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Aetiology, timing and clinical predictors of early vs. late readmission following index hospitalization for acute heart failure: insights from ASCEND-HF

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Abstract

Aims—Patients hospitalized for heart failure (HF) are at high risk for 30-day readmission. This study sought to examine the timings and causes of readmission within 30 days of an HF hospitalization.

Methods and results—Timing and cause of readmission in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure) trial were assessed. Early and late readmissions were defined as admissions occurring within 0–7 days and 8–30 days post-discharge, respectively. Patients who died in hospital or remained hospitalized at day 30 post-randomization were excluded. Patients were compared by timing and cause of readmission. Logistic and Cox proportional hazards regression analyses were used to identify independent risk factors for early vs. late readmission and associations with 180-day outcomes. Of the 6584 patients (92%) in the ASCEND-HF population included in this analysis, 751 patients (11%) were

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Supplementary Information

Additional Supporting Information may be found in the online version of this article:

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readmitted within 30 days for any cause. Overall, 54% of readmissions were for non-HF causes. The median time to rehospitalization was 11 days (interquartile range: 6–18 days) and 33% of rehospitalizations occurred by day 7. Rehospitalization within 30 days was independently associated with increased risk for 180-day all-cause death [hazard ratio (HR) 2.38, 95% confidence interval (CI) 1.93–2.94; $P < 0.001$]. Risk for 180-day all-cause death did not differ according to early vs. late readmission (HR 0.99, 95% CI 0.67–1.45; $P = 0.94$).

Conclusions—In this hospitalized HF trial population, a significant majority of 30-day readmissions were for non-HF causes and one-third of readmissions occurred in the first 7 days. Early and late readmissions within the 30-day timeframe were associated with similarly increased risk for death. Continued efforts to optimize multidisciplinary transitional care are warranted to improve rates of early readmission.

Keywords

Acute heart failure; Timing of readmission; Cause of readmission

Introduction

Acute heart failure (HF) hospitalization is a global problem; over 1 million such hospitalizations occur annually in the USA and a similar number is reported in Europe.[1] Heart failure is one of the most common diagnoses for readmission in developed countries and accounts for 1–3% of all admissions and roughly a quarter of all 30-day readmissions in patients aged >65 years.[2,3] Although countries worldwide have instituted different readmission policies, 30 days is the common benchmark for readmission.[4] As previously demonstrated, the risk for death appears to increase with each subsequent readmission for HF.[5,6] However, despite a rapid increase in the allocation of resources targeting the prevention of readmission, readmission rates following HF hospitalization remain persistently high,[7] and interventions to reduce readmissions vary widely among institutions and often lack scientific rigour.[8]

Current guidelines strongly suggest the multidisciplinary management of patients admitted for HF, but place heavy emphasis on HF-specific modifiers such as volume management, and the initiation of guideline-directed medical therapy (GDMT).[9,10] Although prior studies have suggested that patients are readmitted disproportionately early and in about half of cases for causes other than HF, no study has rigorously explored relationships between the precise timing of readmission within the 30-day timeframe, the cause of readmission, and associations with subsequent clinical outcomes.[11–15] No study has investigated whether early readmission is related to worse outcome.

Thus, the objectives of this secondary analysis of the global ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure) trial were to: (i) describe causes of readmission after hospitalization for HF; (ii) characterize the timing of readmission within the 30-day timeframe; (iii) determine the comparative prognostic values of early vs. late readmission within the 30-day timeframe, and (iv) identify patient or regional characteristics that may predict timing of readmission.

Methods

Overview

The study design[16] and primary results[17] of the ASCEND-HF trial have been previously published. Briefly, ASCEND-HF was a global, prospective, randomized, double-blind, placebo-controlled trial designed to examine the short- and long-term efficacy and safety of nesiritide, a recombinant natriuretic peptide. A total of 7141 patients hospitalized for HF were randomized to nesiritide or placebo, in addition to standard therapy, within 24 h of the first i.v. HF-related treatment. Pertinent exclusion criteria included a high likelihood of hospital discharge in ≤24 h and a comorbid condition with an associated life expectancy of <6 months. The ASCEND-HF trial was conducted in line with the Declaration of Helsinki; its protocol was approved by the institutional review board or ethics committee at each participating centre, and written consent was obtained from all participants.

Study definitions and endpoints

The primary outcomes of interest were 30-day all-cause and cause-specific hospitalization. Unlike previous ASCEND studies, which looked at hospitalization within 30 days of randomization, the present study used data directly derived from case report forms (CRFs) to calculate time to hospitalization from patient discharge date. Hospitalization for HF was defined as first readmission for worsening signs or symptoms of HF resulting in the new administration of i.v. therapies, mechanical or surgical intervention, or initiation of ultrafiltration, haemofiltration or dialysis. Only patients who remained alive at the day 30 post-randomization follow-up visit were included in the analysis. Data for patients who died after discharge but prior to the 30-day post-randomization follow-up visit, without readmission, were omitted from the endpoint analysis. The study authors then took all post-discharge readmission data reported on ‘30-day’ follow-up visit CRFs and calculated the readmission rate up to 30 days after the discharge date. Adjudicated and institutional data were used to identify and confirm patients readmitted within 30 days of discharge. For the purposes of this analysis, early and late rehospitalizations were defined as readmissions within 0–7 days and 8–30 days post-discharge, respectively. To assess the impact of hospitalization on longer-term outcomes, 180-day all-cause mortality was prespecified as a secondary outcome for the present analysis.

