ORIGINAL RESEARCH

Prognostic Impact of Statin Intensity in Heart Failure Patients With Ischemic Heart Disease: A Report From the CHART-2 (Chronic Heart Failure Registry and Analysis in the Tohoku District 2) Study

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***Background*—**The beneficial prognostic impact of statins has been established in patients with ischemic heart disease but not in those with heart failure (HF). In addition, it is still unclear whether patients benefit from statins regardless of low-density lipoprotein cholesterol levels.

***Methods and Results*—**We examined 2444 consecutive stage C or D HF patients with ischemic heart disease registered in CHART-2 (Chronic Heart Failure Registry and Analysis in the Tohoku District 2), a multicenter, prospective, observational cohort study in Japan. Patients were divided into 3 groups according to the Japanese standard doses of statins and statin-intensity categories defined by the 2013 American College of Cardiology and American Heart Association guidelines: higher (moderate-high)-intensity (n=868), lower (low)-intensity (n=526), and no statin (n=1050). The median follow-up period was 6.4 years (13929 person-years). Analysis with the inverse probability of treatment weighted using a propensity score for multiple treatment revealed that both the higher-intesity group (hazard ratio [HR]: 0.68; $P<0.001$) and the lower-intensity group (HR: 0.82; $P<0.001$) had significantly lower incidence of the primary end point—a composite of all-cause death and HF admission—compared with the no statin group. The higher-intensity statin group had significantly lower incidence of the primary end point (HR: 0.82; $P<0.001$), all-cause death (HR: 0.83; $P<0.001$), and HF admission (HR: 0.78; $P<0.001$) than the lower-intensity statin group. Moreover, the use of statins, either higher- or lower-intensity, was associated with reduced incidence of the primary end point, regardless of low-density lipoprotein cholesterol levels.

***Conclusions*—**These results suggest that statin use, particularly the use of higher-intensity statins, has a beneficial prognostic impact in HF patients with ischemic heart disease, regardless of low-density lipoprotein cholesterol levels.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00418041. **(*J Am Heart Assoc*. 2018;7: e007524. DOI: 10.1161/JAHA.117.007524.)**

Key Words: heart failure • ischemic heart disease • statin therapy

Statins—HMG-CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductase inhibitors—have been widely used for primary and secondary prevention of atherosclerotic events in patients with and those at risk of ischemic heart disease (IHD), as a number of studies have shown a beneficial impact on clinical outcomes in patients with atherosclerotic cardiovascular disease (ASCVD).[1–7] In contrast, the prognostic impact of statins in patients with heart failure (HF) has been controversial: 2 large landmark trials of HF patients—CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca–Heart Failure)—

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An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/7/6/e007524/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In this multicenter, prospective, observational study, use of statins—particularly of higher-intensity statins—was associated with better prognosis in heart failure patients with ischemic heart disease, regardless of low-density lipoprotein cholesterol levels.
- Of note, the use of higher-intensity statins was particularly associated with favorable outcomes in heart failure patients with left ventricular ejection fraction ≥40% and those without left ventricular dilation, cardiac hypertrophy, higher New York Heart Association classes, or high BNP (brain natriuretic peptide) levels.

What Are the Clinical Implications?

- The present study demonstrates the superiority of higher-intensity statins over lower-intensity statins in heart failure patients with ischemic heart disease, in line with the 2013 American College of Cardiology and American Heart Association guidelines, which recommend the use of higher intensity statins.
- We should consider applying higher-intensity stains, particularly to heart failure patients with preserved or borderline left ventricular ejection fraction, without advanced cardiac remodeling, or without significant signs and/or symptoms of heart failure.

failed to demonstrate prognostic benefits of statins in those patients.[8,9] Nevertheless, several observational studies have shown a salutary impact of statin therapy in HF patients,[10–12] and individual-level reanalyzes of the CORONA and GISSI-HF studies have demonstrated a modestly but significantly decreased risk of myocardial infarction.[13] It remains to be examined whether statins could benefit HF patients and particularly those with IHD, which has been rapidly increasing worldwide as a major cause of morbidity and mortality.[14–16]

The 2013 American College of Cardiology and American Heart Association (ACC/AHA) guidelines recommend intensive statin therapy with high or moderate intensity for high-risk patients for secondary prevention of ASCVD, rather than targeting low-density lipoprotein cholesterol (LDL-C) levels.[17] This recommendation is based on findings that intensive lipid-lowering therapies with strong statins have more favorable outcomes in IHD patients.[18–20] However, it remains controversial whether the beneficial prognostic impact of strong statins is attributable to intensive reduction in LDL-C levels in IHD patients.[21] In contrast to the ACC/AHA guidelines, the European Society of Cardiology and European Atherosclerosis Society guidelines and the Japanese Circulation Society guidelines recommend treatments targeting LDL-C levels for secondary prevention of ASCVD.[22,23] In the present study, we examined the prognostic impact of statin use in ischemic HF patients, with special reference to statin intensity and LDL-C levels, using our database for the CHART-2 (Chronic Heart Failure Registry and Analysis in the Tohoku District 2) study.[24–30]

Methods

Data Source

CHART-2 data that support the findings of this study are available from the corresponding author on reasonable request. The CHART-2 study has been described in detail previously.[24–30] Briefly, CHART-2 (n=10219) is a multicenter, prospective, observational cohort study designed to identify the characteristics, mortality, and prognostic risks of patients with a history of HF and those without HF but at high risk of HF in Japan.[24–30] From October 2006 to March 2010, 10219 consecutive stable patients at outpatient clinics or just before discharge aged >20 years were successfully enrolled in CHART-2 if they had stage B, C, or D HF or significant coronary artery disease in stage A, as defined according to the ACC/AHA guidelines.[31] In the present cohort study, patients who were asymptomatic but had structural heart disease and/or impaired left ventricular (LV) function were categorized as being in stage B. Stage C was defined as current or past symptoms of HF associated with underlying structural heart disease. Stage D was defined as refractory HF for which specialized and advanced treatment strategies were indicated. HF was diagnosed by experienced cardiologists using the criteria of the Framingham Heart Study.[32] There were no exclusion criteria in the CHART-2 study. The study protocol was approved by the local ethics committees of 24 participating hospitals in the Tohoku district of Japan. Eligible patients were consecutively enrolled after written informed consent was obtained. Baseline and follow-up data, including medical history, laboratory and echocardiography data, and clinical outcomes, were collected at the time of enrollment and recorded annually thereafter at least once a year. IHD was defined by a present or past history of myocardial infarction, angina pectoris, and/or significant coronary artery stenosis identified on ECG and/or coronary angiography.

Study Design

The study flowchart is shown in Figure 1. Of 10219 patients in CHART-2, 5333 patients in stage A or B, 2424 without IHD, and 18 without sufficient data were excluded; we finally enrolled 2444 eligible stage C or D HF patients with IHD in the present study. These patients were divided into 3 groups according to statin treatment at enrollment and intensity of statin treatment (higher- or lower-intensity) defined based on

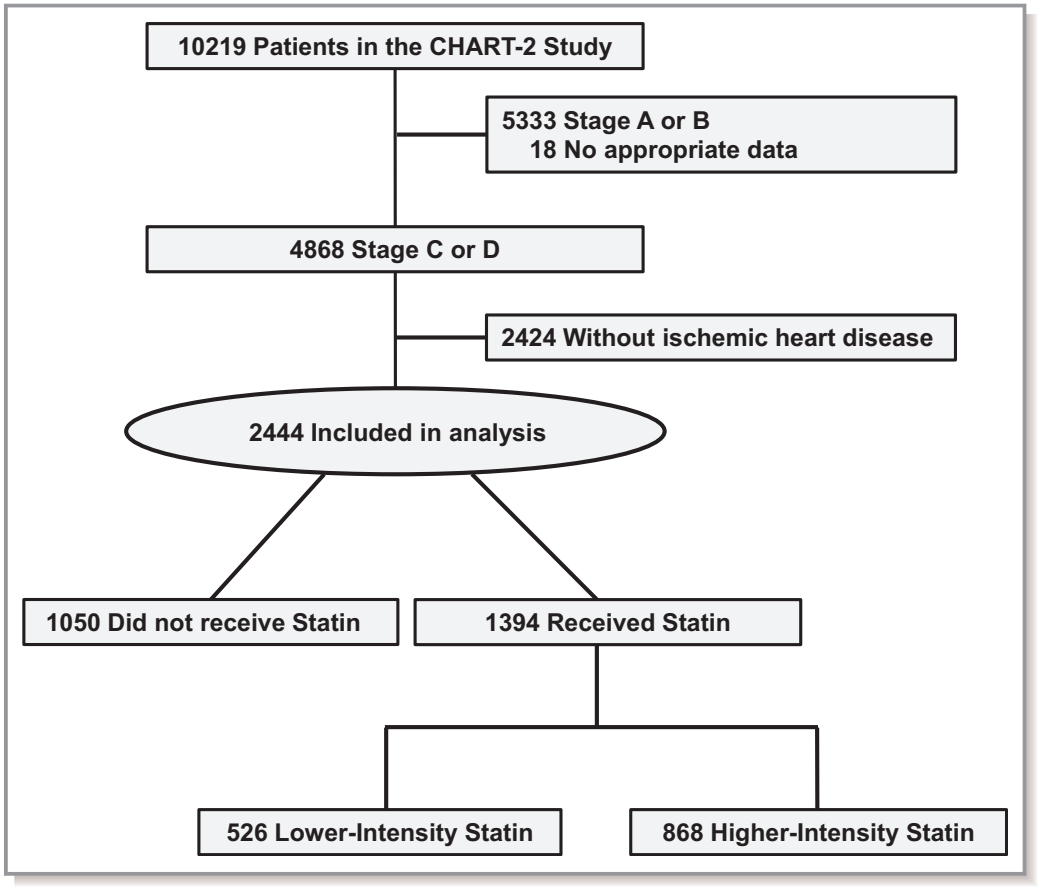


Figure 1. Flowchart of the study population.

