not in those with SBP <89 mmHg. Thus, although HR reduction is an important therapeutic strategy in CHF patients, we should simultaneously pay attention to SBP, as suggested in the COPERNICUS trial.[25] In the present study, hazard ratios for all-cause mortality were comparable in each risk group between patients with and those without β-blocker treatment (**Table 2**). Furthermore, mortality rates of patients with SBP <89 mmHg and β-blocker therapy were equivalent or even higher than those of patients with SBP <89 mmHg or 89–115 mmHg and without β-blocker therapy (**Figure 4**), suggesting that treatment with β-blockers for CHF patients with low SBP was not necessarily associated with reduced mortality, although caution in interpreting this observation is needed. In this context, ivabradine may be an ideal drug for CHF patients with lower SBP and lower LVEF as recommended in the ESC Guidelines,[8] because ivabradine is a pure HR-lowering agent in patients in SR[6,7] and does not affect SBP, myocardial contractility or intra-cardiac conduction.[23] However, it has recently been demonstrated in the SHIFT trial that the effects of ivabradine are prominent in patients with HR >77 beats/min but not so significant in those with HR <77 beats/min.[7] Thus, the potential benefits of HR reduction therapy for high-risk CHF patients remain to be further examined.

HR and SBP in HF Patients With Diabetes

In the present study, HF patients with diabetes in the high-risk group had significant higher hazard ratio for all-cause death compared with those without diabetes. In the present study, patients in the high-risk group had lower DBP levels (**Table 1**) and HF patients with diabetes had a higher prevalence of ischemic etiology compared with those without diabetes (66.7% vs. 41.5%, P<0.001). It has been reported that lower levels of BP, particularly DBP, are associated with decreased coronary perfusion and coronary vascular events in patients with CAD.[26–28] In the present study, however, the event rates of death from myocardial infarction or cardiovascular death were not high enough to detect statistical significance between patients with or without diabetes in the high-risk group. Thus, further study is warranted to reveal the association between diabetes and HR or BP for mortality in CHF patients.

Study Limitations

First, the present results came from analysis of data obtained at entry of subjects to the study and we did not take into consideration possible changes in SBP, HR and other covariates during the follow-up period. Second, both the prescription rate and dose of β-blocker were relatively low compared with other studies that enrolled patients hospitalized with HF.[15,29] In the present study, however, most of the patients (79.5%) were registered on an outpatient basis, and 65.7% had preserved LVEF (≥50%) and 52.9% did not have prior history of hospitalization for HF. These factors might have influenced the relatively low prescription ratio of β-blockers in the present study. Third, the primary design of the present study did not cover chronic lung disease, which has been recognized as an important prognostic factor of HF.[30] Finally, because CHART-2 is an observational study in real-world practice, the present results need to be carefully interpreted, especially when the effects of treatment are evaluated.

Conclusions

The present study demonstrates that SBP <89 mmHg regardless of HR values or SBP 89–115 mmHg and HR >76 beats/min is associated with poor prognosis in CHF patients in SR, indicating the importance of combined risk stratification of HR and SBP in the management of CHF patients.

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Disclosures

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Supplementary Files

Supplementary File 1

Table S1. Modes of death in the present study of patients with chronic heart failure in the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) study

Appendix S1. Organization of the CHART-2 study

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ORIGINAL ARTICLE
Heart Failure

Impact of Physical Activity on Cardiovascular Events in Patients With Chronic Heart Failure

– A Multicenter Prospective Cohort Study –

Yutaka Miura, MD, PhD; Yoshihiro Fukumoto, MD, PhD; Toshiro Miura, MD, PhD; Kazunori Shimada, MD; Masanori Asakura, MD, PhD; Toshiaki Kadokami, MD, PhD; Shin-ichi Ando, MD, PhD; Satoshi Miyata, PhD; Yasuhiko Sakata, MD, PhD; Hiroyuki Daida, MD; Masunori Matsuzaki, MD, PhD; Satoshi Yasuda, MD, PhD; Masafumi Kitakaze, MD, PhD; Hiroaki Shimokawa, MD, PhD

Background: We have previously demonstrated that the prevalence of metabolic syndrome in chronic heart failure (CHF) is more than double compared with the general population in Japan. However, the impact of physical activity on cardiovascular events in CHF patients remains to be fully elucidated.

Methods and Results: We performed a prospective, nationwide large-scale multicenter study of 9,178 patients with stage A/B/C/D CHF in Japan. We obtained the baseline physical activity data for 7,292 and yearly changes in physical activity data during a 3-year follow-up period for 4,353 patients. We divided the patients into high- and low-exercise groups by using the median value of physical activity in the stage A/B and C/D groups. In both groups, patients who exercised more were characterized by younger age and less advanced stage of CHF. Importantly, the baseline physical activity levels were significantly associated with all-cause death, heart failure (HF) hospitalization and other cardiovascular events (except acute myocardial infarction, stroke, HF hospitalization). Furthermore, the yearly change in physical activity level was also significantly associated with HF hospitalization and other cardiovascular events in both groups.

