Impact of Worsening Heart Failure on Long-Term Prognosis in Patients With Heart Failure With Reduced Ejection Fraction

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Worsening heart failure (HF), defined as hospitalization for worsening signs and symptoms of HF or the need for urgent intravenous diuretics, is often considered a surrogate of poor prognosis in clinical trials. However, data on the prognostic implications of worsening HF in patients with HF and reduced ejection fraction is limited. Patients who had a first echocardiographic diagnosis of left ventricular systolic dysfunction, defined as left ventricular ejection fraction (LVEF) ≤45%, were identified. Worsening HF was defined as hospitalization for HF or urgent need for intravenous diuretics. All-cause mortality was chosen as the study end point. A total of 1,801 patients (mean age 64 ± 12 years, 74% men) were analyzed. Worsening HF was observed in 275 patients (15%) during a median follow-up of 20 months, while, 435 patients (24%) died during a median follow-up of 60 months (Interquartile range 28 to 60 months). The 5-year survival rate was significantly lower in the worsening HF cohort compared with the non-worsening HF cohort (Log-rank p <0.0001), and it was significantly different between the worsening HF cohort and the nonworsening HF cohort for LVEF ≤25% (log-rank p <0.0001) and LVEF 26% to 34% (log-rank p = 0.038) but not for LVEF 35% to 45% (log-rank p = 0.14). After adjustment for important clinical and echocardiographic predictors, worsening HF was independently associated with a higher risk of all-cause mortality (hazard ratio 1.46, 95% confidence interval 1.09 to 1.96, p = 0.011). In conclusion, worsening HF, defined by HF hospitalization or the urgent need for intravenous diuretics, is independently associated with poor long-term prognosis in patients with HF and reduced ejection fraction. **(Am J Cardiol 2022;184:63−71)**

Introduction

The prevalence of heart failure (HF) has been increasing over the past decades and causes a major economic and healthcare burden.[1] Although new treatments options, including guideline-directed medical therapy (GDMT), coronary revascularization, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) have improved survival, HF with reduced ejection fraction (HFrEF) is still associated with a significantly increased risk for cardiovascular events and high mortality.[2,3] Hospitalization for worsening HF contributes to increased economic burden, reduced quality of life, and increased risk of death.[2−5] Although different definitions of worsening HF have been used in clinical studies, rehospitalization because of worsening signs or symptoms of HF[6] or the need for intravenous diuretics[7] despite optimal GDMT is the most commonly accepted definition and is utilized in recent major HF trials.[8−10] Worsening HF could occur at any stage of the HF disease process, regardless of baseline left ventricular (LV) systolic function. Integration of echocardiographic and clinical variables reflecting the severity of HF may further improve the risk stratification of patients with HF and reduced ejection fraction (HFrEF). A better understanding of the relation between worsening HF, baseline LV systolic function, and long-term outcomes is important and could have major implications for clinical care and postdischarge surveillance. In the present study, we investigated the association between worsening HF and all-cause mortality along with important echocardiographic parameters of LV systolic function using data from a large, real-life registry of patients with HFrEF who were treated with optimal GDMT.

Methods

From an ongoing registry of patients with HF and a first echocardiographic diagnosis of LV systolic dysfunction, defined as an LV ejection fraction (LVEF) ≤45% (Leiden University Medical Center, The Netherlands), patients ≥18 years who presented between November 1993 to June 2020 were identified. Patients diagnosed with active cancer at baseline or who died within the first 30 days of follow-up were excluded. Patients underwent complete clinical and

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echocardiographic evaluation at the time of the first diagnosis. Baseline clinical data were collected from the departmental information system (EPD-Vision, Leiden University Medical Centre, Leiden, The Netherlands) at the time of the first echocardiogram on which a LVEF ≤45% was documented. Baseline clinical data included demographic data, cardiovascular risk factors, co-morbidities, and laboratory results. Most patients received up-titration of GDMT within the first year after diagnosis of HF (LVEF ≤45%). Accordingly, maximum tolerated GDMT was defined at 1 year follow-up. Similarly, data on invasive procedures including percutaneous coronary intervention, coronary artery bypass graft surgery, ICD, and CRT were also considered 1 year after the index echocardiography. All data used in the present study were collected for routine clinical purposes and handled anonymously. Written informed consent was waived by the Institutional Review Board. The study was performed according to the principles outlined in the Declaration of Helsinki.[11]