Statistical analysis

Clinical characteristics at randomization were used as representative of baseline characteristics because the data collected at discharge were less complete and referred to a smaller number of prespecified collected variables. Histograms were used to display the distribution of time to first hospitalization from discharge. Time to rehospitalization was stratified by non-HF vs. HF causes, as well as reduced vs. preserved left ventricular ejection fraction (LVEF) (40% cut-off). Non-parametric Wilcoxon rank sum tests were conducted to determine differences between the distributions of non-HF and HF time to readmission.

Multivariable generalized logistic regression analysis was used to determine risk factors for both any-cause rehospitalization and HF-related rehospitalization, categorized as no rehospitalization, early rehospitalization and late rehospitalization. Considering all baseline

characteristics listed in Table 1 (excluding BNP and estimated glomerular filtration rate) as candidate variables, stepwise selection was used to determine final models of independent risk factors for both any-cause and HF-related rehospitalization, respectively, using as a selection criterion a *P*-value of <0.10 for inclusion in the final model. After the final multivariable model had been created, additional adjustment variables were forced into the model; these represent characteristics found to be significant predictors for early vs. late readmission in the subset of patients who actually experienced readmission. For any-cause rehospitalization, forced adjustment covariates included digoxin use, orthopnoea, nitrate use and baseline weight. For HF-related rehospitalization, forced adjustment covariates included digoxin use and history of ischaemic heart disease. Levels of missing data among candidate variables ranged from 0% to 8%. Assuming that these data were missing at random, multiple imputation was utilized to account for missingness. Results were reported as odds ratios (ORs) for early vs. no, late vs. no, and early vs. late rehospitalization. In addition, a sensitivity analysis was conducted to determine risk factors for any-cause rehospitalization and HF-related rehospitalization in patients for whom data on LVEF were available. The sensitivity analyses included an LVEF of <40% as an additional risk factor in the final multivariable model.

Cox regression models were used to determine the relationship between the presence (vs. absence) of 30-day readmission and the timing of 30-day readmission (i.e. early vs. late) with 180-day mortality. This analysis set a landmark at 30 days after discharge, and only patients who survived to that point were included in this analysis. Rates of 180-day mortality were calculated from randomization. Adjustment variables consisted of the risk factors from the final multivariable models previously identified above. All analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA). A two-tailed *P*-value of <0.05 was considered to indicate differences of statistical significance.

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Results

Study population

In total, 6584 patients were included in the analysis. The mean ± standard deviation (SD) age of study participants was 65 ± 14 years; 66% were male, and 44% self-identified as non-White. Ischaemic heart disease was reported in 60% of patients, and the mean ± SD LVEF was 30 ± 12.8%. Prevalences of cardiac and non-cardiac comorbidities were high, and the majority of patients were treated with GDMT on admission [in patients with LVEF <40%, levels of use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and beta-blockers, amounted to 62% and 58%, respectively]. Table 1

shows the baseline characteristics of patients who were readmitted either early or late, or were not readmitted during the first 30 days after discharge.

A total of 751 patients (11% of the total population) were readmitted within 30 days after discharge for any cause. Compared with patients who were not readmitted, patients who were readmitted for any cause within 30 days were more likely to be older, African American and enrolled at a site in North America, compared with patients not readmitted. Further, patients who were readmitted for any cause tended to have a higher body mass index (BMI), to carry higher numbers of cardiac and non-cardiac comorbidities, to have a higher rate of prior HF hospitalization, and to be receiving more cardiovascular medications at baseline. These patients also exhibited worse baseline renal function and more severe congestion on physical examination and by laboratory markers. Baseline characteristics by cause of rehospitalization are displayed in the supplementary material online, Table S1. Average time from randomization to discharge (i.e. length of stay) was 5 days, regardless of cause of readmission (supplementary material online, Table S2).

Cause of readmission

Among patients who were rehospitalized, 345 patients (46% of the readmitted population and 5% of the total cohort) were readmitted within 30 days after discharge for HF, and 406 patients (54% of the readmitted population and 6% of the total cohort) were readmitted for non-HF causes. Non-HF causes included myocardial infarction (2.5%), resuscitated sudden cardiac death (0.6%), other cardiovascular events (30.5%) and other non-cardiovascular events (66.5%) (Figure 1). Thus, the total rate of readmission for non-cardiovascular causes was 36%. Non-cardiovascular causes of readmission included respiratory disease, infections and renal disorders.

Timing of readmission following heart failure hospitalization

Among all patients readmitted within 30 days of discharge, the median time of readmission was day 11. By day 7, 33% of patients had been readmitted, and by day 15, 67% had been rehospitalized. Heart failure-related readmissions within the 30-day mark occurred at a median of 11 days. By day 7, 31% of patients had been readmitted, and by day 15, 66% had been rehospitalized (Figure 2). Non-HF-related readmissions occurred at a median of 12 days. By day 7, 35% of patients had been readmitted, and by day 15, 63% had been rehospitalized. There was no significant difference in time to readmission between HF- vs. non-HF-related readmission ($P = 0.453$).