Conclusions: The baseline level of physical activity and its yearly changes are significantly associated with all-cause death and major cardiovascular events in both stage A/B and C/D patients, suggesting that physical activity could be an important therapeutic target to improve the long-term prognosis of CHF patients. (*Circ J* 2013; **77:** 2963–2972)

Key Words: Chronic heart failure; Heart failure hospitalization; Physical activity; Prognosis

The prevalence of lifestyle diseases, such as diabetes mellitus, dyslipidemia, hypertension, and their combination in metabolic syndrome (MetS), has been rapidly increasing in Japan over the past decades, because of westernization of lifestyle.[1] Recently, we performed a prospective, nationwide large-scale multicenter study supported by the Japanese government on the current status of chronic heart failure (CHF) patients in Japan, with a special reference to lifestyle diseases, and demonstrated that the prevalence of MetS in CHF patients is more than double compared with the general population in Japan.[2] This suggests that lifestyle diseases have a substantial impact on the development of both ischemic and non-ischemic CHF.[2,3]

CHF is a complex clinical syndrome in which both HF with preserved ejection fraction (HFpEF) and HF with reduced EF (HFrEF) are substantially involved.[3–7] We have also demonstrated that the prevalence of the metabolic components is comparable between HFpEF and HFrEF.[2] In Japan, CHF has become a growing social issue as the number of CHF patients has been rapidly increasing because of the aging of the popu-

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Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai (Y.M., Y.F., S.M., Y.S., H.S.); Division of Cardiology, Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, Ube (T.M., M.M.); Department of Cardiovascular Medicine, Juntendo University School of Medicine, Tokyo (K.S., H.D.); Cardiovascular Division of Internal Medicine, National Cerebral and Cardiovascular Center, Suita (M.A., S.Y., M.K.); and Division of Cardiovascular Medicine, Saiseikai Futsukaichi Hospital, Chikushino (T.K., S.A.), Japan

The Guest Editor for this article was Hiroshi Ito, MD.

Mailing address: Hiroaki Shimokawa, MD, PhD, Professor and Chairman, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: shimo@cardio.med.tohoku.ac.jp

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Table 1. Baseline Characteristics of CHF Patients with Low and High Physical Activity Levels in Stages A/B and C/D

	Stage A/B (n=4,435)			Stage C/D (n=2,857)		
	Low-Ex (n=2,097)	High-Ex (n=2,338)	P value	Low-Ex (n=1,525)	High-Ex (n=1,332)	P value
Age (years)	69.1±0.3	66.7±0.2	<0.001	69.5±0.3	66.4±0.3	<0.001
Sex (male)	1,498 (71.4%)	1,641 (70.2%)	NS	1,032 (67.7%)	925 (69.4%)	NS
Cigarette smoking, n (%)			NS			NS
Never	985 (66.7%)	1,136 (68.1%)		755 (68.2%)	693 (69.8%)	
Former	119 (8.1%)	144 (8.6%)		87 (7.9%)	70 (7.0%)	
Current	372 (25.2%)	387 (23.2%)		265 (23.9%)	230 (23.2%)	
Alcohol intake, n (%)			NS			0.001
Never	928 (49.0%)	1,010 (47.8%)		648 (47.1%)	644 (52.7%)	
Former	136 (7.2%)	178 (8.4%)		118 (8.6%)	65 (5.3%)	
Current	831 (43.9%)	926 (43.8%)		611 (44.4%)	512 (41.9%)	
BMI (kg/m^2)	24.0±0.8	24.0±0.8	NS	24.1±0.1	24.2±0.1	NS
Waist (cm)	86.0±0.2	86.1±0.2	NS	86.0±0.3	86.5±0.3	NS
Blood pressure (mmHg)						
Systolic	128.5±0.4	128.5±0.4	NS	128.0±0.5	128.9±0.5	NS
Diastolic	73.5±0.3	73.8±0.2	NS	73.5±0.3	73.6±0.3	NS
Heart rate (beats/min)	70.4±0.3	70.3±0.3	NS	70.9±0.4	71.3±0.4	NS
NYHA						
III/IV	–	–	–	99 (6.5%)	70 (5.3%)	NS
EF (%)	61.8±0.3	62.4±0.3	NS	61.3±0.4	61.2±0.4	NS
HFpEF (EF ≥50%)	1,616 (81.9%)	1,826 (82.6%)	NS	1,159 (79.6%)	1,007 (79.2%)	NS
HT	1,589 (76.1%)	1,803 (77.3%)	NS	1,208 (79.4%)	1,041 (78.5%)	NS
DM or fasting glucose ≥110 mg/dl	515 (24.8%)	580 (24.9%)	NS	423 (27.9%)	330 (24.9%)	NS
Dyslipidemia	1,513 (72.6%)	1,692 (72.5%)	NS	1,145 (75.2%)	979 (73.9%)	NS
Serum creatinine ≥3.0 mg/dl	33 (1.6%)	38 (1.6%)	NS	31 (2.0%)	27 (2.0%)	NS
Hemodialysis	23 (1.1%)	24 (1.0%)	NS	16 (1.1%)	19 (1.4%)	NS
IHD	1,124 (53.6%)	1,201 (51.4%)	NS	785 (51.5%)	708 (53.2%)	NS
HHD	217 (10.3%)	284 (12.1%)	NS	153 (10.0%)	144 (10.8%)	NS
CM	257 (12.3%)	281 (12.0%)	NS	221 (14.5%)	179 (13.4%)	NS
VHD	406 (19.4%)	474 (20.3%)	NS	299 (19.6%)	274 (20.6%)	NS
CHD	31 (1.5%)	42 (1.8%)	NS	27 (1.8%)	22 (1.7%)	NS
BNP	127.0±4.1	131.9±5.1	NS	140.3±5.6	155.6±9.0	NS
Exercise	2.0±0.03	14.3±0.2	<0.001	1.7±0.03	14.2±0.3	<0.001
Medications						
ACEI/ARB	1,261 (60.1%)	1,348 (57.7%)	NS	1,097 (71.9%)	957 (71.8%)	NS
β-blocker	776 (37.0%)	759 (32.5%)	<0.01	783 (51.3%)	679 (51.0%)	NS
Statin	988 (47.1%)	1,120 (47.9%)	NS	616 (40.4%)	568 (42.6%)	NS