The index echocardiography was the first examination from which an LVEF ≤45% was diagnosed. All patients underwent transthoracic echocardiography in the left lateral decubitus position using a commercially available echocardiography system (Vivid 7, E9, and E95, GE Vingmed Ultrasound, Horten, Norway). M-mode and 2-dimensional images were obtained, saved in cine loop format, and digitally archived for offline analysis (EchoPac 202 and 203, GE Vingmed Ultrasound, Horten, Norway). The LV end-diastolic volume and LV end-systolic volume were measured and LVEF was calculated from the apical 4- and 2-chamber views using the Simpson's biplane method.[12] Left atrial (LA) volume was measured from the apical 4- and 2-chamber views using the biplane method of disks at LV end-systole[12] and indexed for body surface area (LA volume index). The severity of mitral regurgitation and tricuspid regurgitation was evaluated and graded according to current recommendations.[13–15]

The study end point was all-cause mortality. Worsening HF was defined as the first hospital admission for HF or a visit to the emergency department which required intensification of intravenous diuretic use after the index echocardiography. On the basis of the presence or absence of worsening HF, the study population was divided into 2 groups, "worsening HF" and "non-worsening HF." Data on mortality were obtained from the departmental cardiology information system (EPD-Vision, Leiden University Medical Centre, Leiden, The Netherlands), which is linked to the governmental death registry database. Data on worsening HF were acquired by reviewing medical records archived in the departmental information system. Follow-up time was calculated from the date on which LVEF ≤45% was first documented on index echocardiography. All patients were followed up until the occurrence of the study end point, loss of follow-up, or 5-year follow-up.

Normally distributed (assessed by the Shapiro-Wilk test and distribution histograms), continuous variables are presented as mean ± SD and not normally distributed variables as median and interquartile range. Categorical variables are presented as frequencies and percentages. Continuous variables were compared using independent samples *t* tests when normally distributed, whereas the Mann-Whitney *U* test was used to compare continuous variables that were not normally distributed. Categorical variables were compared using chi-square test. Survival curves were generated using the Kaplan−Meier method and differences between the worsening HF groups were compared with the log-rank test. Separate survival curves were generated according to different LVEF subgroups at baseline: LVEF ≤25%, LVEF 26% to 34%, and LVEF 35% to 45%. Univariable and multivariable Cox proportional hazard regression analyses were used to determine the relation between separate variables and all-cause mortality. The multivariable analysis included the variables which showed significant association with the univariable analysis. For both univariable and multivariable analyses, hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. The time-dependent effect of worsening HF was assessed using an additional landmark analysis defined as 24 months from the index echocardiography. Patients who died or were lost to follow-up before the prespecified landmark time were excluded from the landmark analysis.[16] Finally, an unadjusted time-depending covariate analysis of all-cause mortality for worsening HF versus no worsening HF was modeled to correct the time dependency of worsening HF events. All statistical tests were two-sided, and a $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using SPSS for Windows version 25.0 (IBM Corporation, Armonk, New York) and R version 4.2.0 (survival package v3.1-12 and survminer 0.4.9 package, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1,801 patients were included (mean age 64 ± 12 years, 74% men). Baseline clinical and echocardiographic characteristics of the overall population and differences between patients who experienced and who did not experience worsening HF at follow-up are summarized in Table 1. Worsening HF was observed in 275 patients (15%) during a median follow-up of 20 months. Patients who experienced worsening HF at follow-up had a higher prevalence of family history of coronary artery disease (27% vs 18%, $p = 0.004$), myocardial infarction (49% vs 39%, $p = 0.010$), percutaneous coronary intervention (35% vs 27%, $p = 0.010$), ICD implantation (51% vs 31%, $p < 0.001$) and CRT implantation (29% vs 17%, $p < 0.001$). The use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (72% vs 63%, $p = 0.010$), diuretics (71% vs 55%, $p < 0.001$), antiarrhythmic drugs (22% vs 14%, $p = 0.003$) and digoxin (16% vs 9%, $p < 0.001$) were significantly higher in the patients who experienced worsening HF at follow-up compared with patients who did not. The differences in baseline echocardiographic parameters between patients who experienced worsening HF and those who did not are summarized in Table 2. LV end-diastolic volume (167 ± 84 ml vs 149 ± 72 ml, $p < 0.001$), LV end-systolic volume (122 ± 71 ml vs 106 ± 57 ml, $p < 0.001$), and LA volume index (43 ± 21 ml/m^2 vs 40 ± 20 ml/m^2, $p = 0.041$) were significantly larger, whereas LVEF (29 ± 9% vs 30 ± 9%, $p = 0.010$) was significantly lower in patients who experienced worsening HF compared with those who did not.