Early vs. late readmission

Compared with late readmission, early readmission occurred more frequently at North American sites and in patients with hypertension and coronary artery disease. On discharge, patients readmitted early had a higher weight and worse renal function (creatinine and blood urea nitrogen). Further, patients readmitted early were more likely to be on GDMT with a comparable rate of diuretic use at discharge. Average lengths of stay were 5 days for patients readmitted either early or late, irrespective of HF or non-HF causes (Table S2).

Independent predictors of all-cause and HF rehospitalization are shown in Tables 2 and 3. When the no-readmission group was used as the reference group, baseline chronic respiratory disease was associated with an increased likelihood of early all-cause readmission [OR 1.51, 95% confidence interval (CI) 1.11–2.07], whereas history of cerebrovascular disease and history of cardiac resynchronization therapy (CRT) were associated with increased likelihoods of late readmission [OR 1.52 (95% CI 1.18–1.96) and OR 1.39 (95% CI 1.07–1.82), respectively]. Chronic loop diuretics use on admission was associated with increased risk for late HF rehospitalization (OR 2.37, 95% CI 1.56–3.61), and baseline use of ACEI or ARB and systolic blood pressure were associated with decreased likelihoods of late HF readmission [OR 0.66 (95% CI 0.49–0.89) and OR 0.91 (95% CI 0.85–0.97), respectively] in comparison with no HF readmission. Nesiritide use was not associated with either early or late readmission in a comparison between the early and late all-cause readmission groups (OR 1.04, 95% CI 0.76–1.42) or no rehospitalization (early vs. no rehospitalization: OR 1.04, 95% CI 0.79–1.36; late vs. no rehospitalization: OR 1.00, 95% CI 0.83–1.21). Odds ratios for direct comparisons between early and late readmission are presented in Tables 2 and 3.

In patients for whom data on LVEF were available ($n = 4887$), LVEF was found to be an independent predictor of all-cause readmission ($P = 0.005$). Specifically, LVEF <40% was associated with a decreased likelihood of early all-cause readmission (OR 0.59, 95% CI 0.42–0.83) in comparison with no readmission; however, LVEF was not associated with HF-specific rehospitalization. The relationship between LVEF and the timing of readmission is displayed in Figure 3.

Relationship between readmission and mortality

Any-cause [univariable hazard ratio (HR) 2.81, 95% CI 2.30–3.43 ($P < 0.001$); multivariable HR 2.38, 95% CI 1.93–2.94 ($P < 0.001$)] or HF-specific [univariable HR 2.83, 95% CI 2.18–3.67 ($P < 0.001$); multivariable HR 2.04, 95% CI 1.56–2.67 ($P < 0.001$)] readmission within 30 days of discharge were associated with increased 180-day all-cause mortality. However, timing of readmission for any cause, whether it was early or late, was not predictive of 180-day all-cause mortality using a univariable model (HR 0.90, 95% CI 0.61–1.31; $P = 0.57$). This was confirmed in the multivariable model (HR 0.99, 95% CI 0.67–1.45; $P = 0.94$). The lack of association between timing and 180-day all-cause mortality remained for patients readmitted for HF-related (univariable HR 1.04, 95% CI 0.1–1.75; $P = 0.9$) or non-HF-related (univariable HR 0.79, 95% CI 0.45–1.34; $P = 0.39$) causes. The full model for all-cause and HF-related readmission in relation to 180-day all-cause mortality can be found in Tables 4 and 5.

Discussion

Outcomes at 30 days after discharge from HF-related hospitalization are used by the Centers for Medicaid and Medicare Services (CMS) as a health care quality metric. The present analysis from a large trial in patients with acute HF found that one-third of patients readmitted after an initial HF hospitalization were readmitted within 7 days and two-thirds were rehospitalized within 15 days, which suggests that all-cause and HF-related

readmissions are skewed and occur disproportionately more frequently in the first 2 weeks after discharge. A large portion of readmissions are driven by non-HF-related (54%) or even non-cardiovascular (36%) causes. Although readmission within 30 days by itself was associated with increased all-cause mortality, there was no differential association between early (0–7 days) or late (8–30 days) readmission, regardless of cause, with outcomes.

Patients who are discharged from HF-related hospitalization enter what is called the 'vulnerable phase'. Although it is not clearly defined, the vulnerable phase includes the period immediately after discharge until 2–3 months later[18,19] and is marked by high rates of mortality and readmission. The present findings regarding timing and cause of readmission are in agreement with previous analyses of Medicare populations,[14] State Inpatient Databases,[12] and smaller randomized HF trials.[15] In fact, most descriptive characteristics, such as median day of readmission, percentage of patients readmitted within 7 days and the proportion of HF-related and non-HF-related readmissions are strikingly similar, despite differences in study cohorts (national registries vs. randomized controlled trials), age groups (mean ± SD ages are 80.3 ± 7.9 years in the Medicare patient cohort,[14] 74.7 ± 14.1 years in the State Inpatient Database cohort,[12] and 65.0 ± 14.1 years in the ASCEND-HF trial cohort), and time of sampling (Medicare: 2004–2006; State Inpatient Databases: 2007–2011; ASCEND-HF: 2007–2010). Notably, geographic site appears to play a role: in the present study, the likelihoods of early and late all-cause readmission were higher at North American trial sites than at sites in all other continents. Both early and late HF-specific readmissions were more likely to occur in North America in comparison with Asian-Pacific or Central European countries, and late readmission was more likely at North American sites than in Western European and Latin American countries.