Results are expressed as mean±SEM.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CHD, congenital heart disease; CHF, chronic heart failure; CM, cardiomyopathy; DM, diabetes mellitus; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HHD, hypertensive heart disease; HT, hypertension; IHD, ischemic heart disease; NS, not significant; VHD, valvular heart disease.

lation,[3–7] so not only westernization of lifestyle but also reduced physical activity may be involved.[8]

Although physical activity is important for improvement lifestyle diseases, its impact on cardiovascular events in CHF remains to be elucidated, especially in terms of yearly changes in physical activity level. Thus, in the present study, we examined whether the baseline level of and yearly changes in physical activity influenced the occurrence of major cardiovascular events in CHF patients in our multicenter prospective cohort study.

Methods

The ethics committees of each institute approved the study protocol and all patients provided written informed consent.

Study Population

In this multicenter study, we prospectively enrolled 9,178 CHF patients in stages A/B/C/D by the ACC/AHA Guidelines[9] between September 2006 and December 2010 from 5 institutes in Japan.[2] For each patient, we used an online data collection system (Fujitsu Systems East Limited, Tokyo, Japan) to prospectively collect data from the participating hospitals: baseline demographic data; medications; comorbidities (previous myocardial infarction (MI) or stroke, dialysis, and atrial fibrillation); physical activity; cardiovascular events (acute MI [AMI], stroke, and HF hospitalization), and death.

Physical activity level (Exercise units) was assessed using a shortened version of the Japanese Exercise Guide 2006 published by the Japanese Ministry of Health, Labor, and Welfare

Table 2. Physical Activity Level at Baseline and Follow-up in Patients With Chronic Heart Failure

	Stage A/B (n=2,756)			Stage C/D (n=1,597)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value
Male	5.8, 9.4±0.2	4.3, 7.2±0.2	<0.001	5.0, 8.6±0.3	3.4, 6.3±0.2	<0.001
Female	4.9, 8.4±0.3	3.2, 5.6±0.3	<0.001	3.9, 7.7±0.5	2.3, 4.9±0.3	<0.001

Results are expressed as median, mean±SEM.
Abbreviation as in Table 1.

(Table S1): 1 Exercise (Ex) equals 1 METS×1 h (unit of physical activity).[10] Because of non-normal distribution, we divided the patients in stages A/B and C/D into high- and low-exercise groups according to the median value of physical activity in each group. Furthermore, we divided the patients into 4 groups, depending on each median of the baseline and follow-up physical activity levels: "low to low", "low to high", "high to low" and "high to high" groups.

Data Collection

Data for baseline demographics (age, sex, height, body weight, waist circumference, blood pressure and heart rate), CHF stage, medications (angiotensin-converting enzyme inhibitor [ACEI], angiotensin-receptor blocker [ARB], β-blocker, and statins), risk factors (hypertension, glucose intolerance/diabetes mellitus and dyslipidemia), biochemical data (lipid profile and glucose), plasma levels of brain natriuretic peptide (BNP), and comorbidities (ischemic heart disease [IHD], clinically diagnosed hypertensive heart disease, cardiomyopathy, valvular heart disease, and congenital heart disease) were based on the medical records.[2] Left ventricular ejection fraction (LVEF) was measured by echocardiography.[2]

The primary endpoints included all-cause death, AMI, stroke, HF hospitalization, and other cardiovascular events (except AMI, stroke, and HF hospitalization), such as percutaneous coronary intervention for stable effort angina and intervention for peripheral artery disease.

Definition of Metabolic Disorders

Dyslipidemia was diagnosed by use of lipid-lowering drugs and/or elevated lipid levels defined as low-density lipoprotein ≥140 mg/dl, plasma triglycerides ≥150 mg/dl or high-density lipoprotein <40 mg/dl in men and 50 mg/dl in women. Glucose intolerance/diabetes mellitus was diagnosed by use of antidiabetic drugs and/or fasting glucose ≥110 mg/dl. Hypertension was diagnosed by use of antihypertensive drugs and/or systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80 mmHg.

Definition of Heart Failure

According to the ESC 2007 Guidelines, we further divided the patients with stages A/B/C/D CHF into 2 groups: HFpEF (LVEF ≥50%, n=5,608) and HFrEF (LVEF <50%, n=1,684).[11]

Statistical Analysis

Continuous variables are expressed as means and standard errors of mean (SEM), and categorical variables as counts and percentages. Comparisons between 2 groups were conducted with Welch's t-test for continuous variables and the chi-squared test for categorical variables. Statistical analyses were performed using SPSS (SPSS Inc, Chicago, IL, USA) and the statistical computing software R version 2.15.1 (http://www.r-project.org). P<0.05 was considered to be statistically significant.