the standard doses of statins in Japanese guidelines and the criteria defined in the ACC/AHA guidelines[17]: (1) patients treated with higher (moderate or high)-intensity statin therapy (n=868), (2) those treated with lower (low)-intensity statin therapy (n=526), and (3) those treated without statins (n=1050). Incidence of clinical end points was compared among the 3 groups. The primary end point of this study was a composite of all-cause death and the first HF admission after enrollment. Secondary end points included all-cause death, mode of death, and first HF admission after enrollment.

Table 1. Standard Doses of Statins in Japan

	Minimum Dose (mg/d)	Standard Dose (mg/d)	Maximum Dose (mg/d)
Pravastatin	2.5	10	20
Simvastatin	2.5	5	20
Fluvastatin	10	20	60
Atorvastatin	2.5	10	40
Pitavastatin	0.5	1–2	4
Rosuvastatin	1.25	2.5	20

Statin Intensity

In this study, we used the definitions in the ACC/AHA guidelines[17] for the intensity of statin therapy. Because Japanese patients need lower doses of statins to achieve appropriate LDL-C reduction than patients in Western countries (Table 1), only a few patients received high-intensity statin therapy. Consequently, we combined the moderate- and high-intensity categories in the ACC/AHA guidelines[17] and made a category of *higher-intensity* as the intensity high enough for the Japanese population (Table 2). Patients with rosuvastatin 2.5 mg were included in the higher-intensity group because this dosage reduces LDL-C comparably to atrovastatin 10 mg or pitavastatin 2 mg in Japanese and Western populations.[33,34]

Statistical Analyses

Baseline patient characteristics are described as mean (standard deviation) or median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables. To compare the 3 groups, ANOVAs or Kruskal–Wallis tests were used for continuous variables, as appropriate, and

Table 2. Statin Intensity in This Study

Intensity	Dose, mg					
Lower						
Pravastatin	2.5 (n=1)	5 (n=39)	10 (n=218)	20 (n=20)		
Simvastatin	2.5 (n=1)	5 (n=69)	10 (n=11)			
Fluvastatin	10 (n=2)	20 (n=49)	30 (n=35)	40 (n=3)		
Atorvastatin	2.5 (n=1)	5 (n=53)	7.5 (n=1)			
Pitavastatin	1 (n=22)					
Rosuvastatin	1.25 (n=1)					
Higher						
Fluvastatin	60 (n=1)					
Atorvastatin	10 (n=477)	15 (n=4)	20 (n=46)	30 (n=1)	40 (n=3)	
Pitavastatin	2 (n=151)	3 (n=1)	4 (n=5)			
Rosuvastatin	2.5 (n=138)	5 (n=32)	7.5 (n=1)	10 (n=6)	20 (n=1)	25 (n=1)

the Pearson χ^2 test with Yate's continuity correction was used for categorical variables. To adjust for confounding effects and differences in patient backgrounds among 3 groups, the inverse probability of treatment weighted (IPTW) with a propensity score (PS) for multiple treatments was used. The PS for multiple statin treatment was estimated using generalized boosted modeling (GBM)[35] implemented by the *mnps* command in the twang version 1.5 package of R with 37 baseline variables: age, sex, body mass index (BMI; kg/m^2), systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin, estimated glomerular filtration rate, brain natriuretic peptide (BNP), New York Heart Association (NYHA) class, sodium, potassium, total protein, LV ejection fraction (LVEF), LV dimension at end diastole, left atrial diameter, interventricular septum thickness at diastole, posterior wall thickness at end diastole, smoking, history of HF admission, hypertension, diabetes mellitus, hyperuricemia, atrial fibrillation, stroke, myocardial infarction, cancer, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, β-blocker, calcium channel blocker, thiazide or loop diuretic, aldosterone antagonist, digitalis, antiplatelet, nitrate, percutaneous coronary intervention, and coronary artery bypass grafting. LDL-C, high-density lipoprotein cholesterol, triglyceride, and C-reactive protein (CRP), which were likely affected by statin use itself, were excluded from variables to estimate the PS. Once the PS was estimated, optimization of the balance statistics of treatments was graphically assessed by convergence of the balance measures after iterations of the model. Before and after weighting by PS, the absolute standardized mean differences were also compared (Figure 2).[36] All outcomes in the overall cohort were assessed with Kaplan–Meier analysis, log-rank tests, and Cox proportional hazards models. Cox proportional hazards models were used to estimate the hazard ratios and their 95% confidence intervals of covariates between higher-intensity versus no statin, lower-intensity versus no statin, and higher-versus lower-intensity statin. Analyses of subgroups defined by age, sex, BMI, NYHA class, BNP levels, CRP levels, LVEF, LV mass index, LV dimension at end diastole, and cachexia were performed. Cachexia was defined according to the current standard criteria[37]: weight loss (BMI <20 kg/m^2) and the presence of increased inflammatory markers (CRP >5.0 mg/L), anemia (hemoglobin <12 g/dL), and/or low serum albumin (<3.2 g/dL). To elucidate the prognostic impact of LDL-C level, the additive Cox regression models were used to describe the nonlinear relationship between LDL-C levels and the primary event in this cohort. The statistical computing software R version 3.3.2. was used for all statistical analyses.[38] *P* values and *P* values for interaction <0.05 were considered statistically significant.

Results

Patient Characteristics

In the total cohort, the mean age was 70.4 years, and 77% of patients were male. Baseline patient characteristics of the 3 groups are shown in Table 3. A significant difference was noted for mean age, which was highest in the no statin group, followed by the lower-intensity statin group and then the higher-intensity group; in contrast, BMI was highest in the higher-intensity group, followed by the lower-intensity group and then the no statin group. Prevalence of female sex and smoking history did not differ among groups. Compared with the higher-intensity statin group, the no statin and lower-intensity statin groups had lower prevalence of diabetes mellitus and higher prevalence of stroke and cancer, whereas