Similarly, patients were at increased risk for early and late all-cause readmission if they were enrolled at a trial site in North America, had a history of prior hospitalization in the past year, or were on chronic loop diuretics at admission. Interestingly, although an LVEF of ≤35% in the ASCEND-HF population was associated with worse outcomes,[20] LVEF did not predict the timing of HF-related readmission, which may suggest that the physiology leading to recurrent decompensation is similar in both HF with preserved EF and HF with reduced EF patients.

Although the present analysis is the first to evaluate the association of early vs. late readmission after an initial hospitalization for HF with subsequent mortality, similar analyses have been performed for in-hospital worsening HF. Analyses using data from ASCEND-HF[21] and PROTECT[22] stratified in-hospital worsening HF by early (before hospital day 4) or late (from day 5 until discharge) events and did not find an association between timing and outcomes. However, in an analysis of ADHERE data,[23] a different definition of early (HF worsening on day 1) and late (HF worsening after day 1) worsening yielded different results. Early HF compared with late in-hospital worsening HF was associated with a lower rate of all-cause mortality, but similar rates of HF-related and all-cause rehospitalization at 30 days and 1 year. It is possible that, in the present analysis, alternative choices for the early vs. late cut-off would have changed the results. Although the choice of 1 week as a cut-off is arbitrary, it has been used in prior analyses[11,12,14] and hospitals that conduct follow-up appointments within 1 week appear to have lower rates of

30-day readmission.[24] Further, the 1-week cut-off has been the target of quality improvement programmes[25] and, most importantly, is clinically relevant by virtue of being suggested as a target follow-up date by the current American College of Cardiology/ American Heart Association (ACC/AHA) guidelines.[9]

Current guidelines and financial penalties place a strong emphasis on minimizing 30-day rehospitalization with a particular focus on HF-specific measures. However, the present analysis complements prior retrospective studies by showing that a third of patients readmitted within the 30-day window may present to hospital within 1 week, and a majority of readmissions will be for causes other than HF. Registry and trial data indicate that comorbidities such as chronic obstructive lung disease and diabetes mellitus are present in more than 30% of patients with HF,[26–28] and the presence of comorbidities in acute HF patients is associated with added morbidity and mortality.[27,29] Additionally, the number of non-cardiac chronic conditions increases the risk for hospitalization.[30] Current strategies to reduce hospitalization in patients with HF place strong emphasis on weight and vitals monitoring (telemonitoring),[31,32] as well as invasive pressure monitoring.[33,34] So far, strategies to reduce hospitalization rates have shown mixed results. Given that the majority of readmissions may occur for reasons other than HF, inadequate diuresis[35] and short-term worsening of haemodynamics[36] are not to be viewed as solely responsible for the high rate of rehospitalization. The wide range of acute conditions precipitating readmission exposes the heightened vulnerability of patients with HF and particularly those admitted for an acute decompensation. Hospitalized patients frequently develop a new impairment, suffer a loss of mobility and strength,[37,38] and become nutritionally deficient.[39] Whereas the ASCEND-HF trial did not test the effectiveness of any specific post-discharge interventions, a multidisciplinary approach[40] might address a greater number of potential causes of readmission in comparison with a single intervention.[41] Finally, current ACC/AHA guidelines recommend a follow-up visit at 7–14 days[9] and early telephone follow-up within 3 days, and the European Society of Cardiology (ESC) guidelines recommend a first visit within 7 days.[10] The present findings, in aggregate with existing work, support added emphasis on early follow-up appointment and increased preventive efforts during the discharge phase.

Limitations

Firstly, this study was designed post hoc and thus is subject to the potential biases intrinsic to secondary analyses of randomized clinical trials, including unmeasured or residual confounding. However, unlike prior retrospective analyses, by virtue of its use of a clinical trial database with comprehensive data capture and adjudicated outcomes, the present analysis of the ASCEND-HF trial allows for a greater degree of detail. Secondly, despite the large size of the original trial, the current analysis remains limited by low 30-day readmission rates in comparison with those seen in real-world practice, as suggested by CMS data.[7] The discrepancy in readmission rates can potentially be explained by the fact that the present study used randomized trial data with specific inclusion and exclusion criteria, a more definitive diagnosis of HF and improved follow-up compared with those in the general population. Thirdly, despite the strength of the adjudication process and investigator-reported outcomes in ASCEND-HF, readmission events were attributed to only

a limited number of diagnoses and about a third of non-cardiovascular events were not attributed to a specific diagnosis. Fourthly, post-randomization and/or discharge patient characteristics would be preferable covariates for an analysis of 30-day outcomes. The present group chose to use patient characteristics at randomization in view of the superior quality and quantity of the data in ASCEND-HF at that time-point. Finally, the endpoint analysis using 30-day readmission data was limited by the exclusion of patients who died before the landmark analysis. The characteristics of all excluded patients can be found in the supplementary material online, Table S3.