Table 1
Baseline characteristics

Variable	Overall population (n = 1801)	Worsening HF		p-Value
		Yes (n = 275)	No (n = 1526)	
Age (years)	64±12	63±12	64±13	0.168
Men	1334 (74%)	214 (78%)	1120 (73%)	0.123
BSA (m^2)	1.98±0.23	1.99±0.23	1.97±0.23	0.433
Hemoglobin (mg/dl)	148±24	152±24	147±24	0.009
eGFR (ml/min/1.73m^2)	68±26	66±26	68±26	0.272
Current smoker	284 (16%)	53 (19%)	231 (15%)	0.178
Ex-smoker	430 (24%)	72 (26%)	358 (24%)	0.629
DM	363 (20%)	61 (22%)	302 (20%)	0.610
Arterial hypertension	711 (40%)	112 (41%)	599 (39%)	0.833
Hyperlipidemia	519 (29%)	79 (29%)	440 (29%)	0.568
Family history of CAD	355 (20%)	74 (27%)	281 (18%)	0.004
CAD	955 (53%)	164 (60%)	791 (52%)	0.081
MI	724 (40%)	134 (49%)	590 (39%)	0.008
COPD	193 (11%)	36 (13%)	157 (10%)	0.270
CKD	461 (26%)	79 (29%)	382 (25%)	0.484
AF	500 (28%)	82 (30%)	418 (27%)	0.731
PCI	501 (28%)	97 (35%)	404 (27%)	0.010
CABG	417 (23%)	68 (25%)	349 (23%)	0.805
ICD implantation	611 (34%)	141 (51%)	470 (31%)	<0.001
CRT implantation	343 (19%)	79 (29%)	264 (17%)	<0.001
Valvular intervention	449 (25%)	62 (23%)	387 (25%)	0.140
Beta-blocker	1110 (62%)	187 (68%)	923 (61%)	0.058
ACEi/ARB	1154 (64%)	198 (72%)	956 (63%)	0.010
MRAs	508 (28%)	92 (34%)	416 (27%)	0.093
Ca2+ channel antagonist	206 (11%)	42 (15%)	164 (13%)	0.057
Diuretic	1028 (57%)	194 (71%)	834 (55%)	<0.001
OACs	840 (47%)	147 (54%)	693 (45%)	0.052
Anti-arrhythmic	274 (15%)	60 (22%)	214 (14%)	0.003
Digoxin	177 (10%)	44 (16%)	133 (9%)	<0.001
Statin	1002 (56%)	170 (62%)	832 (55%)	0.096
LVEDV (ml)	152±74	167±84	149±72	<0.001
LVESV (ml)	108±60	122±71	106±57	<0.001
LVEF (%)	30±8.6	29±9.0	30±8.5	0.010
LAVi (ml/m^2)	41±20	43±21	40±20	0.041
Moderate-to-severe MR	653 (36%)	113 (41%)	540 (35%)	0.064
Moderate-to-severe TR	438 (24%)	78 (28%)	360 (24%)	0.074

Values are mean±SD.

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; DM = diabetes mellitus; ICD = implantable cardioverter-defibrillator; LAVi = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR = mitral regurgitation; OACs = oral anticoagulants; PCI = percutaneous coronary intervention; TR = tricuspid regurgitation.

During a median follow-up of 60 months (interquartile range 28 to 60 months), 435 patients (24%) died. The cumulative event rates for all-cause mortality at 5 years of follow-up were higher in the worsening HF group (37%, 95% CI 31% to 43%) compared with the nonworsening HF group (23%, 95% CI 21% to 25%) (log-rank p <0.0001) (Figure 1). A landmark analysis, which compared the survival rates between worsening HF and non-worsening HF groups from the landmark time of 24 months, demonstrated that the worsening HF group had significantly lower survival rates compared with the nonworsening HF group (log-rank p <0.0001) (Figure 1). The association between worsening HF and all-cause mortality was tested by constructing univariable and multivariable Cox regression models (Table 2). On multivariable analysis, worsening HF was significantly associated with a higher risk of all-cause mortality (HR 1.46, 95% CI 1.09 to 1.96, p = 0.011). In addition, worsening HF was significantly associated with all-cause mortality in the landmark analysis (HR 1.68, 95% CI 1.22 to 2.30, p = 0.001) (Table 3). Unadjusted time-dependent covariate analysis of worsening HF demonstrated that the effect of worsening HF on all-cause mortality was neutral in the first 24 months from diagnosis of HFrEF (HR 0.99, 95% CI 0.70 to 1.41, p = 0.964), but was associated with an increased risk of all-cause mortality after 24 months of follow-up (HR 2.84, 95% CI 2.11 to 3.82, p <0.001).