Results

Of the 9,178 consecutive patients with stages A/B and C/D of CHF, we were able to obtain baseline physical activity data for 7,292 (Table S2). There were 3,139 male and 1,296 female patients in stage A/B, and 1,957 male and 900 female patients in stage C/D (Table 1). Among them, data of the yearly changes in physical activity level during the 3-year follow-up were available for 4,353 patients (Table S3).

Baseline Physical Activity Level

The median level of physical activity was 8.9 Ex in men and 7.6 Ex in women in stage A/B, and 8.0 Ex in men and 6.6 Ex in women in stage C/D (Table 2). When the patients were divided into high- and low-exercise groups using the median value of physical activity, the high-exercise group was characterized by younger age, earlier stages of CHF, and less likelihood of taking medications such as ACEI/ARB or β-blocker (Tables 1,S2).

Baseline Physical Activity Level and Cardiovascular Events and Mortality

In all patients, as well as in both stages A/B and C/D, the prognosis for all-cause death was significantly better in the high-exercise group (Figures 1A–C), especially male patients in stage C/D (Figure 1D). It was also the case for admission for worsening HF except for female patients with stage A/B (Figures 2A–D).

Similarly, regarding other cardiovascular events (except AMI, stroke and HF hospitalization), the prognosis was significantly better in patients in the high-exercise group in both stage A/B and C/D (Figures 3A–C). In particular, multivariate analysis showed that a high level of physical activity is an independent prognostic factor for both male and female CHF patients in stages A–D (Figure 3D).

Regarding the occurrence of AMI, the prognosis of stage C/D patients was significantly better in the high-exercise group (Figures S1A–C); however, multivariate analyses showed only a significant correlation between baseline physical activity level and AMI in patients in stages A–D (Figure S1D). In stroke, the prognosis of stage A/B patients was significantly better in the high-exercise group (Figures S3A–C). Multivariate analyses showed a significant correlation between baseline physical activity level and stroke in stage A/B patients (Figure S3D).

Yearly Change in Physical Activity Level

During follow-up of 1.4±0.01 years, the physical activity level in male patients decreased from 9.4±0.2 to 7.2±0.2 Ex in stage A/B and from 8.6±0.3 to 6.3±0.2 Ex in stage C/D, and that in female patients also decreased from 8.4±0.3 to 5.6±0.3 Ex in stage A/B and from 7.7±0.5 to 4.9±0.3 Ex in stage C/D (Table 2). In the high-exercise group, a high level of physical activity was maintained in 809 (29%) stage A/B patients