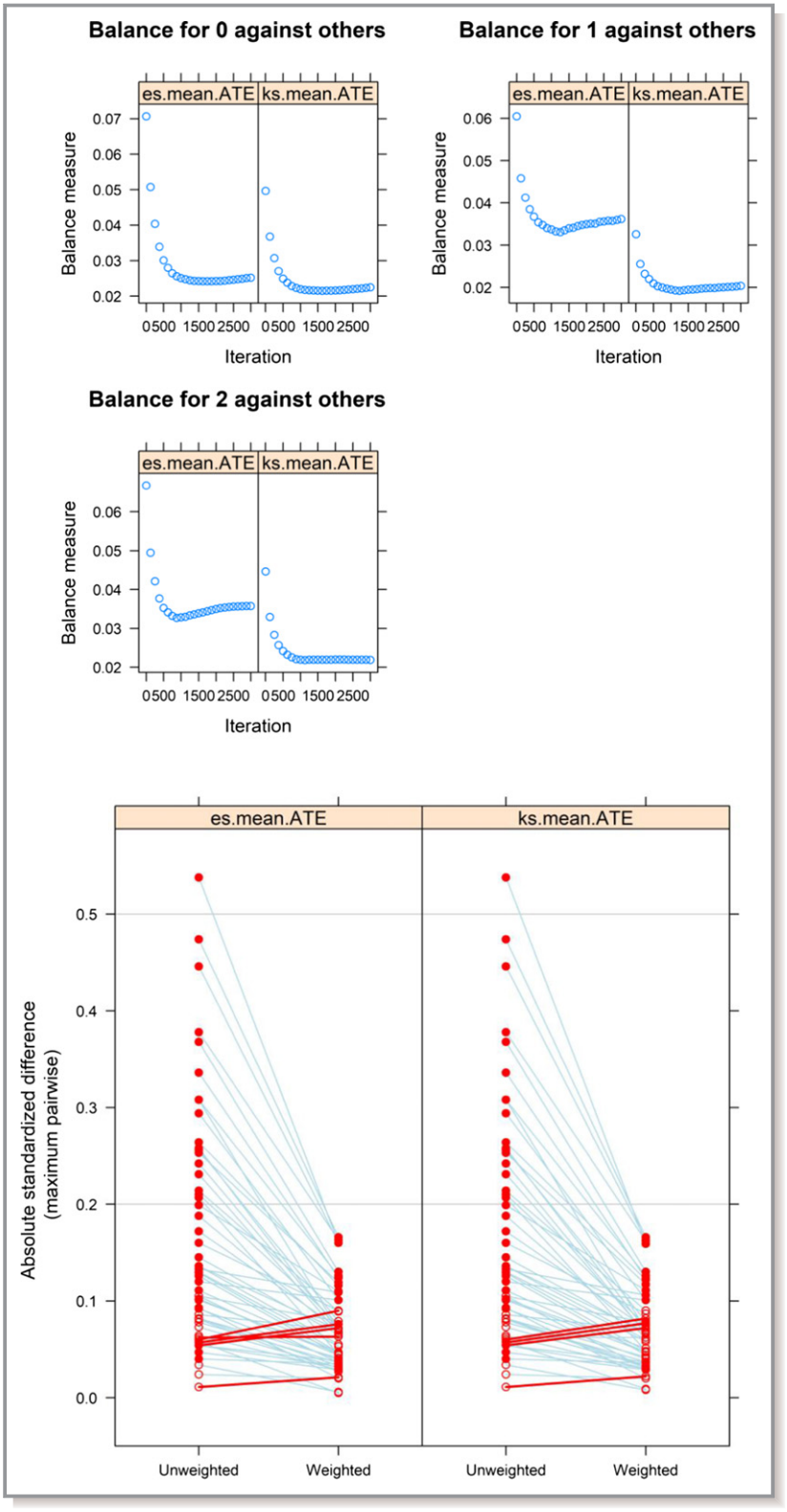


Figure 2. The diagnostic plots for propensity score with multiple treatments using generalized boosted models. ATE, average treatment effect; es, effect size; ks, Kolmogorov-Smirnov.

Table 3. Baseline Patient Characteristics

	No Statin (n=1050)	Lower-Intensity Statin (n=526)	Higher-Intensity Statin (n=868)	*P* Value
Age, y, mean (SD)	72.7 (9.8)	71.2 (9.6)	67.1 (10.9)	<0.001
Female sex, n (%)	230 (21.9)	122 (23.2)	210 (24.2)	0.49
BMI, kg/m^2, mean (SD)	23.4 (3.4)	24.3 (3.3)	24.6 (3.6)	<0.001
Systolic BP, mm Hg, mean (SD)	127.6 (18.8)	129.0 (18.3)	127.0 (18.8)	0.16
Diastolic BP, mm Hg, mean (SD)	71.6 (11.3)	72.8 (10.8)	73.1 (11.5)	0.01
Heart rate, beats/min, mean (SD)	71.7 (14.3)	71.1 (13.3)	70.5 (13.0)	0.13
Smoking, n (%)	498 (50.8)	258 (51.0)	445 (54.4)	0.26
NYHA class, n (%)				
I	254 (24.3)	140 (26.9)	273 (31.6)	
II	657 (62.9)	334 (64.2)	521 (60.2)	<0.001
III or IV	134 (12.8)	46 (8.9)	71 (8.2)	
Medical history, n (%)				
HF admission	493 (47.0)	184 (35.0)	354 (40.8)	<0.001
Hypertension	960 (91.4)	495 (94.1)	808 (93.2)	0.12
Diabetes mellitus	463 (44.1)	245 (46.6)	452 (52.1)	0.002
Dyslipidemia	785 (74.8)	526 (100)	868 (100)	<0.001
Hyperuricemia	573 (54.6)	273 (51.9)	471 (54.3)	0.58
Myocardial infarction	643 (61.2)	379 (72.1)	636 (73.3)	<0.001
Atrial fibrillation	362 (34.5)	95 (18.1)	160 (18.4)	<0.001
Stroke	252 (24.0)	126 (24.0)	162 (18.7)	0.01
Cancer	186 (17.7)	73 (13.9)	93 (10.7)	<0.001
Echocardiography data, mean (SD)				
LVEF, %	55.6 (14.7)	56.8 (15.2)	56.1 (14.9)	0.36
LVDd, mm	52.2 (8.4)	52.4 (8.4)	52.7 (8.7)	0.40
LAD, mm	41.8 (8.6)	40.7 (7.5)	41.1 (7.7)	0.049
IVSTDd, mm	11.0 (2.7)	10.3 (2.5)	10.5 (2.5)	<0.001
PWd, mm	10.8 (2.3)	10.3 (2.2)	10.3 (2.2)	<0.001
Laboratory data				
LDL-C, mg/dL, mean (SD)	110.6 (30.5)	100.1 (24.4)	96.2 (30.2)	<0.001
HDL-C, mg/dL, mean (SD)	49.2 (14.4)	50.7 (14.4)	49.4 (14.4)	0.13
Triglycerides, mg/dL, mean (SD)	121.6 (70.2)	131.4 (67.0)	136.7 (97.0)	<0.001
Hemoglobin, g/dL, mean (SD)	12.9 (2.0)	13.4 (1.8)	13.3 (1.9)	<0.001
eGFR, mL/min/1.73 m^2, mean (SD)	56.6 (21.6)	59.3 (19.6)	60.9 (20.6)	<0.001
Total protein, g/dL, mean (SD)	7.1 (0.7)	7.2 (0.5)	7.2 (0.6)	<0.001
Albumin, g/dL, mean (SD)	4.0 (0.5)	4.1 (0.4)	4.1 (0.5)	<0.001
HbA1c, %, mean (SD)	6.3 (1.0)	6.5 (0.9)	6.5 (1.1)	<0.001
BNP, pg/mL, median (IQR)	115.3 (47.0–267.8)	78.8 (34.3–175.0)	77.1 (29.8–191.0)	<0.001
Sodium, mmol/L, mean (SD)	140.6 (2.9)	140.7 (2.6)	141.2 (2.7)	<0.001
Potassium, mmol/L, mean (SD)	4.4 (0.5)	4.4 (0.4)	4.4 (0.4)	0.36
CRP, mg/L, median (IQR)	2.0 (1.0–5.0)	2.0 (1.0–4.0)	1.0 (1.0–3.0)	<0.001
Medical treatment, n (%)				
ACE-I or ARB	693 (66.0)	384 (73.0)	676 (77.9)	<0.001

Continued

Table 3. Continued

	No Statin (n=1050)	Lower-Intensity Statin (n=526)	Higher-Intensity Statin (n=868)	*P* Value
β-blocker	431 (41.0)	248 (47.1)	490 (56.5)	<0.001
Calcium channel blocker	471 (44.9)	261 (49.6)	372 (42.9)	0.047
Diuretics	476 (45.3)	218 (41.4)	335 (38.6)	0.01
Aldosterone antagonist	178 (17.0)	93 (17.7)	167 (19.2)	0.42
Digitalis	182 (17.3)	54 (10.3)	77 (8.9)	<0.001
Antiplatelet	812 (77.3)	490 (93.2)	812 (93.5)	<0.001
Nitrate	442 (42.1)	290 (55.1)	334 (38.5)	<0.001
PCI	568 (54.1)	338 (64.3)	656 (75.6)	<0.001
CABG	158 (15.1)	106 (20.2)	175 (20.2)	0.005

SI conversions: To convert LDL-C and HDL-C to mmol/L, multiply by 0.0259. To convert triglycerides to mmol/L, multiply by 0.0113. To convert BNP to μg/L, multiply by 1000. To convert CRP to μg/L, multiply by 1000. To convert hemoglobin, total protein, and albumin to g/L, multiply by 10. BMI was calculated as weight in kilograms divided by height in meters squared. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; IQR, interquartile range; IVSTd, interventricular septum thickness at diastole; LAD, left atrial diameter; LDL-C, low-density lipoprotein cholesterol; LVDd, left ventricular dimension diastolic; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PWd, posterior wall thickness at end diastole; SD, standard deviation.

the lower- and higher-intensity groups had higher prevalence of prior myocardial infarction and lower prevalence of atrial fibrillation compared with the no statin group. In contrast, LVEF and LV dimension at end diastole values were comparable among the 3 groups, although LV wall thickness was slightly but significantly greater in the no statin group compared with the lower- and higher-intensity statin groups. A significant difference was noted for mean LDL-C levels, which were highest in the no statin group, followed by the low-intensity statin group and then the higher-intensity statin group; in contrast, median CRP levels were significantly lower in the higher-intensity statin group. The prescription rates for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and for β-blockers were significantly different: highest for the higher-intensity statin group, followed by the lower-intensity statin group and then the no statin group.