Patients who experienced worsening HF had higher 5-year cumulative mortality rates when compared with those who did not experience worsening HF according to baseline

Table 2
Univariable and multivariable Cox hazard regression analyses for all-cause mortality

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Age	1.04	1.03-1.04	<0.001	**1.03**	**1.01-1.04**	**<0.001**
Male	1.16	0.93-1.45	0.189			
BSA	0.65	0.41-1.01	0.057			
Hemoglobin*	0.91	0.87-0.95	<0.001	1.00	0.95-1.06	0.889
eGFR*	0.79	0.76-0.83	<0.001	**0.87**	**0.79-0.96**	**0.005**
Current smoker	0.91	0.70-1.19	0.498			
Ex-smoker	0.86	0.69-1.09	0.213			
DM	1.68	1.35-2.09	<0.001	**1.39**	**1.06-1.81**	**0.016**
Arterial hypertension	1.12	0.91-1.38	0.279			
Hyperlipidemia	1.04	0.84-1.28	0.751			
Family history of CAD	0.94	0.73-1.20	0.601			
CAD	1.17	0.94-1.46	0.170			
MI	1.03	0.84-1.27	0.763			
PCI	0.89	0.71-1.12	0.322			
CABG	1.14	0.91-1.43	0.266			
COPD	1.85	1.43-2.40	<0.001	1.31	0.95-1.80	0.100
CKD	2.52	2.00-3.19	<0.001	1.05	0.68-1.62	0.845
AF	1.53	1.25-1.89	<0.001	1.02	0.76-1.38	0.895
ICD implant	0.92	0.74-1.14	0.433			
CRT implant	1.07	0.84-1.36	0.589			
Valvular intervention	1.09	0.87-1.36	0.474			
Beta-blocker	0.73	0.58-0.92	0.008	**0.65**	**0.49-0.87**	**0.004**
ACEi/ARB	0.65	0.51-0.83	<0.001	**0.70**	**0.52-0.95**	**0.020**
MRA	1.26	1.02-1.56	0.034	1.14	0.87-1.50	0.341
Ca^{2+} channel antagonist	1.08	0.81-1.45	0.589			
Diuretics	3.13	2.29-4.28	<0.001	**2.05**	**1.37-3.06**	**<0.001**
OACs	1.40	1.12-1.74	0.003	1.17	0.86-1.58	0.317
Anti-arrhythmic	1.45	1.14-1.86	0.003	1.21	0.89-1.64	0.221
Digoxin	1.65	1.26-2.16	<0.001	1.25	0.89-1.76	0.199
Statin	1.04	0.83-1.30	0.759			
LVEDV*	1.01	1.00-1.03	0.035	1.13	0.98-1.30	0.091
LVESV*	1.02	1.01-1.04	0.006	0.87	0.72-1.04	0.128
LVEF	0.98	0.97-0.99	<0.001	0.98	0.95-1.01	0.245
LAVi	1.01	1.01-1.01	<0.001	1.00	0.99-1.01	0.756
Moderate-to-severe MR	1.59	1.31-1.94	<0.001	1.01	0.77-1.33	0.945
Moderate-to-severe TR	1.67	1.36-2.05	<0.001	0.97	0.73-1.30	0.852
Worsening HF	1.71	1.37-2.13	<0.001	**1.46**	**1.09-1.96**	**0.011**

* 10 unit increase.

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; DM = diabetes mellitus; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LAVi = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR = mitral regurgitation; OACs = oral anticoagulants; PCI = percutaneous coronary intervention; TR = tricuspid regurgitation.

LVEF subgroups: LVEF ≤25% (50% [95% CI 40 to 60%] vs 26% [95% CI 22 to 30%]), LVEF 26% to 34% (35% [95% CI 25 to 45%] vs 26% [95% CI 22 to 30%]) and LVEF 35% to 45% (27% [95% CI 17 to 37%] vs 18% [95% CI 14 to 22%]). The 5-year survival rates of the worsening HF cohort and the non-worsening HF cohort were significantly different for LVEF ≤25% (log-rank p <0.0001) (Figure 2) and LVEF 26% to 34% (log-rank p = 0.038) (Figure 2) but not for LVEF 35% to 45% (log-rank p = 0.14) (Figure 2). Corresponding landmark analyses demonstrated that the survival rates, which were calculated from the landmark time of 24 months, were significantly lower in the worsening HF group for LVEF ≤25% (log-rank p <0.0001) (Figure 2) and LVEF 26% to 34% (log-rank p = 0.0092) (Figure 2), but not for LVEF 35% to 45% (log-rank p = 0.11) (Figure 2).