Conclusions

In this analysis of a large randomized clinical trial of patients with acute HF, 54% of 30-day readmissions were attributable to non-HF-related causes and a third of readmissions occurred within the first 7 days. Early and late readmissions within the 30-day timeframe, regardless of cause of readmission, were associated with similar increases in risk for death. The present analysis underscores the fact that given the high burden of early and non-HF-related readmissions, there is a need for a multidisciplinary approach to patients admitted for HF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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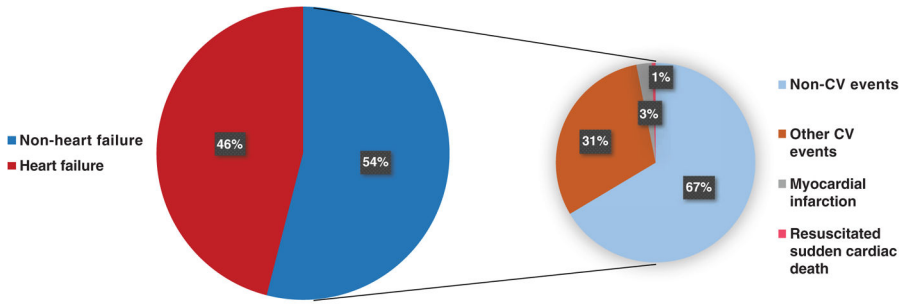

Figure 1.

Adjudicated and investigator-reported causes of rehospitalization after heart failure (HF)-related hospitalization stratified by HF and non-HF causes. Non-HF causes are further stratified by cardiovascular (CV) and non-CV causes.

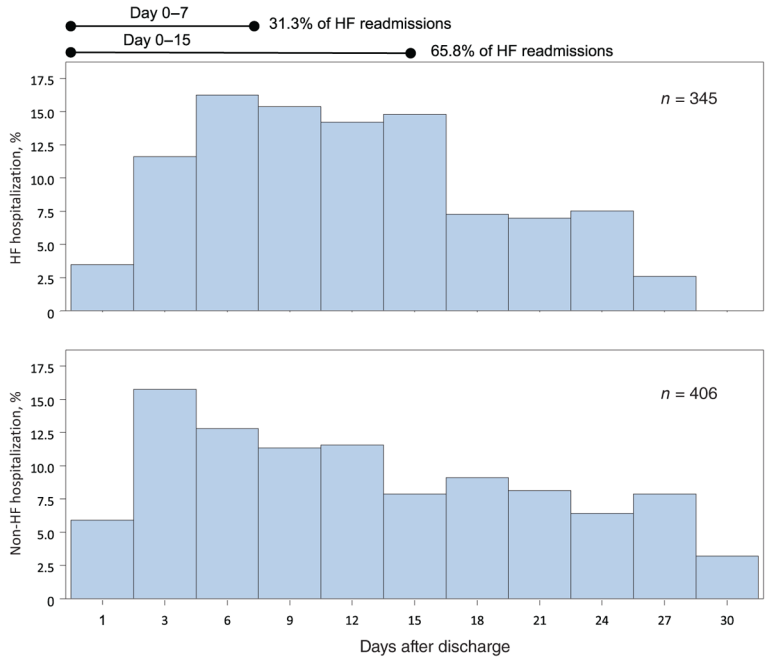

Figure 2.
Timing of rehospitalization for heart failure (HF) and non-HF-related rehospitalization.

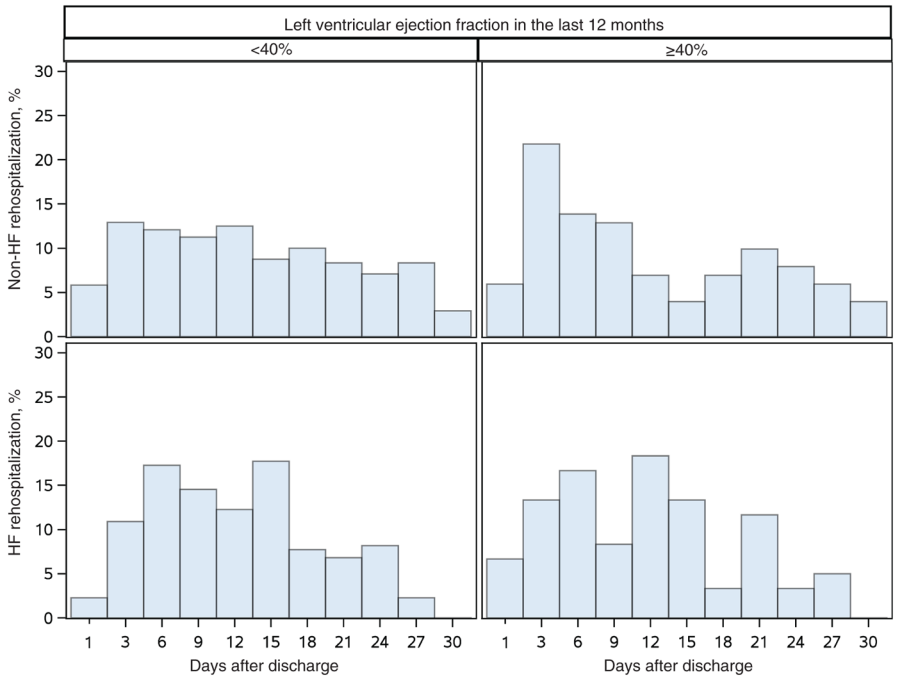

Figure 3.

Time to rehospitalization by left ventricular ejection fraction (<40% vs. ≥40%) and heart failure (HF) vs. non-HF-related rehospitalization.