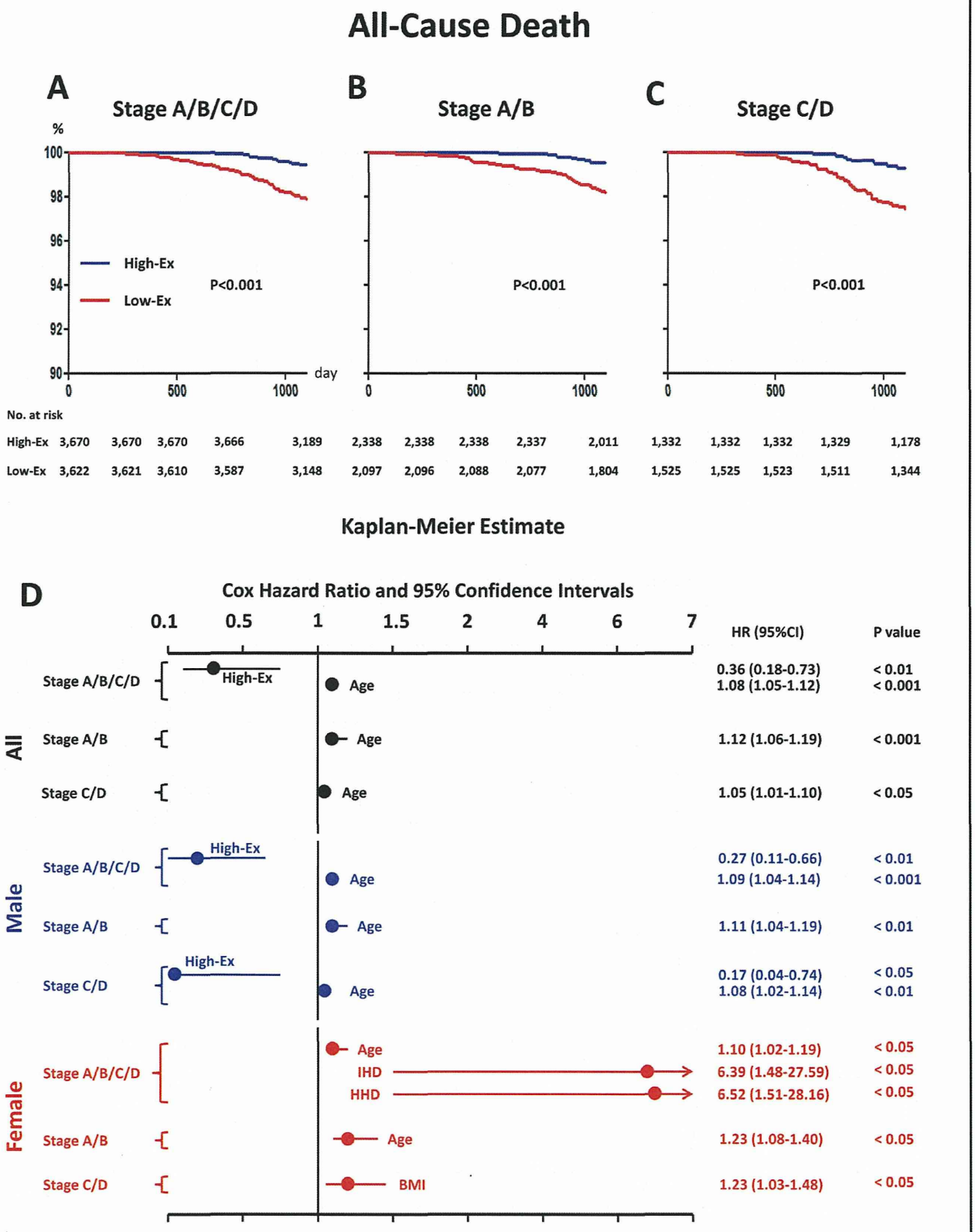
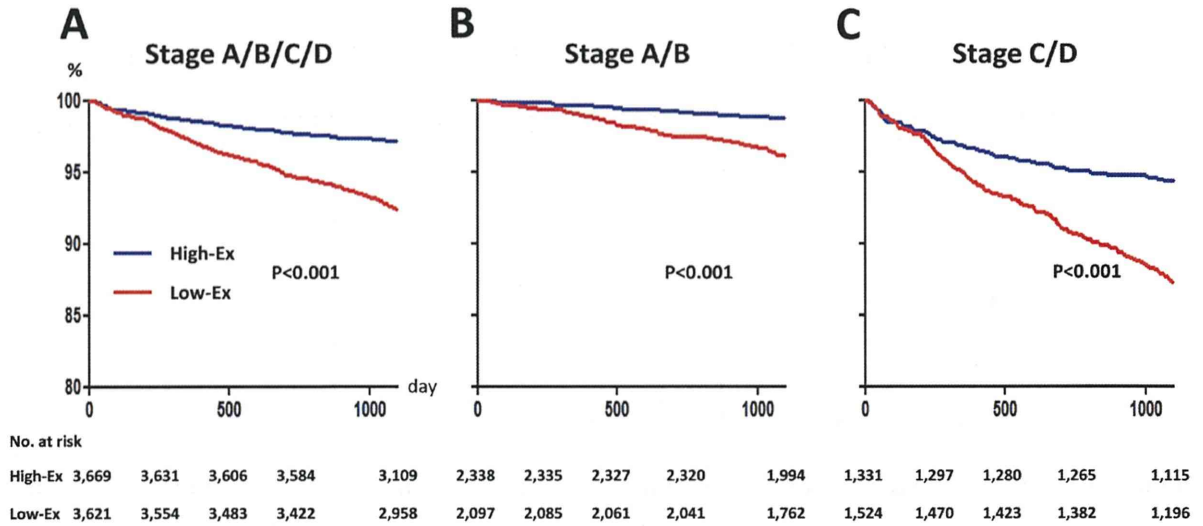


Figure 1. Baseline physical activity level and all-cause death in patients with chronic heart failure. The high-exercise (High-Ex) group showed better prognosis for all-cause death in all patients (**A**), as well as in stage A/B (**B**) and stage C/D (**C**) patients. The prognosis for male patients in stage C/D was significantly associated with a high-exercise level (**D**). BMI, body mass index; HHD, hypertensive heart disease; IHD, ischemic heart disease.



