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ORIGINAL RESEARCH ARTICLE

Clinical presentation at first heart failure hospitalization does not predict recurrent heart failure admission

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Abstract

Aims   There are limited data on whether clinical presentation at first heart failure (HF) hospitalization predicts recurrent HF events. We aimed to assess predictors of recurrent HF hospitalizations in mild HF patients with an implantable cardioverter defibrillator or cardiac resynchronization therapy with defibrillator.

Methods and results   Data on HF hospitalizations were prospectively collected for patients enrolled in MADIT-CRT. Predictors of recurrent HF hospitalization (HF2) after the first HF hospitalization were assessed using Cox proportional hazards regression models including baseline covariates and clinical presentation or management at first HF hospitalization. There were 193 patients with first HF hospitalization, and 156 patients with recurrent HF events. Recurrent HF rate after the first HF hospitalization was 43% at 1 year, 52% at 2 years, and 55% at 2.5 years. Clinical signs and symptoms, medical treatment, or clinical management of HF at first HF admission was not predictive for HF2. Baseline covariates predicting recurrent HF hospitalization included prior HF hospitalization (HR = 1.59, 95% CI: 1.15–2.20, $P = 0.005$), digitalis therapy (HR = 1.58, 95% CI: 1.13–2.20, $P = 0.008$), and left ventricular end-diastolic volume >240 mL (HR = 1.62, 95% CI: 1.17–2.25, $P = 0.004$).

Conclusions   Recurrent HF events are frequent following the first HF hospitalization in patients with implanted implantable cardioverter defibrillator or cardiac resynchronization therapy with defibrillator. Neither clinical presentation nor clinical management during first HF admission was predictive of recurrent HF. Prior HF hospitalization, digitalis therapy, and left ventricular end-diastolic volume at enrolment predicted recurrent HF hospitalization, and these covariates could be used as surrogate markers for identifying a high-risk cohort.

Introduction

Most clinical trials conducted in heart failure (HF) patients utilized the endpoint of time to first HF hospitalization. However, given that HF is generally a chronic condition characterized by recurrent hospitalizations, it may be more relevant to assess recurrent HF hospitalization events, and predictors of recurrent HF hospitalization events to identify high-risk cohorts.

In MADIT-CRT, it was shown that cardiac resynchronization therapy with defibrillator (CRT-D) was associated with reduction in the risk of recurrent HF events.[1] Data are however not available on risk factors for recurrent HF hospitalization in patients with mild HF and an implantable cardioverter defibrillator (ICD) or CRT-D. Furthermore, the predictive value of parameters at the first HF admission to predict recurrent HF hospitalizations is not well understood. Specifically, it is not known whether the clinical presentation or clinical management during the first HF hospitalization is associated with risk for recurrent HF hospitalization.

Therefore, in this substudy from MADIT-CRT, we aimed to characterize patients at the time of their first HF hospitalization and describe predictive factors for recurrent hospital

admission for HF using (i) clinical parameters at enrolment in the study, (ii) clinical presentation of HF at first HF hospitalization, and (iii) clinical management of HF during the initial HF admission.

Methods

Study population

The design, protocol, and results of the MADIT-CRT study have been published previously.[2,3] Briefly, 1820 patients with ischaemic cardiomyopathy [New York Heart Association (NYHA) functional class I or II] or non-ischaemic cardiomyopathy (NYHA functional class II only), LVEF of less than 30%, and a QRS duration >130 ms were randomized to receive CRT-D or ICD therapy in a 3:2 ratio. All eligible patients met the guideline criteria for ICD.[4] Patients were excluded if they had an indication for CRT, implanted pacemaker; NYHA III/IV class in the past 90 days; or coronary artery bypass graft surgery, percutaneous coronary intervention or myocardial infarction within the past 90 days. A total of 110 hospital centres from North America and Europe participated in this international multicenter trial. The study was in compliance with the Declaration of Helsinki, and all enrolling sites had the protocol approved by the local institutional review board. All patients provided informed consent before enrolment. The present study sample comprised of 1820 patients enrolled in MADIT-CRT. Analyses were performed on an intention-to-treat basis.

Data acquisition and follow-up

The MADIT-CRT trial was carried out from 22 December 2004 to September 2010. After the device implantation, patients had an ambulatory follow-up at 1 month and every 3 months thereafter until the termination of the trial. The mean follow-up of enrolled patients was 40 ± 28 months. All patients had clinical evaluation at each follow-up visit or at any meaningful clinical event.

Endpoints and definitions

The primary endpoint of the study was the occurrence of a recurrent HF admission (HF2) after the first post-enrolment HF admission (HF1).