Table 1

Baseline patient characteristics by all-cause rehospitalization status (n = 6584)

Characteristic	Any-cause rehospitalization status			*P*-value[a]
	No readmission (n =5833)	Early readmission (n =248)	Late readmission (n =503)	
Demographics				
Age, years, mean ± SD	65 ± 14.0	67 ± 14.6	66 ± 14.7	0.033
Female gender, n (%)	1997 (34.2%)	83 (33.5%)	175 (34.8%)	0.936
Race, n (%)				<0.001
White	3224 (55.3%)	150 (60.5%)	302 (60.0%)	
Black or African American	849 (14.6%)	54 (21.8%)	115 (22.9%)	
Asian	1494 (25.6%)	31 (12.5%)	75 (14.9%)	
Other	263 (4.5%)	13 (5.2%)	11 (2.2%)	
Baseline weight, kg, median (IQR)	78 (64–95)	83 (69–102)	83 (68–97)	<0.001
Region, n (%)				<0.001
Asia-Pacific	1491 (25.6%)	31 (12.5%)	74 (14.7%)	
Central Europe	875 (15.0%)	5 (2.0%)	20 (4.0%)	
Latin America	557 (9.6%)	18 (7.3%)	35 (7.0%)	
North America	2511 (43.1%)	184 (74.2%)	350 (69.6%)	
Western Europe	397 (6.8%)	10 (4.0%)	24 (4.8%)	
Medical history				
NYHA classification, n (%)				0.041
NYHA class not assessed	1014 (17.4%)	61 (24.6%)	89 (17.7%)	
NYHA class I	231 (4.0%)	4 (1.6%)	13 (2.6%)	
NYHA class II	914 (15.7%)	31 (12.5%)	80 (15.9%)	
NYHA class III	2338 (40.1%)	105 (42.3%)	207 (41.2%)	
NYHA class IV	1336 (22.9%)	47 (19.0%)	114 (22.7%)	
Ischaemic heart disease, n (%)	3493 (59.9%)	163 (65.7%)	310 (61.6%)	0.150
HF hospitalization past year, n (%)	2116 (36.3%)	134 (54.0%)	283 (56.3%)	<0.001
LVEF in previous 12 months, %, mean ± SD	30 ± 12.6	33 ± 15.3	30 ± 14.0	0.187
LVEF <40% past year, n (%)	3529 (81.0%)	141 (68.8%)	319 (76.7%)	<0.001
History of hypertension, n (%)	4191 (71.9%)	202 (81.5%)	387 (76.9%)	<0.001
History of diabetes mellitus, n (%)	2428 (41.6%)	124 (50.0%)	255 (50.7%)	<0.001
History of coronary artery disease, n (%)	3151 (54.0%)	158 (63.7%)	296 (59.0%)	0.002
History of cerebrovascular disease, n (%)	643 (11.0%)	38 (15.3%)	94 (18.7%)	<0.001
History of peripheral arterial vascular disease	589 (10.1%)	41 (16.5%)	68 (13.5%)	<0.001
Baseline chronic respiratory disease, n (%)	899 (15.4%)	69 (27.8%)	122 (24.3%)	<0.001
History of atrial fibrillation/flutter, n (%)	2133 (36.6%)	118 (47.6%)	217 (43.1%)	<0.001
History of ICD/CRT, n (%)	456 (7.8%)	38 (15.3%)	89 (17.7%)	<0.001
Current smoker, n (%)	799 (13.7%)	31 (12.5%)	71 (14.1%)	<0.001
Laboratory values at baseline, median (IQR)				
Systolic BP, mmHg,	124 (110–140)	122 (110–138)	120 (110–137)	0.008
Diastolic BP, mmHg,	75 (67–84)	72 (64–83)	71 (64–80)	<0.001

Characteristic	Any-cause rehospitalization status			*P*-value[a]
	No readmission (*n* =5833)	Early readmission (*n* =248)	Late readmission (*n* =503)	
Heart rate, b.p.m.	82 (72–95)	80 (70–94)	82 (70–94)	0.110
Respiratory rate, breaths/min	23 (21–26)	22 (20–24)	22 (20–25)	0.058
Sodium, mmol/L	139 (136–141)	138 (136–141)	139 (136–141)	0.090
BUN, mg/dL	25 (18–37)	28 (19–41)	28 (20–40)	<0.001
Creatinine, mg/dL	1.2 (1.0–1.5)	1.4 (1.1–1.8)	1.3 (1.1–1.7)	<0.001
Haemoglobin, g/dL	13 (11–14)	12 (11–13)	12 (11–14)	<0.001
NT-proBNP, pg/mL	4242 (1982–8668)	6002 (2991–12 197)	5545 (2768–12 280)	<0.001
BNP, pg/mL	957 (523–1801)	1019 (602–1906)	1221 (671–2087)	<0.001
GFR	60 (45–76)	54 (38–68)	53 (40–70)	<0.001
Medication at/before baseline, *n* (%)				
ACEIs or ARBs	3549 (60.9%)	161 (64.9%)	321 (63.8%)	0.207
Beta-blockers	3346 (57.4%)	164 (66.1%)	353 (70.2%)	<0.001
Aldosterone antagonists	1611 (27.6%)	67 (27.0%)	154 (30.6%)	0.342
Chronic use of loop diuretics	3578 (61.4%)	195 (78.6%)	408 (81.1%)	<0.001
Nitrates	1344 (23.0%)	77 (31.0%)	123 (24.5%)	0.012
Hydralazine	368 (6.3%)	42 (16.9%)	69 (13.7%)	<0.001
Digoxin	1510 (25.9%)	57 (23.0%)	162 (32.2%)	0.004
Oral anticoagulants	1332 (22.8%)	82 (33.1%)	175 (34.8%)	<0.001
Aspirin	2819 (48.3%)	144 (58.1%)	287 (57.1%)	<0.001
Clinical profile				
Baseline BMI, kg/m^2, median (IQR)	27.4 (23.7–32.6)	29.0 (25.0–33.8)	28.8 (24.7–33.1)	<0.001
Orthopnoea, *n* (%)	4451 (76.4%)	212 (85.5%)	396 (78.9%)	0.002
Rales >1/3 lung fields, *n* (%)	3070 (52.6%)	116 (46.8%)	255 (50.7%)	0.022
JVD, *n* (%)	3204 (55.0%)	158 (63.7%)	330 (65.6%)	<0.001
Peripheral oedema, *n* (%)	4317 (74.0%)	190 (76.6%)	394 (78.3%)	0.079
Clinical course				
Actual treatment group, *n* (%)				0.977
Placebo	2863 (49.7%)	123 (50.0%)	247 (50.2%)	
Nesiritide	2895 (50.3%)	123 (50.0%)	245 (49.8%)	