Prognostic Impact of Higher- or Lower-Intensity Statin Therapy

During the median follow-up of 6.4 years after enrollment (13929 person-years), 1071 primary outcomes occurred, including 825 deaths and 581 HF admissions. Figure 3 shows the unadjusted event curves for the primary end point, all-cause death, HF admission, cardiovascular death, and noncardiovascular death. The impact of statin therapies on the primary and secondary end points is shown in Figure 4A through 4C. In the univariable analyses, compared with the no statin group, both the higher- and lower-intensity statin groups had significantly lower incidence of the primary end point, all-cause death, noncardiovascular death, and HF admission. Incidence of cardiovascular death was significantly lower in the higher-intensity statin group but not in the lower-intensity statin group compared with the no statin group. IPTW using a PS for multiple treatments showed that, compared with the no statin group, the higher-intensity statin group had significantly lower incidence of primary end point, all-cause death, cardiovascular death, noncardiovascular death, and HF admission both before and after adjustment with LDL-C levels (Figure 4C). The univariable Cox proportional hazards model showed that the lower-intensity statin group had significantly decreased incidence of the primary end point, all-cause death, noncardiovascular death, and HF admission but not of cardiovascular death, which was confirmed by the IPTW method (Figure 4B). Moreover, incidence of the primary end point, all-cause death, cardiovascular death, and HF admission was significantly lower in the higher-intensity statin group compared with the lower-intensity statin group, but incidence of noncardiovascular death was not; this result was confirmed by the IPTW analysis, both with and without adjustment for LDL-C levels (Figure 4A through 4C). In particular, both the higher- and lower-intensity statin groups had lower incidence of cancer death, and infection death, which was also confirmed by the IPTW analysis both with and without adjustment for LDL-C levels (Figure 4A through 4C). Moreover, compared with the no statin and lower-intensity statin groups, the higher-intensity statin group had significantly lower incidence of HF death, which was also confirmed by the IPTW analysis both before and after adjustment with LDL-C levels (Figure 4A through 4C).

Subgroup Analyses

Subgroup analyses with the IPTW method showed that the effect of higher-intensity statin on the incidence of the

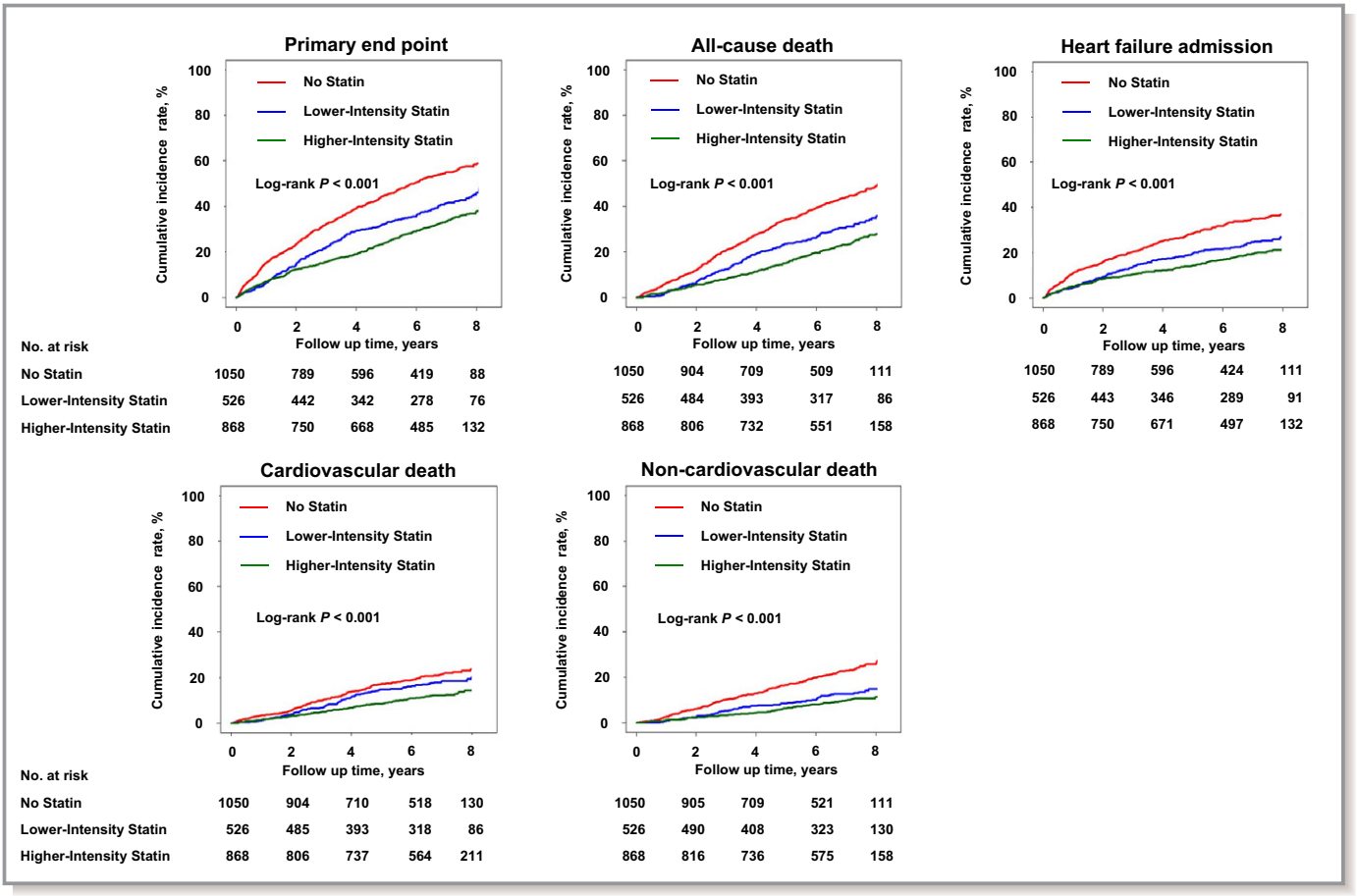


Figure 3. Kaplan–Meier curves for primary and secondary end points.

primary end point did not differ by age; tended to differ by sex and BNP; and significantly differed by BMI, cachexia, CRP levels, NYHA class III or IV, LVEF <40%, LV dimension at end diastole ≥55 mm, and LV mass index ≥95 g/m^2 (female) or ≥115 g/m^2 (male; all *P* values for interaction <0.05; Figure 5A and 5B). In contrast, the beneficial impact of lower-intensity statin use differed only by CRP levels and did not differ by other factors (Figure 5A and 5B).

Prognostic Impact of LDL-C Levels by Treatment Group

Table 4 shows the prognostic impact of LDL-C levels among the 3 groups, evaluated by the univariable and multivariable Cox proportional hazards models. In the univariable analysis, compared with LDL-C <70 mg/dL, LDL-C 70 to 99 mg/dL was associated with a reduced incidence of the primary end point in the higher-intensity statin group but not in the lower-intensity or no statin group, and LDL-C ≥100 mg/dL was associated with reduced incidence of the primary end point only in the no statin group. However, after adjustment in the multivariable Cox proportional hazards models, there were no significant differences in the incidence of the primary end point for LDL-C <70, 70 to 99, and ≥100 mg/dL in all 3 groups. Figure 6 shows the nonlinear relationships between LDL-C levels and log hazard ratio (95% confidence interval) for the primary end point, indicating that LDL-C levels ≈100 mg/dL, but not those <70 mg/dL, had the lowest hazard ratios, regardless of statin use.

Discussion

In this large prospective cohort study, we demonstrated that statin use, particularly use of higher-intensity statins, was associated with a beneficial prognostic impact in HF patients with IHD and that lower LDL-C levels were not necessarily associated with better outcomes with statin treatment. These findings are of clinical significance because it has been controversial whether statins have a beneficial prognostic impact on HF patients and whether higher-intensity statin therapy has a greater benefit than lower-intensity statin therapy in those patients, particularly in relation to LDL-C levels.