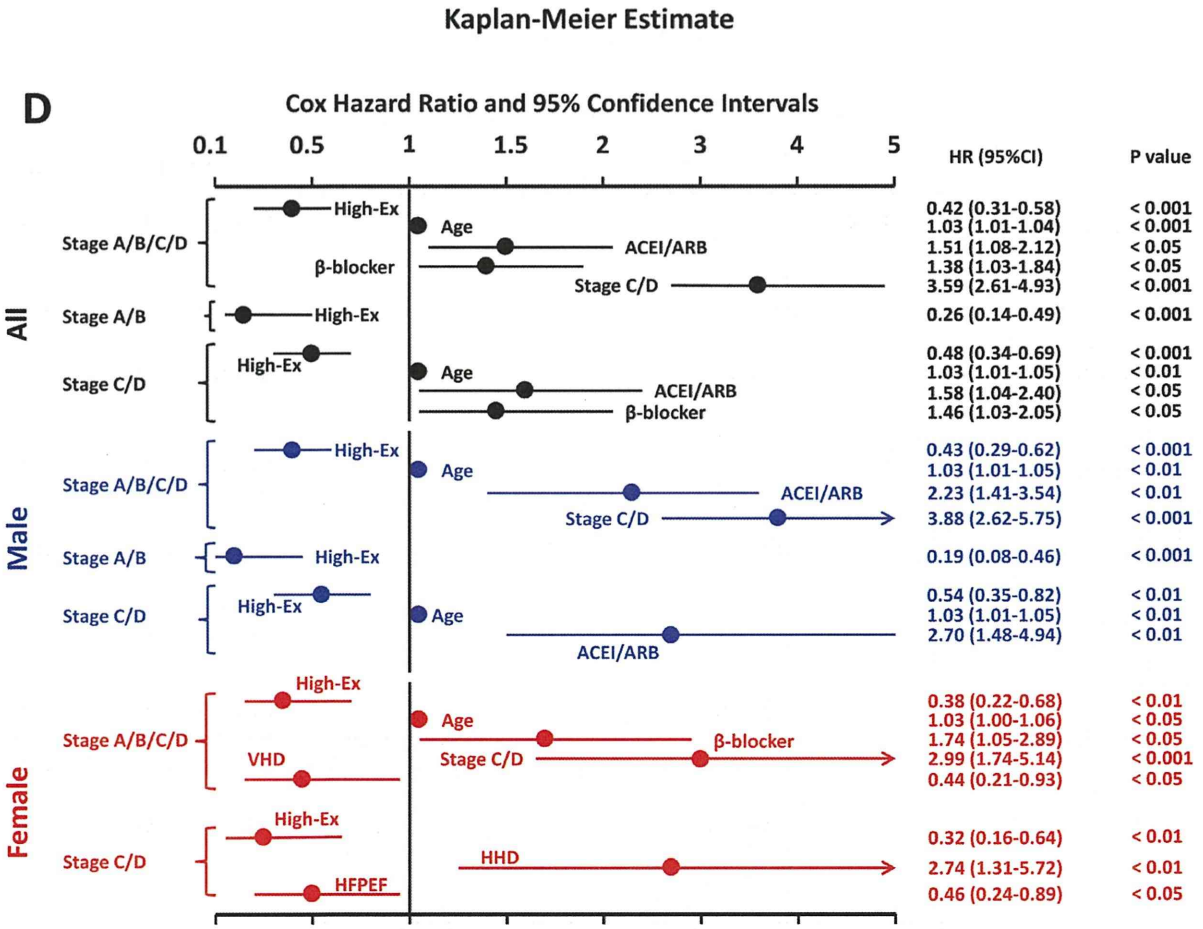


Figure 2. Baseline physical activity level and admission for worsening heart failure (HF). The high-exercise (High-Ex) group showed better prognosis for admission for worsening HF in all patients (**A**), as well as in stage A/B (**B**), and stage C/D (**C**) patients. The better prognosis was significantly associated with high-exercise level except for female patients in stage A/B (**D**). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; HHD, hypertensive heart disease; HFpEF, HF with preserved ejection fraction; VHD, valvular heart disease.

