors in the management of Stage B patients, regardless of before or after HF development, since implementation of evidence-based medication to prevent DNHF could reduce incidence of DNHF, inevitably resulting in a relative increase of non-HF events in the contemporary era.

4.3. Predictive precursors for DNHF in Stage B patients

The present study demonstrated that older age, DM, stroke, AF, lower DBP, lower Hb, lower eGFR and lower LVEF were the statistically significant predictors for DNHF development in Stage B patients. Although the evidence on the predictors in asymptomatic patients is limited [7,9], the predictors for DNHF development have been well documented in the general population, particularly in the Framingham Heart Study. Haider et al. reported that SBP, DBP and pulse pressure were all significantly related to the risk for CHF [23]. In particular, low DBP has been repeatedly reported as a risk factor for adverse outcomes in the general population, in patients with stable CAD, HF with preserved LVEF and AF [24–27]. Moreover, a J-shaped association between DBP and risk of adverse outcome was demonstrated [24], indicating that lower perfusion at diastolic phase could lead to adverse outcomes. Our finding that low DBP predicted future DNHF extends this knowledge to stage B patients, and may have clinical implications for hypertension treatment, since goals only for SBP, but not for DBP have been defined for HF patients with preserved LVEF. Ho et al. found that older age, DM, and a history of VHD were commonly associated with development of DNHF regardless of HF with reduced or preserved LVEF [11]. Furthermore, Lam et al. found that after adjustment for established HF risk factors, antecedent left ventricular systolic and diastolic dysfunctions were associated with increased HF risk, while higher serum creatinine, lower ratio of forced expiratory volume in 1 s to forced vital capacity, and lower Hb concentrations were associated with increased HF risk, after adjustment for cardiac dysfunction [7]. In addition, Wang et al. reported that among 382 individuals who developed both AF and HF in the Framingham Heart Study, 38% had AF first, and that the incidence of CHF among AF subjects was 33 per 1000 person-years [28]. Thus, the predictors for DNHF shown in the present study, such as age, DM, stroke, AF, DBP, Hb, eGFR and LVEF are consistent with the findings in the general population, indicating that both cardiac and non-cardiac factors are commonly involved in future development of DNHF in both the general and Stage B populations.

4.4. Network modeling and risk score for DNHF

To better understand the mechanisms to develop DNHF, we further analyzed communications among the factors related to DNHF in the network modeling. Bayesian structural equation modeling showed that cardiac and non-cardiac factors were cooperatively associated with DNHF development in Stage B patients. In this modeling, it was noted that AF and DM had significant impacts on DNHF development. Not only with age, AF contributed DNHF development in a negative association with LVEF, indicating an importance of AF management considering LVEF for the prevention of DNHF in Stage B patients. From this viewpoint, catheter ablation in the early stage of AF onset could be a practical option to prevent DNHF in Stage B patients, although it is still unclear whether catheter ablation of AF is beneficial in patients with left ventricular systolic dysfunction [29]. Next, since DM was a strong contributor for DHNF independently of other factors, management targeting DM could be effective to prevent DNHF. Indeed, recent clinical trials showed that sodium–glucose cotransporter 2 (SGLT2) inhibitors significantly reduced the risk of HF development in both primary and secondary prevention for patients with or at high risk of cardiovascular diseases [30–32]. Considering the recent increase of DM patients worldwide, DM management may play a significant role in prevention of DNHF in Stage B patients. However, it should be noted that just the better blood glucose control may not necessarily contribute to prevention of DNHF, since no anti-diabetics except for SGLT2 inhibitors have reduced HF incidence of DM patients in the previous randomized clinical trials [33,34]. Finally, it was noted that age was positively associated with DNHF both directly and in associations with AF and low DBP, Hb and eGFR levels, indicating that management and/or prevention of AF, diastolic hypotension, anemia and renal dysfunction is important to prevent DNHF, particularly in the elderly Stage B patients. Thus, treatment strategies for Stage B patients should include multidisciplinary approaches considering both cardiovascular and non-cardiovascular factors to improve their prognosis.

4.5. Study limitations

Several limitations should be mentioned for the present study. First, the study population included only patients with IHD or HHD. Thus, interpretation and generalization of our findings should be done carefully after considering the heterogeneity of our Stage B cohort. Second, we only used the data at the entry and did not take into consideration the possible changes during the follow-up period. Third, all subjects in the CHART-2 Study were Japanese, which may limit generalization of the present results to patients in other populations.

5. Conclusions

Stage B patients had a high incidence of DNHF as well as that of death due to causes other than HF, including non-cardiovascular death. Both cardiac and non-cardiac factors were cooperatively associated with DNHF development in Stage B patients. Thus, management of Stage B patients should include multidisciplinary approaches considering both cardiac and non-cardiac factors, in order to prevent DNHF as well as non-HF death as a competing risk.

5.1. Clinical perspectives

Preventing an onset of HF is worldwide issue, because pandemic of HF has come up in the world. However, predictors for de-novo HF were still unclear. The CHART2 study is a unique designed study, which including high risk patients for de-novo HF, to elucidate factors for de-novo HF.

5.2. Translational outlook

Our findings cleared the predictors for de-novo HF in asymptomatic patients with structural heart diseases, who are high risk group for de-novo HF. Management of these factors could leaded to prevention of de-novo HF in those high risk patients.

CRediT authorship contribution statement

Tsuyoshi Takada: Methodology, Writing - original draft, Software. **Yasuhiko Sakata:** Conceptualization, Methodology, Software. **Kotaro Nochioka:** Data curation. **Masanobu Miura:** Data curation. **Ruri Abe:** Data curation. **Shintaro Kasahara:** Data curation. **Masayuki Sato:** Data curation. **Hajime Aoyanagi:** Data curation. **Takahide Fujihashi:** Data curation. **Shinsuke Yamanaka:** Data curation. **Kota Suzuki:** Data curation. **Takashi Shiroto:** Data curation. **Koichiro Sugimura:** Data curation. **Jun Takahashi:** Data curation. **Satoshi Miyata:** Software, Formal analysis. **Hiroaki Shimokawa:** Supervision, Writing - review & editing, Project administration.

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Declaration of competing interest

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Appendix A. Supplementary data

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