ACEI, angiotensin converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; JVD, jugular venous distension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

[a] *P*-value from comparison for no readmission vs. early readmission vs. late readmission.

Table 2

Baseline predictors of all-cause rehospitalization after discharge

Variable	OR (95% CI)			Wald	*P*-value
	Early vs. No readmission	Late vs. No readmission	Early vs. Late readmission		
History of cerebrovascular disease	1.11 (0.76–1.64)	1.52 (1.18–1.96)	0.73 (0.47–1.14)	10.302	0.006
Chronic respiratory disease	1.51 (1.11–2.07)	1.25 (0.99–1.58)	1.21 (0.84–1.76)	9.254	0.010
Prior CRT (with or without ICD)	1.01 (0.67–1.52)	1.39 (1.07–1.82)	0.73 (0.46–1.15)	5.951	0.051
Current smoker vs. never smoked	0.94 (0.60–1.47)	1.13 (0.84–1.53)	0.83 (0.49–1.40)	0.746	0.689
Past smoker vs. never smoked	1.27 (0.94–1.71)	1.18 (0.95–1.46)	1.07 (0.75–1.53)	4.343	0.114
Hospitalization in last year	1.63 (1.22–2.17)	1.70 (1.38–2.08)	0.96 (0.68–1.35)	34.446	<0.001
Asia Pacific vs. North America	0.49 (0.31–0.78)	0.52 (0.38–0.71)	0.94 (0.54–1.64)	23.980	<0.001
Central Europe vs. North America	0.11 (0.05–0.28)	0.19 (0.12–0.30)	0.60 (0.22–1.70)	68.157	<0.001
Latin America vs. North America	0.47 (0.26–0.85)	0.60 (0.41–0.87)	0.78 (0.39–1.56)	12.625	0.002
Western Europe vs. North America	0.45 (0.24–0.88)	0.53 (0.34–0.82)	0.85 (0.40–1.85)	12.928	0.002
Chronic loop diuretic use	1.46 (1.02–2.09)	1.94 (1.49–2.52)	0.76 (0.49–1.17)	27.453	<0.001
Hydralazine use	1.56 (1.03–2.34)	1.38 (1.01–1.90)	1.12 (0.69–1.83)	7.636	0.022
Digoxin use	0.73 (0.52–1.01)	1.18 (0.96–1.46)	0.61 (0.42–0.90)	6.495	0.039
Orthopnoea	1.49 (1.01–2.19)	0.94 (0.74–1.19)	1.59 (1.02–2.46)	4.509	0.105
Nitrate use	1.15 (0.83–1.58)	0.78 (0.62–1.00)	1.46 (1.00–2.15)	4.947	0.084
Baseline heart rate, per 5 b.p.m.	1.00 (0.96–1.05)	1.03 (1.00–1.06)	0.98 (0.93–1.03)	3.497	0.174
Baseline weight < 85 kg, per 5 kg	1.02 (0.95–1.20)	1.04 (0.99–1.09)	0.98 (0.90–1.07)	2.762	0.251
Baseline weight ≥85 kg, per 5 kg	1.01 (0.97–1.04)	0.97 (0.94–1.00)	1.04 (0.99–1.09)	4.368	0.113
Baseline sodium, per 5 mmol/L	0.89 (0.76–1.05)	0.87 (0.78–0.97)	1.03 (0.85–1.24)	7.541	0.023

CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; OR, odds ratio.