Unadjusted time-dependent covariate analysis of worsening HF showed that the effect of worsening HF was attenuated in the first 24 months of follow-up for baseline LVEF subgroups: (HR 1.23, 95% CI 0.73 to 2.06, p = 0.446), (HR 0.83, 95% CI 0.46 to 1.48, p = 0.520) and (HR 0.80, 95% CI 0.34 to 1.86, p = 0.602) for LVEF ≤25%, LVEF 26% to 34% and LVEF 35% to 45%, respectively. However, the risk of mortality was significantly higher after 24 months of follow-up for the baseline LVEF subgroups: (HR 3.58, 95% CI 2.18 to 5.88, p <0.001), (HR 2.41, 95% CI 1.50 to 3.85,

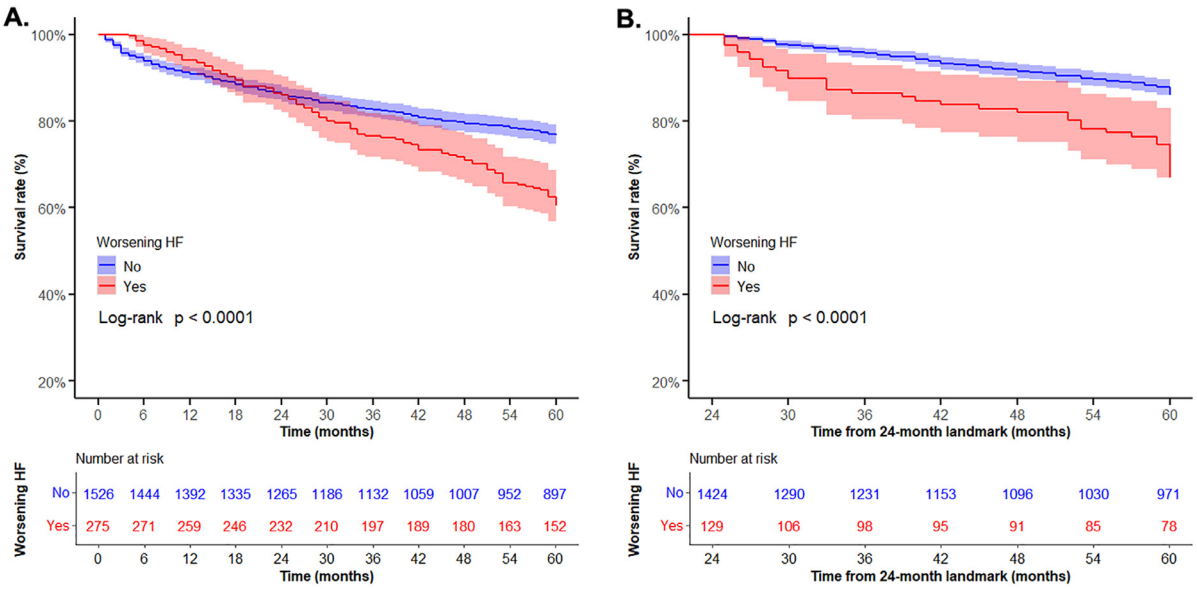

Figure 1. Kaplan−Meier curves for all-cause mortality (*A*) and the landmark analysis for all-cause mortality (*B*).

p <0.001) and (HR 2.38, 95% CI 1.25 to 4.52, p = 0.008) for LVEF ≤25%, LVEF 26% to 34% and LVEF 35% to 45%, respectively.

Discussion

The main findings of the present study, with data obtained from a large, ongoing registry including patients with a first diagnosis HFrEF, can be summarized as follows: (1) the incidence of worsening HF (defined as HF hospitalization or the urgent need for intensification of intravenous diuretics) was 15%; and (2) worsening HF was independently associated with poor outcomes, regardless of baseline LV systolic function.