The diagnosis of an HF admission was made by physicians aware of the implanted devices and required signs and symptoms consistent with congestive HF that were responsive to intravenous decongestive therapy or an augmented decongestive regimen with oral or parenteral medications during an in-hospital stay. An independent committee blinded to assigned treatment arm or other clinical information carried

out adjudication of the HF hospitalization events. Data for patients who experienced recurrent HF admissions within 2 weeks of an initial HF admission were further reviewed to distinguish ongoing HF events from new recurrent HF events. Ongoing HF events were classified as a hospitalization that occurred within 2 weeks of a prior HF admission in which the patient continued to experience HF symptoms at hospital discharge or after outpatient intravenous diuretic therapy. New recurrent HF events were defined as events occurring at any time after a prior HF event in which the patient was considered to be fully stabilized at hospital discharge or after outpatient intravenous therapy.

Echocardiography methods

Echocardiography images were captured at baseline and 1 year according to a pre-specified protocol. Recordings were analysed offline at an independent echocardiography core laboratory in a blinded fashion. Left ventricular (LV) volumes were measured by Simpson's disk method in the apical 4-chamber and 2-chamber views, and LVEF was calculated according to the established American Society of Echocardiography protocols.

When analysing echocardiographic response to CRT-D and risk of recurrent HF events, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume, and left atrial volume percent changes at 1 year were assessed. Reverse remodelling effect was defined as percent reduction in LVEDV, left ventricular end-systolic volume, and left atrial volume between enrolment and 1 year echocardiogram (calculated as the difference between 1 year and baseline volumes, divided by baseline volume).

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the pre-specified subgroups of patients with or without HF2 after the first HF hospitalization event, using Kruskal–Wallis test for continuous variables, and chi-squared test or Fisher's exact test for dichotomous variables, as appropriate.

Cumulative probability of recurrent HF2 by subgroups was displayed according to the Kaplan–Meier method, with comparisons of cumulative event rates by the log-rank test.

Multivariate Cox proportional hazards regression analysis was used to identify predictors for recurrent HF hospitalization events after the first HF admission. The Cox model was adjusted for relevant clinical covariates using best subset regression modelling. Candidate covariates included baseline parameters that showed univariate differences among the subgroups, clinical presentation at first HF hospital admission,

Figure 1 Cumulative probability of recurrent heart failure hospitalization after first heart failure admission.
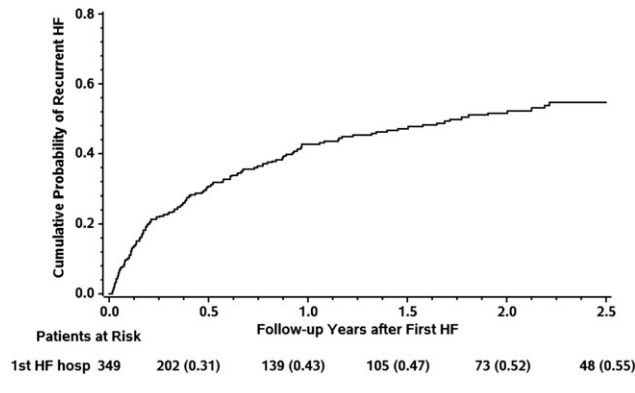
and management during first HF admission (mechanical respirator support and mechanical cardiac support). Treatment arm (CRT-D vs. ICD) was forced in the models using intention-to-treatment assignment.

All statistical tests were two sided, and a *P*-value of <0.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.4, SAS Institute, Cary, NC, USA).

Results

Of the 1820 patients, 193 patients (10.6 %) had HF1, and 156 patients (8.6 %) presented with HF2. There were 31% of patients experiencing recurrent admissions within 6 months: the recurrent HF rate was 43% at 1 year, 52% at 2 years, and 55% at 2.5 years (*Figure 1*).

Table 1 Baseline clinical characteristics of patients by the presence of recurrent heart failure hospitalization after the first heart failure admission