Table 3

Baseline predictors of heart failure-related rehospitalization after discharge

Variable	OR (95% CI)			Wald	*P*-value
	Early vs. No readmission	Late vs. No readmission	Early vs. Late readmission		
History of cerebrovascular disease	0.87 (0.48–1.59)	1.56 (1.10–2.22)	0.56 (0.28–1.10)	6.615	0.037
History of ischaemic heart disease	1.84 (1.14–2.96)	0.83 (0.63–1.10)	2.22 (1.29–3.81)	8.240	0.016
Hospitalization in last year	2.01 (1.30–3.10)	1.85 (1.39–2.46)	1.08 (0.65–1.80)	27.064	<0.001
Latin America vs. North America	0.41 (0.16–1.03)	0.69 (0.42–1.14)	0.59 (0.21–1.68)	5.599	0.061
Western Europe vs. North America	0.42 (0.16–1.06)	0.28 (0.13–0.62)	1.47 (0.44–4.88)	13.176	0.001
ACEI or ARB use	1.00 (0.62–1.60)	0.66 (0.49–0.89)	1.51 (0.88–2.60)	7.613	0.022
Chronic loop diuretic use	1.65 (0.91–2.96)	2.37 (1.56–3.61)	0.69 (0.34–1.42)	18.744	<0.001
Digoxin use	0.81 (0.50–1.32)	1.32 (0.98–1.76)	0.62 (0.35–1.08)	4.239	0.120
Log of creatinine (mg), per doubling	1.40 (0.94–2.08)	1.56 (1.21–2.02)	0.90 (0.56–1.42)	13.887	0.001
Respiratory rate < 20, per 5 breaths/min	0.57 (0.22–1.51)	0.51 (0.27–0.95)	1.13 (0.37–3.43)	5.406	0.067
Respiratory rate ≥20, per 5 breaths/min	1.34 (1.03–1.76)	1.17 (0.96–1.42)	1.15 (0.83–1.59)	6.778	0.034
Systolic BP < 130 mmHg, per 5 mmHg	0.95 (0.85–1.06)	0.91 (0.85–0.97)	1.04 (0.92–1.18)	8.067	0.018
Systolic BP ≥130 mmHg, per 5 mmHg	1.00 (0.91–1.11)	1.04 (0.98–1.11)	0.96 (0.86–1.08)	1.690	0.430

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; OR, odds ratio.

Table 4

All-cause rehospitalization vs. no rehospitalization in relation to 180-day all-cause death

Risk factor	Multivariable		
	HR (95% CI)	SE	*P*-value
Any rehospitalization vs. no rehospitalization	2.38 (1.93–2.94)	0.108	<0.001
History of cerebrovascular disease	1.51 (1.20–1.90)	0.118	0.001
Chronic respiratory disease	1.19 (0.95–1.49)	0.115	0.130
Prior CRT (with or without ICD)	0.83 (0.61–1.12)	0.153	0.212
Baseline heart rate, per 5 b.p.m.	1.00 (0.98–1.03)	0.003	0.861
Current smoker vs. never smoked	0.79 (0.59–1.07)	0.153	0.123
Past smoker vs. never smoked	0.96 (0.80–1.17)	0.098	0.706
Chronic loop diuretic use	1.93 (1.53–2.43)	0.118	<0.001
Hospitalization in last year	1.23 (1.02–1.48)	0.095	0.027
Asia Pacific vs. North America	0.74 (0.57–0.97)	0.138	0.029
Central Europe vs. North America	0.68 (0.48–0.95)	0.173	0.024
Latin America vs. North America	1.22 (0.90–1.65)	0.153	0.198
Western Europe vs. North America	1.18 (0.84–1.66)	0.174	0.337
Hydralazine use	0.89 (0.64–1.25)	0.173	0.504
Baseline sodium, per 5 mmol/L	0.81 (0.73–0.88)	0.010	<0.001
Digoxin use	1.15 (0.95–1.39)	0.097	0.156
Orthopnoea	0.84 (0.69–1.03)	0.104	0.093
Oral/topical nitrate use	1.11 (0.90–1.36)	0.104	0.325
Baseline weight < 85 kg, per 5 kg	0.92 (0.88–0.96)	0.004	<0.001
Baseline weight ≥85 kg, per 5 kg	0.96 (0.92–0.99)	0.004	0.015

CI, confidence interval; CRT, cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; SE, standard error.

Table 5

Heart failure-related rehospitalization vs. no rehospitalization in relation to 180-day all-cause death

Risk factor	Multivariable		
	HR (95% CI)	SE	*P*-value
HF rehospitalization vs. no HF rehospitalization	2.04 (1.56–2.67)	0.137	<0.001
ACEI or ARB use	0.68 (0.56–0.82)	0.097	0.001
Respiratory rate < 20, per 5 breaths/min	1.10 (0.96–1.25)	0.014	0.174
Respiratory rate ≥20, per 5 breaths/min	1.20 (0.88–1.64)	0.032	0.249
Systolic BP <130 mmHg, per 5 mmHg	0.94 (0.90–0.98)	0.005	0.003
Systolic BP ≥130 mmHg, per 5 mmHg	0.99 (0.95–1.04)	0.005	0.801
Chronic loop diuretic use	1.66 (1.31–2.09)	0.119	<0.001
Hospitalization in last year	1.22 (1.02–1.46)	0.093	0.032
Log of creatinine (mg), per doubling	1.45 (1.22–1.72)	0.087	<0.001
Asia Pacific vs. North America	1.12 (0.89–1.41)	0.118	0.339
Central Europe vs. North America	0.67 (0.49–0.96)	0.169	0.026
Latin America vs. North America	1.55 (1.16–2.07)	0.148	0.003
Western Europe vs. North America	1.23 (0.88–1.73)	0.172	0.221
History of cerebrovascular disease	1.50 (1.19–1.89)	0.118	0.001
Digoxin use	1.24 (1.03–1.50)	0.097	0.027
History of ischaemic heart disease	1.19 (0.99–1.44)	0.096	0.067

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CI, confidence interval; HF, heart failure; HR, hazard ratio; SE, standard error.