Different definitions of worsening HF have been used in clinical studies according to different criteria.[6] Nonetheless, rehospitalization because of worsening signs and symptoms of HF or emergency intravenous diuretics despite optimal GDMT is the most commonly accepted definition of worsening HF[6,7] and was utilized in recent major HF trials.[8−10] According to this definition, the prevalence of worsening HF was 15.6%, 13.4%, and 29.6% in the control arms of the Prospective Comparison of ARNI (Angiotensin Receptor−Neprilysin Inhibitor) with ACEI (Angiotensin-Converting−Enzyme Inhibitor) to PARADIGM-HF (Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,[9] DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, [10] and VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial,[8] respectively. In the National Cardiovascular Data Registry PINNACLE, the prevalence of worsening HF was 17% during an average of 1.5 years after the initial diagnosis of HFrEF.[2] In another study, which used data from Danish administrative registers, Madelaire et al[17] identified 7,677 worsening HF events (10.2%) of 74,990 patients with incident HF. In the present study, which was based on a large clinical registry of patients with HFrEF, the prevalence of worsening HF occurred in 15% of the study population after the initial diagnosis of HFrEF despite baseline GDMT.

Worsening HF can be caused by various precipitating factors and may occur at any stage after an initial stable period of HF.[6] Importantly, baseline LV systolic function (LVEF) may remain unchanged during an episode of worsening HF. In their study of worsening HF in ambulatory patients, Mallick et al[18] reported significantly higher values of baseline LVEF in patients who subsequently experienced worsening HF, compared with those who did not (31% vs 25%, p = 0.03). However, the size of the study population was relatively small (n = 151), limiting firm conclusions regarding the prognostic value of baseline LVEF for future worsening HF events. Although in the present study, baseline LVEF was significantly different between the worsening HF and non-worsening HF groups, this difference in baseline LVEF was not clinically relevant (only 1% difference) and was not associated with outcomes in the multivariable analysis.

The prognostic impact of worsening HF has been previously evaluated in large, nationwide registries.[2,3,17,19] Butler et al[2] demonstrated that patients who developed worsening HF within 18 months after the initial diagnosis of HF, had a higher risk of recurrent HF hospitalization or mortality at 2 years of follow-up. In a study of 74,990 patients with a first diagnosis of HF, Madelaire et al[17] showed that 1-year mortality was 18% in patients who needed up-titration of diuretics and 22.6% in patients with subsequent HF hospitalization, with the prevalence in both groups being significantly higher compared with 10.4% in matched controls. Among these large registries, only Solomon et al[3] took baseline LVEF into consideration when studying the influence of nonfatal HF hospitalization on subsequent mortality and reported that, after adjustment for baseline predictors of mortality (including LVEF), HF hospitalization remained significantly associated with all-cause

Table 3
Univariable and multivariable Cox hazard regression landmark analyses for all-cause mortality

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Age	1.03	1.02-1.03	<0.001	**1.02**	**1.01-1.04**	**<0.001**
Male	1.27	1.03-1.55	0.022	**1.18**	**0.88-1.59**	**0.264**
BSA	0.76	0.50-1.15	0.188			
Hemoglobin*	0.96	0.92-1.00	0.058			
Egfr*	0.85	0.82-0.89	<0.001	**0.92**	**0.85-1.01**	**0.071**
Current smoker	1.00	0.80-1.26	0.979			
Ex-smoker	0.89	0.73-1.10	0.287			
DM	1.45	1.18-1.77	<0.001	**1.28**	**1.00-1.65**	**0.054**
Arterial hypertension	1.09	0.91-1.31	0.348			
Hyperlipidemia	1.11	0.92-1.34	0.274			
Family history of CAD	1.06	0.86-1.30	0.587			
CAD	1.11	0.92-1.35	0.275			
MI	1.18	0.99-1.42	0.070			
PCI	0.96	0.79-1.16	0.642			
CABG	1.21	0.99-1.47	0.061			
COPD	1.47	1.14-1.89	0.003	1.17	0.85-1.61	0.337
CKD	2.06	1.64-2.58	<0.001	1.10	0.74-1.62	0.642
AF	1.32	1.10-1.59	0.003	0.87	0.66-1.14	0.313
ICD implant	1.58	1.32-1.90	<0.001	1.51	1.11-2.04	0.008
CRT implant	1.54	1.27-1.87	<0.001	1.11	0.83-1.48	0.468
Valvular intervention	1.00	0.82-1.22	0.998			
Beta-blocker	0.96	0.77-1.20	0.736			
ACEi/ARB	1.09	0.84-1.40	0.523			
MRA	1.21	1.00-1.47	0.049	0.98	0.77-1.25	0.871
Ca^{2+} channel antagonist	1.29	1.01-1.65	0.044	1.31	0.98-1.75	0.064
Diuretics	1.98	1.57-2.49	<0.001	**1.43**	**1.04-1.96**	**0.028**
OACs	1.60	1.32-1.96	<0.001	1.26	0.97-1.64	0.082
Anti-arrhythmic	1.60	1.29-1.99	<0.001	1.37	1.05-1.80	0.023
Digoxin	1.63	1.28-2.09	<0.001	1.45	1.06-1.98	0.021
Statin	1.24	1.00-1.53	0.049	1.14	0.86-1.52	0.356
LVEDV*	1.03	1.01-1.04	<0.001	1.05	0.92-1.19	0.488
LVESV*	1.03	1.02-1.05	<0.001	0.95	0.81-1.13	0.578
LVEF	0.98	0.97-0.99	0.001	1.00	0.97-1.03	0.930
LAVi	1.01	1.00-1.01	0.002	1.00	1.00-1.01	0.380
Moderate-to-severe MR	1.28	1.07-1.54	0.008	1.02	0.80-1.30	0.869
Moderate-to-severe TR	1.07	0.87-1.32	0.536			
Worsening HF	1.82	1.41-2.33	<0.001	**1.68**	**1.22-2.30**	**0.001**