Although 2 large-scale randomized trials—CORONA[8] and GISSI-HF[9]—failed to demonstrate a favorable prognostic impact of statins in HF patients, the benefits of statins for

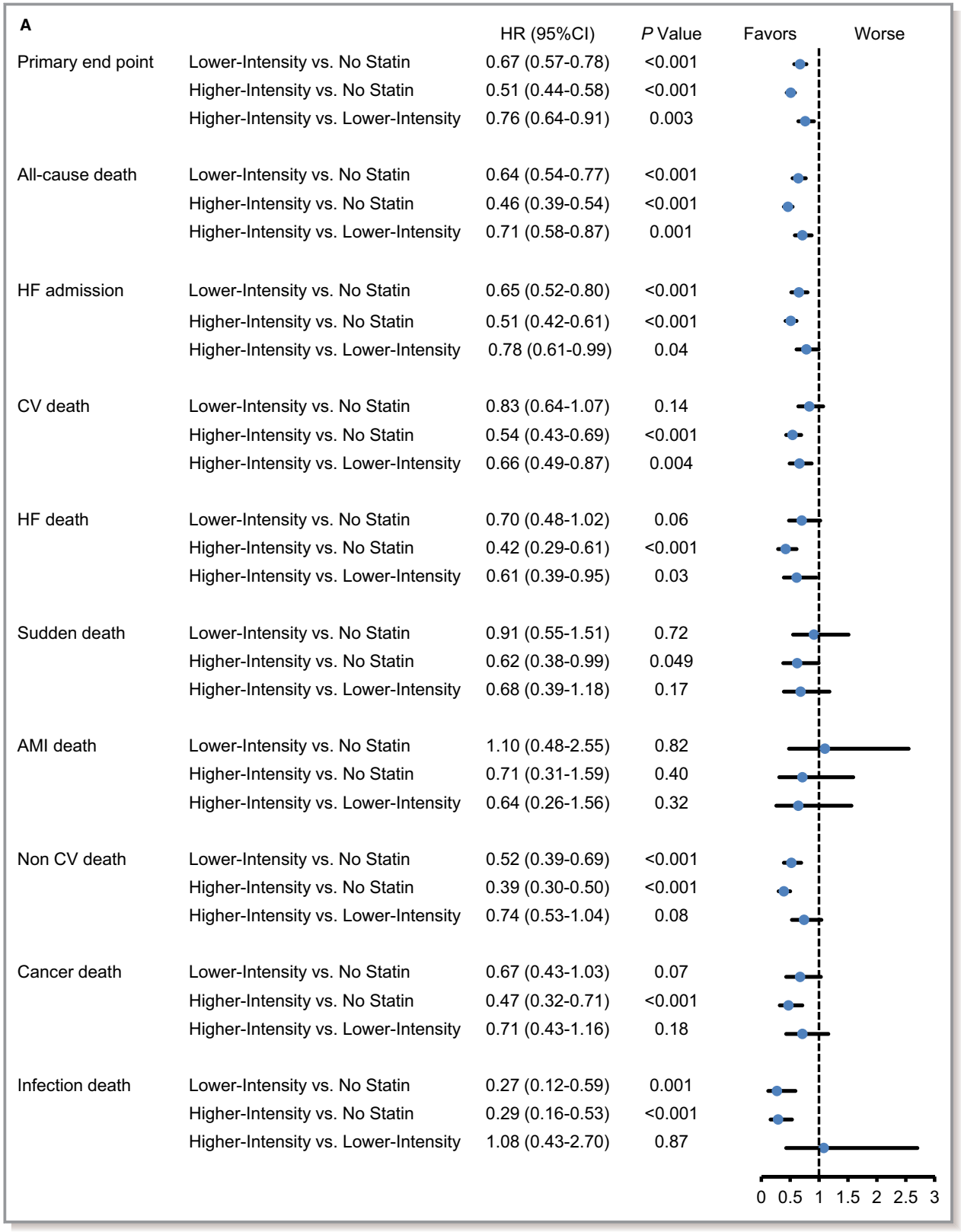


Figure 4. Hazard ratios for primary and secondary end points (A) in univariable Cox proportional hazards models, (B) in Cox proportional hazards models adjusted by IPTW methods using propensity score for multiple treatments, and (C) in Cox proportional hazards models adjusted by IPTW methods using propensity score for multiple treatments and low-density lipoprotein cholesterol levels. AMI indicates acute myocardial infarction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; IPTW, inverse probability of treatment weighted.

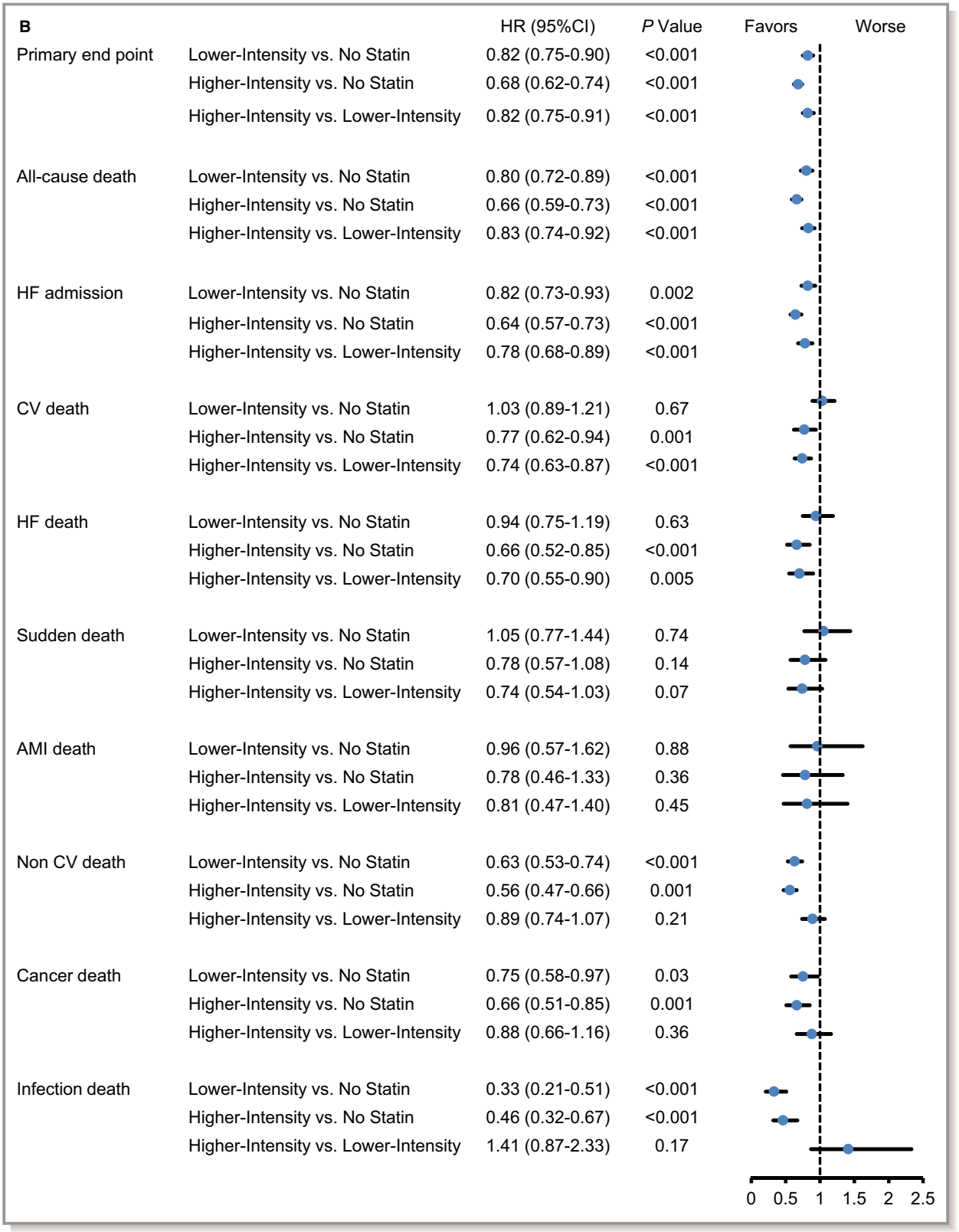
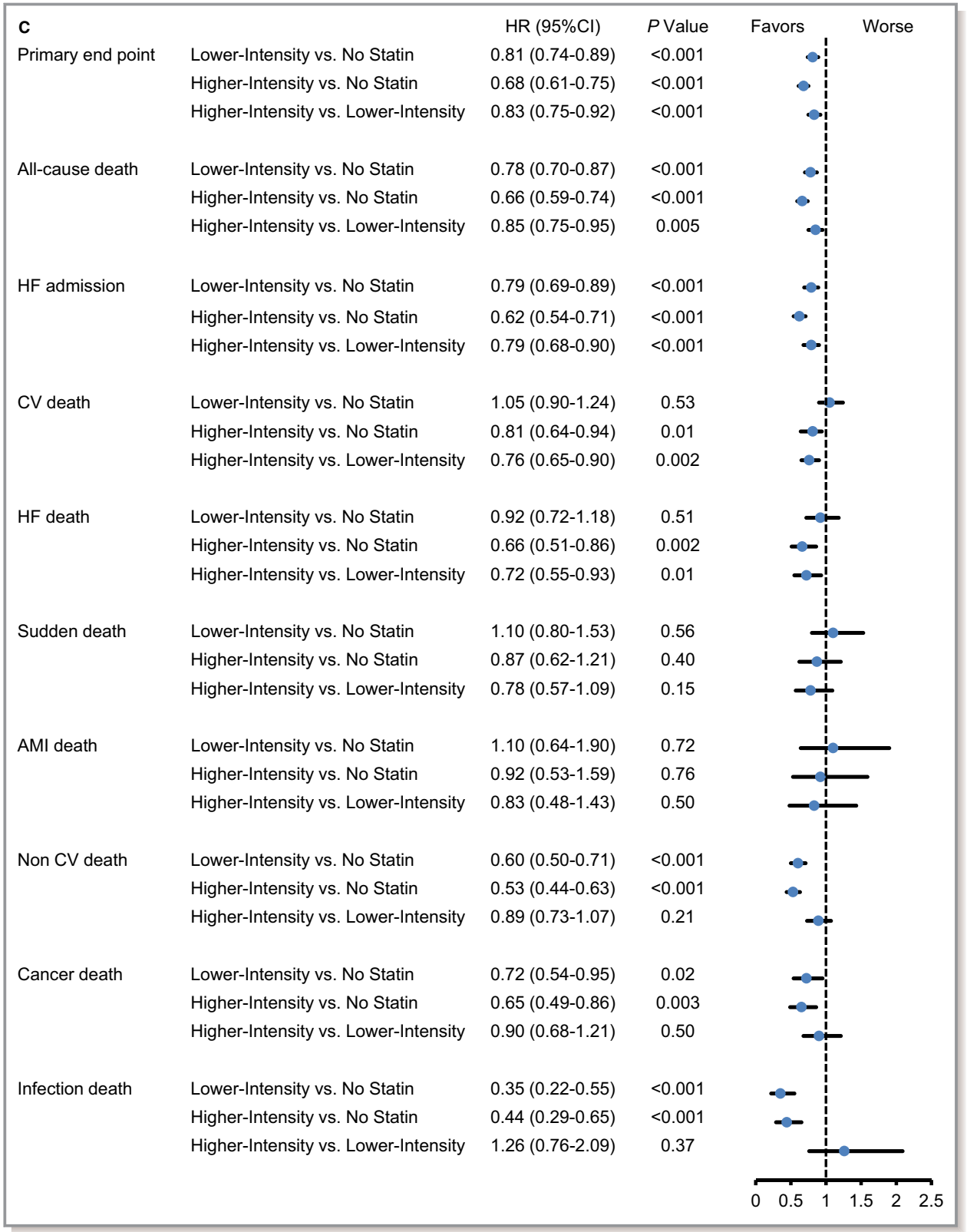