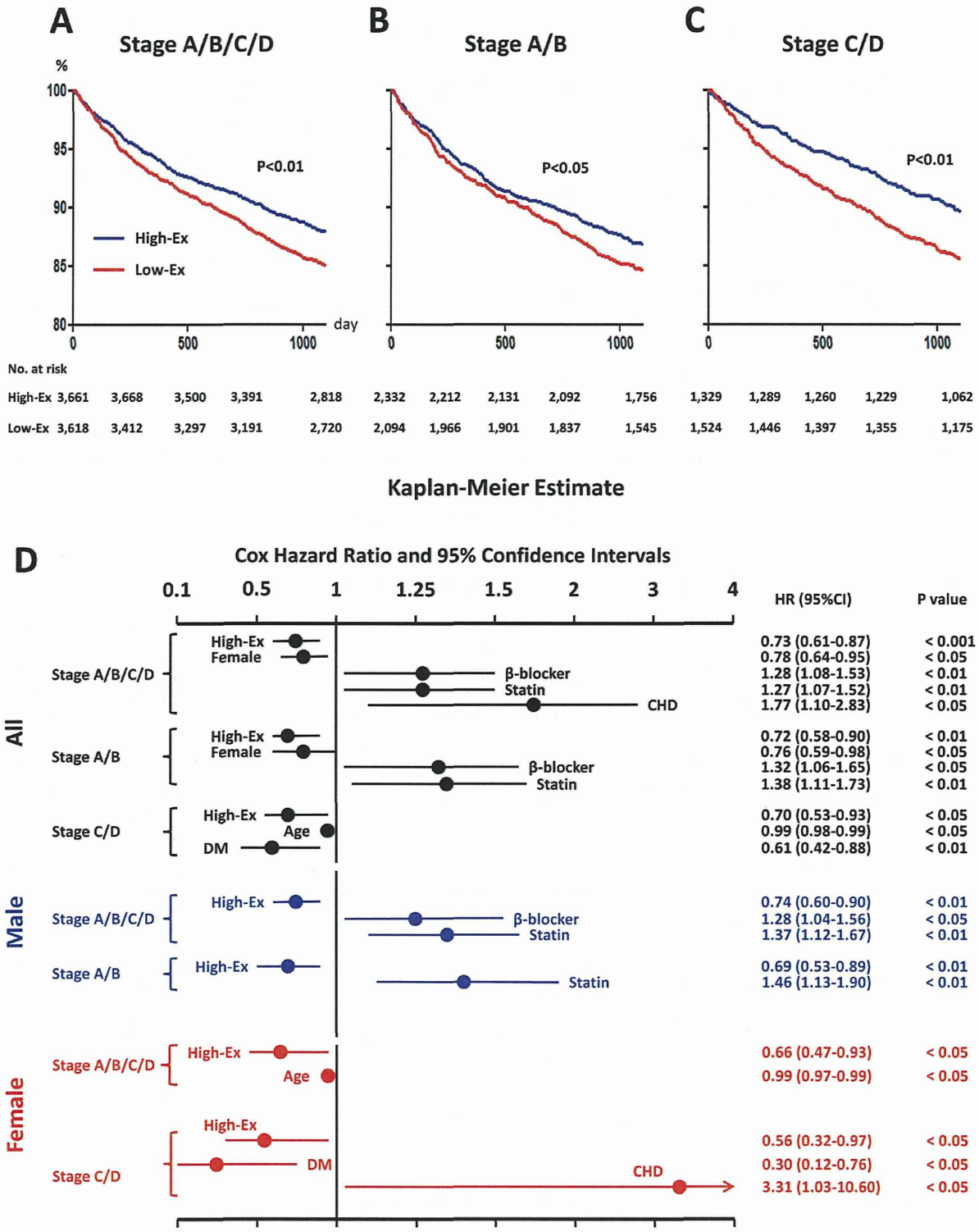


Figure 3. Baseline physical activity level and other cardiovascular events. The high-exercise group (High-Ex) showed better prognosis for other cardiovascular events (except acute myocardial infarction, stroke, and HF hospitalization) in all patients (**A**), as well as in stage A/B (**B**) and stage C/D (**C**) patients. Multivariate analyses also demonstrated a significant correlation between baseline physical activity level and other cardiovascular events in all patients in stages A/B and C/D (**D**). CHD, congenital heart disease; DM, diabetes mellitus.