* 10 unit increase.

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; DM = diabetes mellitus; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LAVi = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR = mitral regurgitation; OACs = oral anticoagulants; PCI = percutaneous coronary intervention; TR = tricuspid regurgitation.

mortality. The present study shows that, after adjusting for multiple, prognostically relevant risk factors, LVEF was not significantly associated with all-cause mortality. Moreover, in the present study, patients with worsening HF had significantly lower survival rates in the three subgroups of LVEF. These results indicate that worsening HF is an important determinant of long-term outcomes in patients with HFrEF, regardless of baseline LV systolic function.

The in-hospital treatment of patients who are hospitalized for worsening HF despite baseline GDMT is mainly symptomatic,[6] targeting congestion by intravenous diuretics, and correcting precipitating factors such as infections, dietary mistakes, sudden arrhythmias, and in rare instances, hypoperfusion.[20] Apart from a few studies,[21,22] most of the randomized controlled trials[8–10] involving HF usually include stable HF patients in an outpatient setting, without including HF patients who have recently experienced worsening HF. As shown in the present study, however, worsening HF is associated with higher long-term mortality and therefore, it is reasonable to consider the early initiation of intensive HF treatment for this high-risk patient population. In the VICTORIA study, including 5,050 patients with worsening HF, the incidence of death from cardiovascular causes or hospitalization for HF was lower among those who received vericiguat than among those who received placebo.[8] Recently, Bhatt et al[23] studied the early initiation of sodium-glucose cotransporter 2 inhibitors in hospitalized patients with worsening HF in the