Figure 4. Continued.

HF patients have been reported in observational studies.[11,12] These previous studies, however, used only Cox proportional hazards models to adjust the substantial differences in the clinical backgrounds between patients with and without statins, raising concern that the beneficial impact of statins could be explained by potential confounders. This is why we



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used the IPTW method for the state-of-the-art statistical analysis to adjust the clinical backgrounds for patients with and without statins. This approach enabled the present study to be the first to demonstrate a beneficial prognostic impact of statin use in HF patients with IHD in a large-scale cohort study. In this study, the use of statins—either higher- or

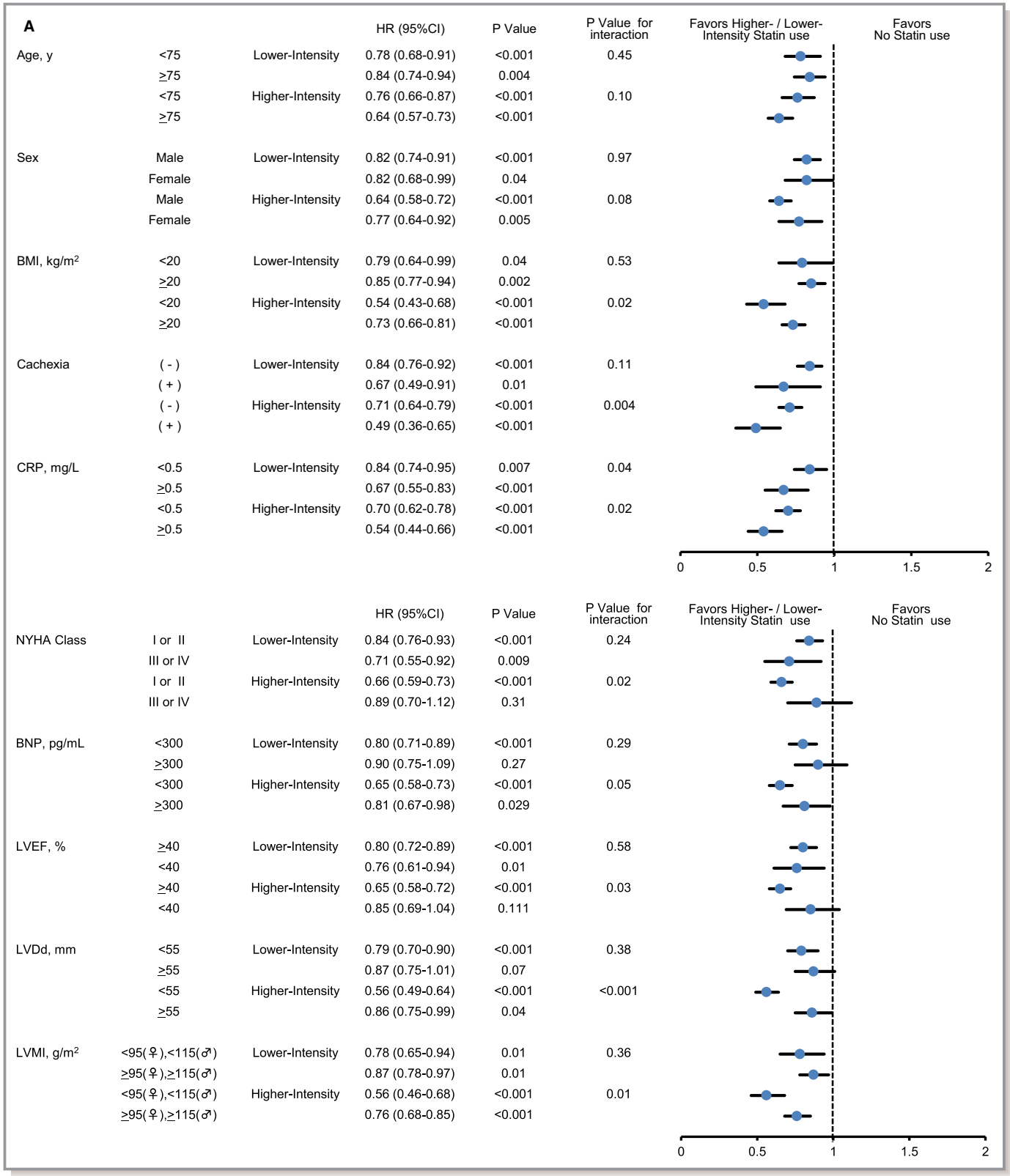

Figure 5. Hazard ratios for primary end point in Cox proportional hazards models adjusted by IPTW methods using propensity score for multiple treatments by subgroups: (A) higher- or lower-intensity vs no statin; (B) higher- vs lower-intensity. BMI indicates body mass index; BNP, brain natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IPTW, inverse probability of treatment weighted; LDL-C, low-density lipoprotein cholesterol; LVDd, left ventricular dimension diastolic; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NYHA, New York Heart Association.