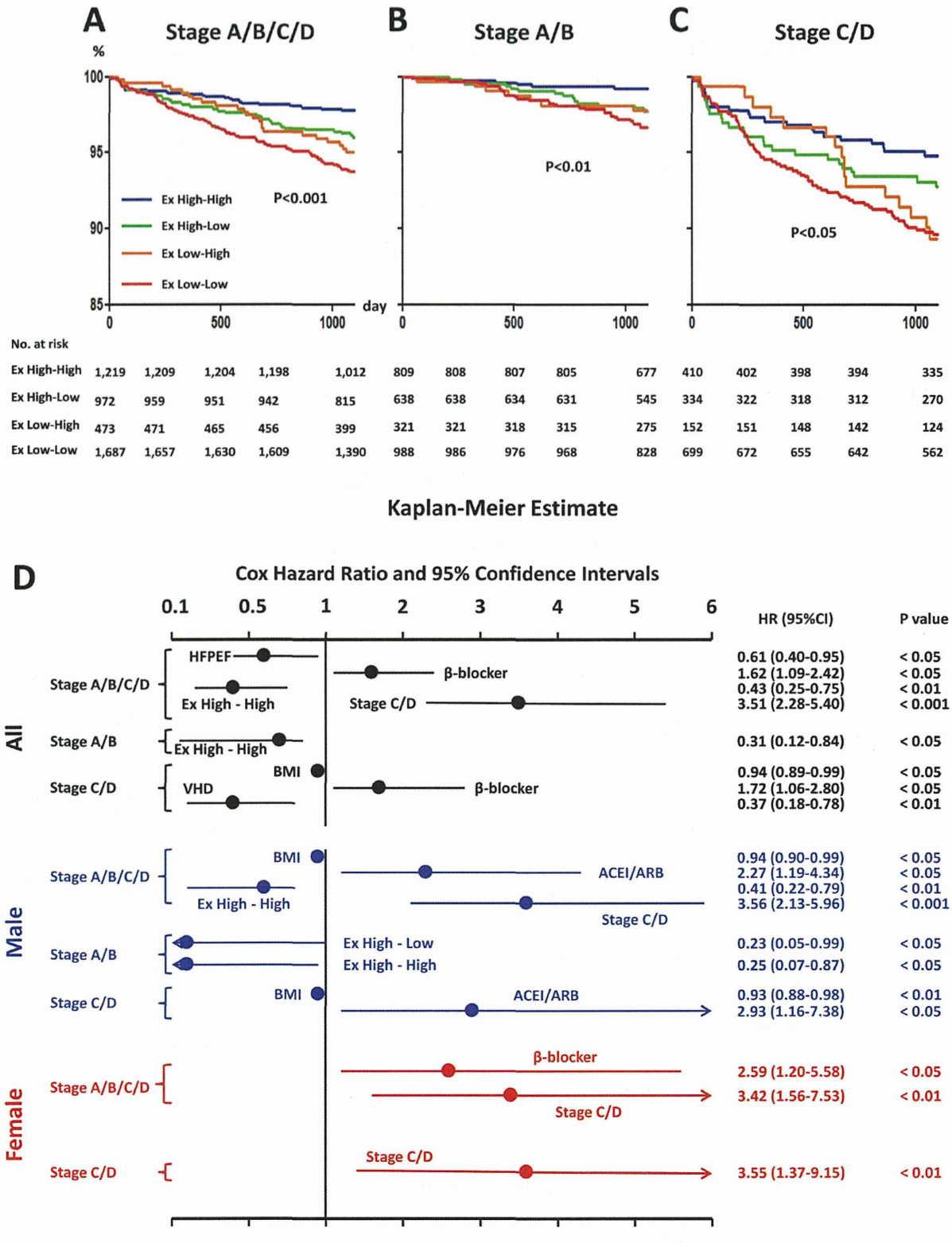


Figure 4. Yearly change in physical activity level and admission for worsening heart failure (HF). Yearly change in physical activity level was significantly associated with admission for worsening HF in all patients (**A**), as well as in stage A/B (**B**) and stage C/D (**C**) patients. Multivariate analyses showed that high-exercise level (High-Ex) was significantly associated with better prognosis for male patients in stage A/B (**D**). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BMI, body mass index; VHD, valvular heart disease.

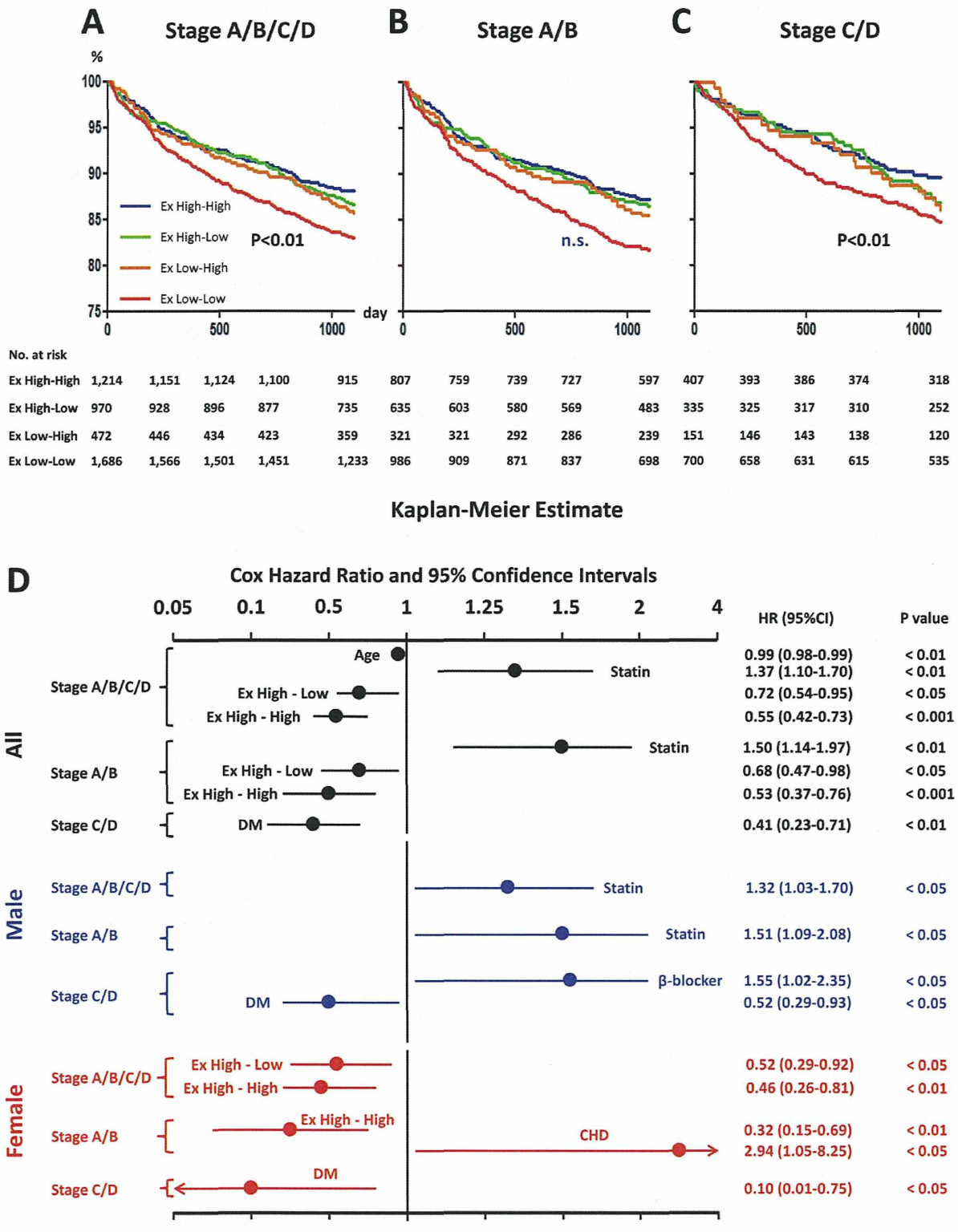


Figure 5. Yearly change in physical activity level and other cardiovascular events. Yearly change in physical activity was significantly associated with other cardiovascular events (except acute myocardial infarction, stroke, and HF hospitalization) in all patients (**A**), as well as in stage A/B (**B**) and stage C/D (**C**) patients. Multivariate analyses showed that high level of physical activity (High-Ex) was significantly associated with better prognosis for female patients in stages A/B and C/D (**D**). CHD, congenital heart disease; DM, diabetes mellitus; HF, heart failure.