Clinical characteristic	No recurrent HF (*N* = 193)	Recurrent HF (*N* = 156)	*P*-value
Baseline demographics			
Female (*n*, %)	41 (21)	30 (19)	0.642
CRT-D (*n*, %)	95 (49)	75 (48)	0.831
Age at enrolment (years)	67.3 ± 9.9	65.1 ± 11.5	0.062
Ischaemic aetiology (*n*, %)	132 (68)	95 (61)	0.144
QRS duration (ms)	156.7 ± 19.9	156.6 ± 22.0	0.764
LBBB (*n*, %)	123 (64)	100 (65)	0.879
RBBB (*n*, %)	21 (11)	21 (14)	0.448
IVCD (*n*, %)	48 (25)	34 (22)	0.521
Heart rate (bpm)	67.2 ± 10.7	68.8 ± 11.1	0.123
SBP (mmHg)	121.7 ± 16.5	120.4 ± 17.8	0.412
DBP (mmHg)	71.0 ± 10.0	70.4 ± 11.3	0.356
Creatinine (mg/dL)	1.26 ± 0.36	1.27 ± 0.37	0.748
BNP level (pg/mL)	207.3 ± 255.9	181.8 ± 174.0	0.963
Worst NYHA >2 before enrolment (*n*, %)	15 (8)	26 (17)	0.010
Medical history			
Hospitalization in prior year (*n*, %)	107 (56)	87 (57)	0.833
Prior HF hospitalization (*n*, %)	74 (40)	82 (54)	0.008
Prior CABG (*n*, %)	78 (40)	51 (33)	0.137
Diabetes (*n*, %)	78 (40)	64 (41)	0.869
Hypertension (*n*, %)	137 (71)	102 (66)	0.342
Prior MI (*n*, %)	104 (56)	77 (50)	0.331
Smoking (*n*, %)	19 (10)	27 (18)	0.041
Past atrial arrhythmias (*n*, %)	33 (17)	25 (16)	0.805
Past ventricular arrhythmias (*n*, %)	15 (8)	16 (10)	0.402
Baseline medical therapy			
ACE inhibitor or ARB (*n*, %)	181 (94)	150 (96)	0.319
Beta-blocker therapy (*n*, %)	177 (92)	142 (91)	0.821
Aldosterone (*n*, %)	47 (24)	61 (39)	0.003
Digitalis (*n*, %)	40 (21)	58 (37)	<0.001
Diuretic (*n*, %)	145 (75)	133 (85)	0.019
Baseline echocardiographic parameters			
LVEF (%)	28.3 ± 3.7	28.3 ± 3.6	0.478
LVEDV (mL)	246.2 ± 60.2	264.9 ± 71.5	0.010
LVESV (mL)	177.5 ± 50.4	191.3 ± 57.4	0.014
LAV (mL)	97.7 ± 22.6	105.6 ± 25.1	0.002

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy with defibrillator; DBP, diastolic blood pressure; HF, heart failure; IVCD, intraventricular conduction delay; LAV, left atrial volume; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; NYHA, New York Heart Association Class; RBBB, right bundle branch block; SBP, systolic blood pressure.

Baseline clinical characteristics

Clinical characteristics of patients with one vs. recurrent HF hospitalizations are listed in *Table 1*. Patients with HF2 more often had prior HF hospitalization (*P* = 0.009) (*Figure 2*) and NYHA class III HF in their history greater than II, three or more months prior to enrolment (*P* = 0.010) than patients with no recurrent HF hospitalization. However, patients with or without recurrent HF hospitalization had similar aetiology of HF (ischaemic vs. non-ischaemic), baseline electrocardiogram morphology (left bundle branch block vs. non-left bundle branch block), gender, or age at enrolment. Importantly, assigned treatment of CRT-D vs. ICD (intention-to-treat) was not different in patients with HF1 or HF2.

A greater proportion of patients with recurrent HF hospitalization were prescribed diuretics (*P* = 0.019), aldosterone antagonists (*P* = 0.003), and digitalis (*P* < 0.001). There were no significant differences in beta-blocker or angiotensin converting enzyme inhibitor/angiotensin receptor blocker usage between the groups, and both medication classes were prescribed in over 90% in the total cohort.

While left ventricular ejection fraction (LVEF) was similar in the two groups, patients with recurrent HF had significantly increased left ventricular end-diastolic, end-systolic, and left atrial volumes at baseline (*P* < 0.05 for all) (*Figure 3* and *Table 1*).

Cardiac resynchronization therapy with defibrillator-induced cardiac reverse remodelling and recurrent HF hospitalization

Although there were no differences in CRT-D vs. ICD treatment between the subgroups, we found a positive relationship between echocardiographic reverse remodelling to CRT-D at 1 year and recurrent HF hospitalizations. Namely, patients