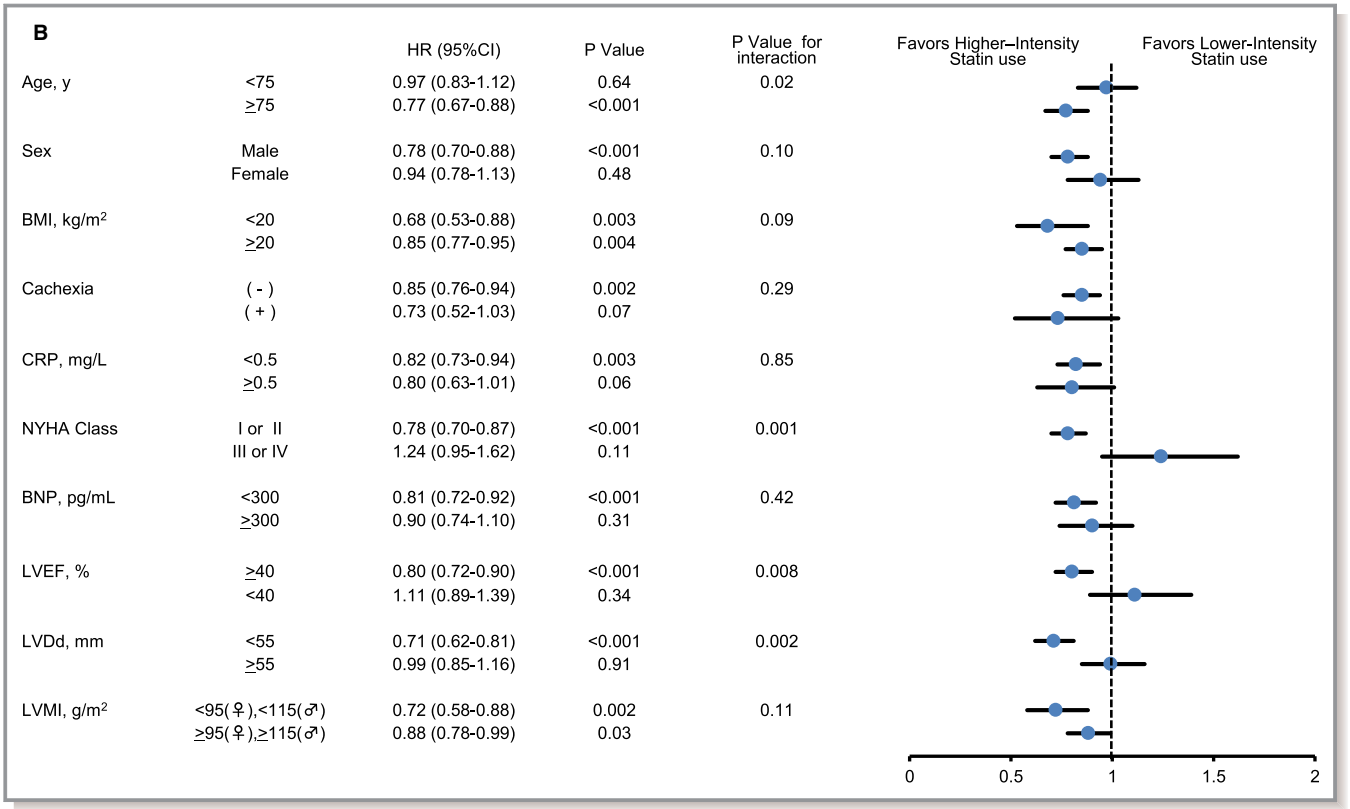

Figure 5. Continued.

lower- intensity—was associated with reduced incidence of the primary end point, all-cause death, noncardiovascular death, cancer death, and death from infection, providing evidence that statins were associated with improved prognosis in HF patients with IHD. Furthermore, the IPTW models in this study clearly showed the differences in prognostic impact between higher- and lower-intensity use of statins; the incidence of the primary end point, all-cause death, cardiovascular death, HF death, and HF admission was significantly lower in the higher-intensity statin group compared with the lower-intensity statin group. These findings are consistent with a recent report with ASCVD patients[39] and are clinically important because this study is the first demonstrating the superiority of higher-intensity statins over lower-intensity

Table 4. Impact of LDL-C Levels on Primary End Point by Treatment Group

	Higher-Intensity Statin		Lower-Intensity Statin		No Statin	
LDL-C, mg/dL	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Unadjusted						
<70 (reference)	1.00		1.00		1.00	
70–99	0.70 (0.50–0.96)	0.03	0.96 (0.60–1.54)	0.87	0.76 (0.56–1.04)	0.08
≥100	0.81 (0.58–1.12)	0.20	0.88 (0.55–1.39)	0.57	0.64 (0.48–0.86)	0.003
Adjusted with baseline characteristics						
<70 (reference)	1.00		1.00		1.00	
70–99	0.86 (0.53–1.40)	0.55	1.98 (0.94–4.16)	0.07	0.95 (0.60–1.49)	0.81
≥100	1.32 (0.80–2.18)	0.27	1.34 (0.64–2.78)	0.44	0.99 (0.64–1.54)	0.96

Adjusted with age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, smoking, New York Heart Association class, history of heart failure admission, hypertension, diabetes mellitus, hyperuricemia, myocardial Infarction, atrial fibrillation, stroke, cancer, left ventricular ejection fraction, left ventricular dimension at end-diastole, left atrial diameter, interventricular septum thickness at diastole, posterior wall thickness at end diastole, high-density lipoprotein cholesterol, triglycerides, hemoglobin, estimated glomerular filtration rate, brain natriuretic peptide, sodium, potassium, C-reactive protein, total protein, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, β-blocker, calcium channel blocker, thiazide or loop diuretic, aldosterone antagonist, digitalis, antiplatelet, nitrate, percutaneous coronary intervention, coronary artery bypass grafting. To convert low-density lipoprotein cholesterol to mmol/L, multiply by 0.0259. CI indicates confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

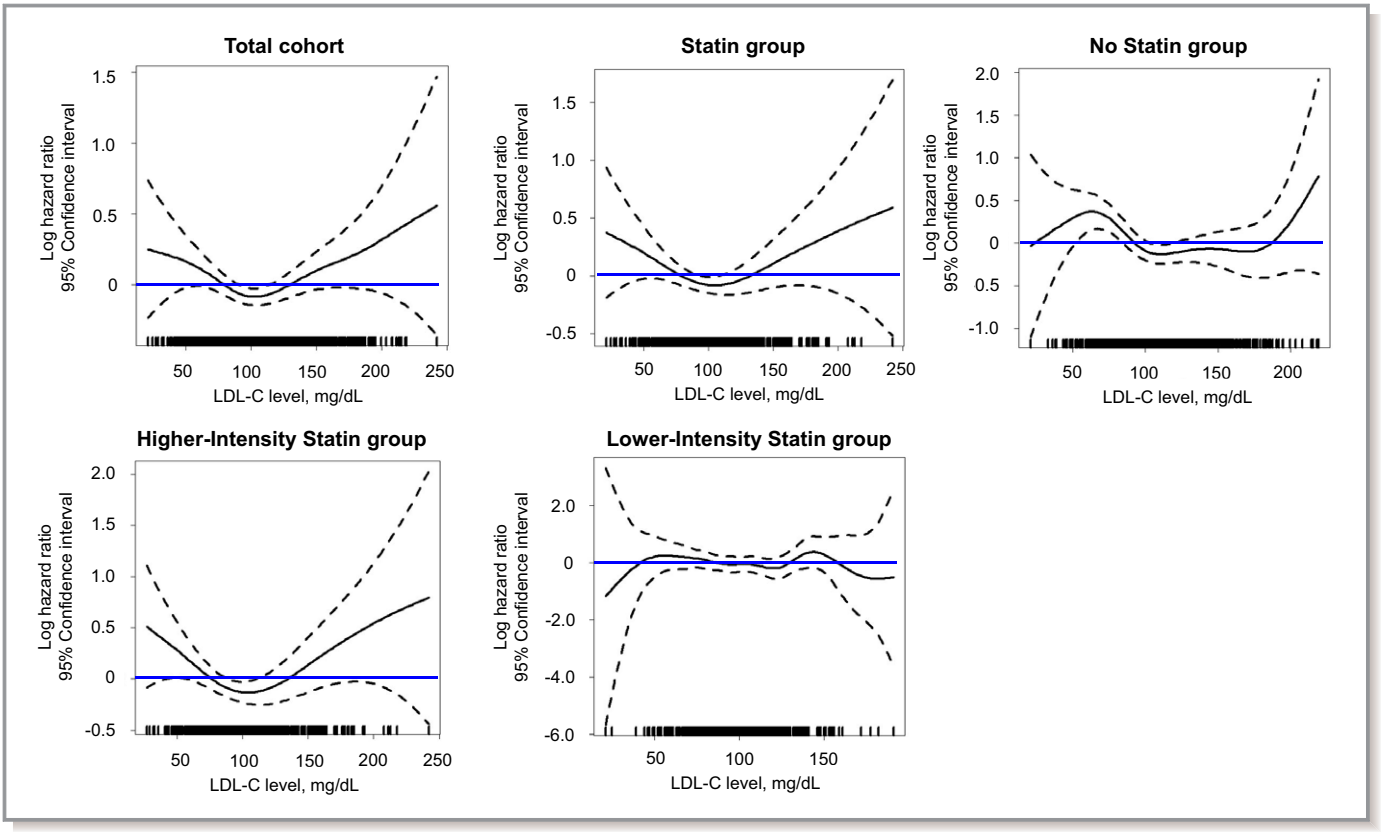

Figure 6. Association between LDL-C level and risk of the primary end point in the additive Cox regression models. LDL-C indicates low-density lipoprotein cholesterol.

statins in an HF population, in line with the 2013 ACC/AHA guidelines, which recommended the use of higher-intensity statins. Another strength of this study is that the CHART-2 study enrolled consecutive HF patients over 20 years without any exclusion criteria, enabling us to confirm a consistent salutary impact of statins regardless of age and any clinical conditions. In particular, given the limited data on older adults with HF,[40] our study provides novel evidence that higher intensity statin may benefit older HF patients with IHD as well as younger patients with these conditions.