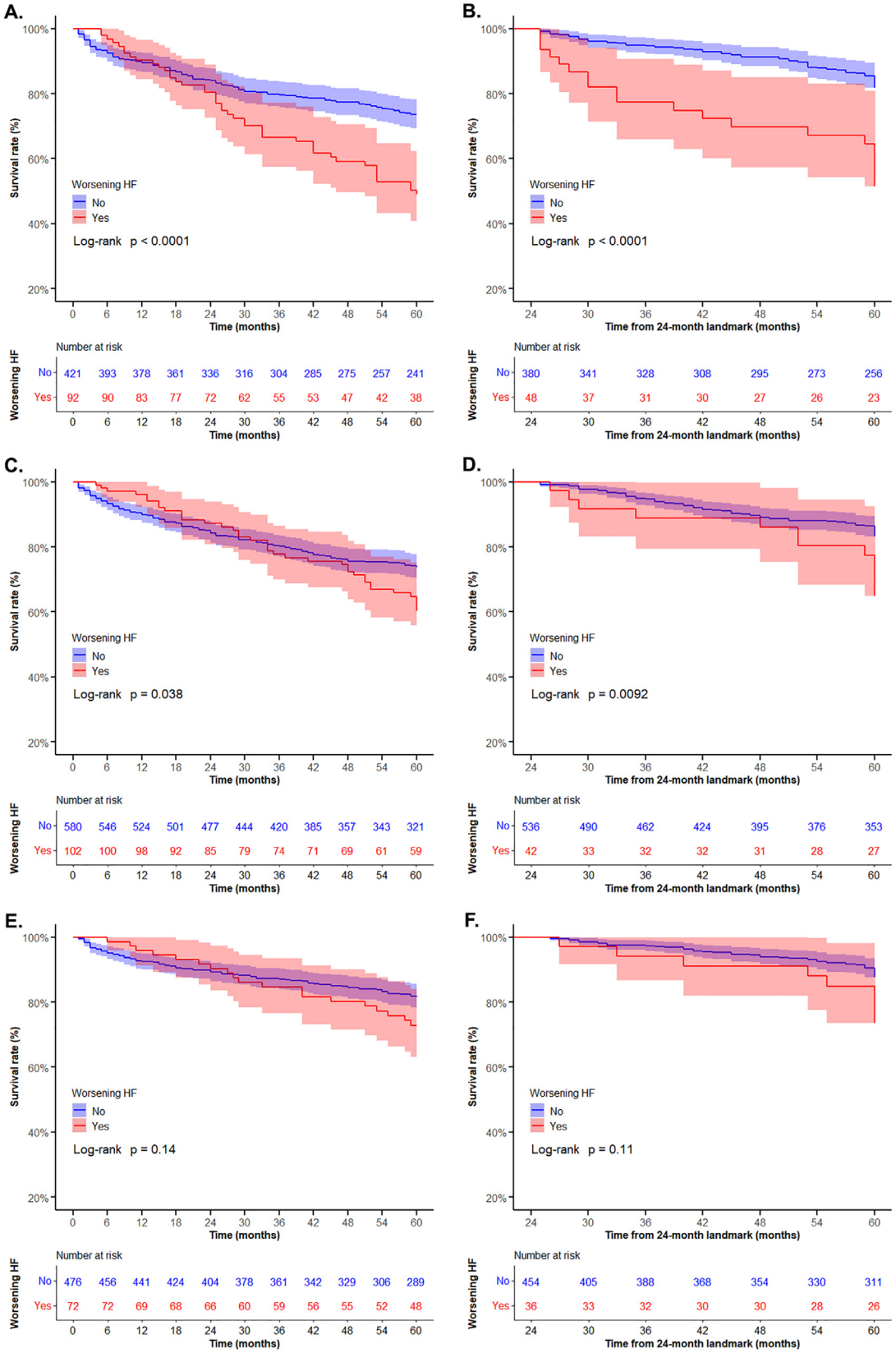

Figure 2. Kaplan-Meier curves for all-cause mortality by LVEF subgroups: LVEF ≤25% (*A*), LVEF 26% to 34% (*C*), LVEF 35% to 45% (*E*), and the corresponding landmark analyses for all-cause mortality by LVEF subgroups (*B, D,* and *F*).

SOLOIST-WHF (Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial. During a median follow-up of 9 months, the cumulative event rate (defined by the composite primary end point of cardiovascular death, hospitalizations, and worsening HF) was significantly lower in the sotagliflozin group than in the placebo group. These studies demonstrate that patients experiencing worsening HF may benefit from the initiation of newly introduced HF treatments during hospitalization.

The present study has several limitations. The data used in the present study originate from a single center and were retrospectively analyzed. However, the study provides clinical data of patients as opposed to research-driven data derived from a large, ongoing registry of patients with HFrEF. Mortality data were only available for all-cause mortality, and information on the exact cause of death is missing.

In conclusion, worsening HF, defined by HF hospitalization or urgent need for intravenous diuretics, in patients with HFrEF is independently associated with poor long-term prognosis. Patients who develop worsening HF during follow-up should be considered very high-risk patients, regardless of baseline LV systolic function. The timely institution of novel HF treatments should be considered after a first episode of worsening HF to improve prognosis.

Disclosures

Dr. Chimed reports a relation with European Society of Cardiology that includes funding grants. Dr. Chimed reports a relation with Turku PET Center that includes funding grants. Dr. Delgado reports a relation with Abbott Vascular that includes speaking and lecture fees. Dr. Delgado reports a relation with Edwards Lifesciences that includes speaking and lecture fees. Dr. Delgado reports a relation with GE Healthcare that includes speaking and lecture fees. Dr. Delgado reports a relation with Medtronic that includes speaking and lecture fees. Dr. Delgado reports a relation with Merck Sharp & Dohme that includes speaking and lecture fees. Dr. Delgado reports a relation with Novartis that includes speaking and lecture fees. Dr. Marsan reports a relation with Abbott Vascular that includes speaking and lecture fees. Dr. Marsan reports a relation with GE Healthcare that includes speaking and lecture fees. Dr. Bax reports a relation with Abbott Vascular that includes speaking and lecture fees. The remaining authors have no conflicts of interest to declare.

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