This study also demonstrates that the impact of statins differs by patient background. First, this study clearly demonstrates that the benefits of statin use were not evident in HF patients with advanced cardiac remodeling or symptoms. Of note, the statin use was associated with improved outcomes in HF patients with borderline (LVEF 40–49%) or preserved (LVEF ≥50%) ejection fraction but not in those with reduced ejection fraction (LVEF <40%), consistent with findings from previous reports showing the benefits of statins in HF patients with preserved ejection fraction[41,42] but not reduced ejection fraction.[8,9,41] In addition, the subgroup analysis further demonstrated that use of higher-intensity statins was not associated with improved outcomes in patients with LV dilation, cardiac hypertrophy, higher NYHA classes, or high BNP levels. These findings suggest that statin use was not associated with prognostic improvement in HF patients with advanced cardiac remodeling and symptoms. Second, the impact of both higher- and lower-intensity statins on the incidence of the primary end point was more evident in patients with higher CRP levels in the present study, a finding consistent with previous reports.[43–46] It is conceivable that pleiotropic effects of statins, including anti-inflammatory and antioxidant effects,[47,48] may play more important roles in patients with higher CRP levels. However, this finding on CRP levels should be interpreted with caution because it remains unclear whether CRP lowering by statins contributes to improve prognosis in HF patients.

Importantly, the present study demonstrates that the prognostic impact of statins, either higher- or lower-intensity, did not differ by LDL-C levels. Furthermore, the additive Cox regression models indicated that patients with LDL-C ≈100 mg/dL had the most reduced risk of the primary end point in patients with and without statin therapy. This finding on the J-curve relationship between LDL-C levels and outcomes is important because it indicates that lower LDL-C levels under statin treatments do not necessarily relate to better outcomes. This finding is consistent with previous studies reporting that a low LDL-C level was a negative

predictor of survival in HF patients[49,50] and a recent population-based observational cohort study with 31619 IHD patients showing no decrease in cardiac events from lowering LDL-C level to <70 mg/dL compared with LDL-C of 70 to 100 mg/dL.[20] Although it is speculative, the lack of statin benefits in patients with low LDL-C levels could be explained, at least in part, by the poor outcomes of patients with cardiac cachexia accompanied by progressive involuntary weight loss and lower LDL-C.[51,52] Indeed, several studies have reported that lower BMI was significantly associated with poor prognosis in HF patients, whereas obese patients have rather better outcomes, known as the "obesity paradox."[53] In addition, Bangalore et al reported that percentage of LDL-C reduction provided incremental prognostic value over statin dose and attained LDL-C levels in the secondary prevention of ASCVD.[54] Consequently, although higher intensity statins could be more beneficial in HF patients with IHD independent of attained LDL-C levels, application of the "fire and forget" theory in HF patients with IHD should be carefully examined in well-designed randomized controlled trials, particularly those enrolling patients who are likely to benefit from statins (eg, those without significant cardiac remodeling or symptoms).

Study Limitations

Several limitations should be mentioned for this study. First, because CHART-2 is a prospective observational study of HF in Japan, caution is needed when generalizing these findings to other populations in different countries. In particular, recommended doses of statins are different in Western countries and in Japan, and our findings should be interpreted with caution. Second, in this study, we used clinical data at enrollment in the CHART-2 study and did not consider the duration of statin treatment before enrollment, drug compliance or discontinuation of statin treatment, or changes in LDL-C levels during the follow-up period. Third, because CHART-2 is an observational study, we cannot rule out significant confounding factors associated with prescription and other biases. Although we used the IPTW method with PS as a state-of-the-art statistical analysis to minimize biases associated with statin treatment, a prescription bias for statins might have substantially affected the results. Finally, this study cohort experienced the Great East Japan earthquake in 2011; however, we recently confirmed that the earthquake itself did not affect the long-term prognosis of this cohort except during the first several weeks.[55]

Conclusions

This study demonstrates that compared with the use of lower-intensity statins, higher-intensity statin use is associated with beneficial outcomes in HF patients with IHD regardless of LDL-C levels. Further studies are warranted to confirm beneficial effects of statins in HF patients with IHD.

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SUPPLEMENTAL MATERIAL

Appendix

CHART-2 Study Investigators

1. **Executive Committee**

   Hiroaki Shimokawa (Chair), Mitsumasa Fukuchi, Toshikazu Goto, Eiji Nozaki, Tetsuya Hiramoto, Satoru Horiguchi, Kanichi Inoue, Atsushi Kato, Hiroshi Kato, Masatoshi Ohe, Tsuyoshi Shinozaki, and Masafumi Sugi.

2. **Steering Committee**

   Tetsuya Hiramoto, Kanichi Inoue, Atsushi Kato, Masahiko Ogata, Shoichi Sato, and Masafumi Sugi.

3. **Collaborating Hospitals and Active Investigators by Prefecture**

Aomori Prefecture

Shigeto Oyama andJun Demachi (Towada City Hospital).

Iwate Prefecture

Eiji Nozaki, Akihiro Nakamura, Tohru Takahashi, Hideaki Endo, Masateru Kondo, Kazuki Noda, Masanori Kanazawa, and Kenjiro Sato (Iwate Prefectural Central Hospital).

Makoto Nakagawa, Tetsuji Nozaki, and Takuya Yagi (Iwate Prefectural Isawa Hospital).

Akita Prefecture

Toshiaki Takahashi, Satoru Horiguchi, Etsuko Fushimi, Kohei Fukahori, Satoru Takeda, and Sota Nakajima (Hiraka General Hospital).

Yamagata Prefecture

Masatoshi Ohe, Takurou Tashima, Katsuhiko Sakurai, and Tadashi Kobayashi (Kojirakawa Shiseido Hospital).

Toshikazu Goto, Motoyuki Matsui, Yoshiaki Tamada, Tomoyasu Yahagi, Akio Fukui, Katsuaki Takahashi, Shigehiko Kato, and Hyuma Daidouji (Yamagata Prefectural Central Hospital).

Miyagi Prefecture

Akihiko Sugimura and Junko Ohashi (Sendai Red Cross Hospital).

Hiroyuki Kanno and Junji Kaneko (Katta General Hospital).

Shu Suzuki and Osamu Kitamukai (KKR Tohoku Kosai Hospital).

Dai Katayose (Miyagi Rifu Ekisaikai Hospital).

Kaoru Iwabuchi , Sachio Onodera, Seiji Komatsu, Masanobu Chida, Masaharu Takeuchi, Hirokazu Yahagi, and Nozomu Takahashi (Osaki Citizen Hospital).

Keiji Otsuka, Yoshito Koseki, and Masaki Morita (Saito Hospital).

Tsuyoshi Shinozaki, Takeshi Ishizuka, Noriko Onoue, Nobuhiro Yamaguchi, and Hiroshi Fujita (Sendai Medical Center).

Atsushi Kato, Shigeto Namiuchi, Tadashi Sugie, Toru Takii, and Ryoichi Ushigome (Sendai Open Hospital).

Yasuharu Matsumoto (Shizugawa Public Hospital).

Kanichi Inoue, Jiro Koyama, Tomoko Tomioka, Hiroki Shioiri, and Yoshitaka Ito (South Miyagi Medical Center).

Mitsuaki Tanaka, Chikako Takahashi, and Akiko Kawana (Tohoku Rosai Hospital).

Tetsuya Hiramoto (Kurihara Central Hospital).

Yasuhiko Sakata, Kenta Ito, Masaharu Nakayama, Koji Fukuda, Jun Takahashi, Satoshi Miyata, Koichiro Sugimura, Kimio Sato, Yasuharu Matsumoto, Makoto Nakano, Takashi Shiroto, Kotaro Nochioka, Masanobu Miura, Hiroaki Yamamoto, Tatsuo Aoki, Kiyotaka Hao, Shunsuke Tatebe, Saori Yamamoto, Yoku Kikuchi, Hideaki Suzuki, Shigeo Godo, Kensuke Nishimiya, Nobuhiro Yaoita, and Tomohiko Shindou (Tohoku University Hospital).

Fukushima Prefecture

Masafumi Sugi, Yoshito Yamamoto, Sunao Toda, Yusuke Takagi, Kentaro Aizawa, Taro Nihei, and Masato Segawa (Iwaki Kyouritsu Hospital).

Koji Fukuda (Watanabe Hospital).

4. Head Office and Coordinating Center

Yasuhiko Sakata, Jun Takahashi, Satoshi Miyata, Takashi Shiroto, Kotaro Nochioka, Masanobu Miura, Takeshi Yamauchi, Kanako Tsuji, Takeo Onose, Ruri Abe, Takuya Oikawa, Shintaro Kasahara, Masayuki Sato, Chiharu Saga, Yoko Yamada, Junko Kimura, Hiromi Ogino, Izumi Oikawa, Sanae Watanabe, Yasuko Ikeno, and Tomoyuki Suzuki, Hiroko Hamada.