Figure 2 Cumulative probability of recurrent heart failure hospitalization after first heart failure admission by prior heart failure hospitalization before enrolment.
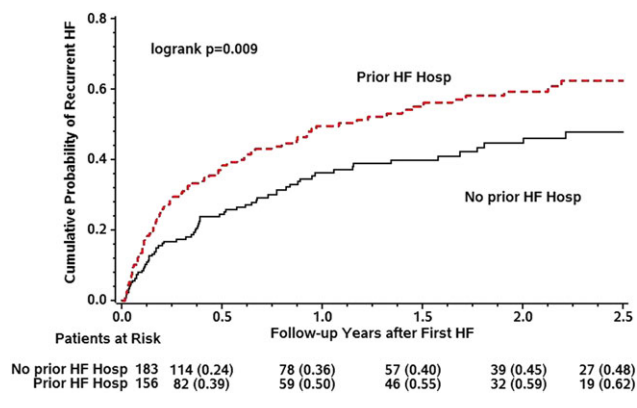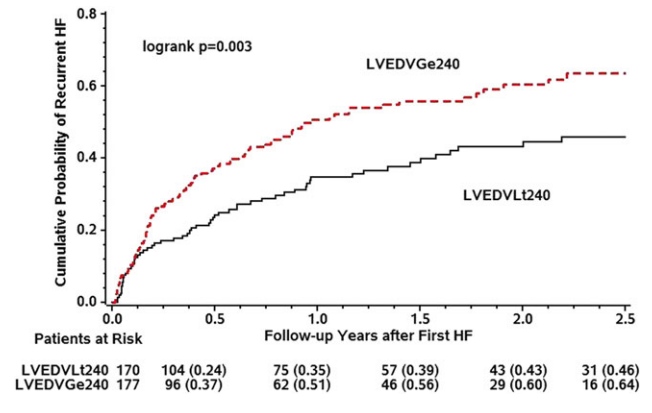

Figure 3 Cumulative probability of recurrent heart failure hospitalization after first heart failure admission by left ventricular end-diastolic volume greater than 240 mL at baseline.

with recurrent HF hospitalizations showed significantly less improvement in LVEF, and reduction in left ventricular end-diastolic, end-systolic volumes, and left atrial volumes, than patients with recurrent HF events (*P* < 0.05 for all) (*Table 2*).

Baseline clinical parameters predicting recurrent HF hospitalization

Multivariate analysis demonstrated that patients with HF hospitalization prior to enrolment had 1.59-fold greater risk of recurrent HF hospitalization (*P* = 0.005). Patients with a LVEDV >240 mL at baseline had a 1.62-fold greater risk for recurrent HF hospitalization (*P* = 0.004) (*Table 3*). Adding medical therapy to the model yielded similar results, and only baseline digitalis improved the predictive accuracy (*Table S1*).

Clinical presentation, medical therapy, and mechanical support at first HF admission and recurrent HF hospitalization

Clinical symptoms at first HF admission, orthopnea, or paroxysmal nocturnal dyspnoea were not associated with an increased risk for recurrent HF admission. Weight before or

Table 2 Echocardiographic changes at 12 months after device implantation in the CRT-D arm (efficacy analysis) by the presence of subsequent HF hospitalization after the first HF admission

Echocardiographic change	N	No recurrent HF	Recurrent HF	P-value
LVEF change	94	9.5 ± 4.7	6.7 ± 5.1	0.008
LVEDV percent change	94	−16.8 ± 9.0	−12.6 ± 10.0	0.025
LVESV percent change	94	−27.4 ± 13.2	−20.1 ± 15.1	0.015
LAV percent change	94	−24.4 ± 13.6	−20.3 ± 11.5	0.143

HF, heart failure; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

Table 3 Predictors for recurrent heart failure hospitalization considering baseline parameters, and clinical presentation and management of patients at first heart failure hospitalization

Patients/events: 337/152	Hazard ratio	95% confidence interval	*P*-value
LVEDV index greater than 240 mL at baseline	1.62	1.17–2.25	0.004
Prior CHF hospitalization before enrolment	1.59	1.15–2.20	0.005

LVEDV, left ventricular end-diastolic volume.
The model was further adjusted for cardiac resynchronization therapy with defibrillator vs. implantable cardioverter defibrillator assigned treatment.

after the admission was not predictive of recurrent HF events. Similarly, findings at hospital admission, including oedema, pulmonary congestion, or rales, were not associated with an increased risk of HF readmission in univariate analyses (*Table 4*).

Furthermore, there was no association between inpatient management during HF1, including the use of intravenous diuretics, need for mechanical cardiac or respiratory support, and the risk for recurrent HF admission (*Table 5*).

Discussion

In this MADIT-CRT sub-study, we have identified important baseline clinical factors, predicting recurrent HF hospitalization. Risk factors at study enrolment included previous HF admission, increased LVEDV index, and digitalis therapy. Interestingly, signs or symptoms at the time of initial HF admission, or medical management during first HF hospitalization, were not predictive for recurrent HF admission.

Despite novel HF therapies, hospital readmission rates remain high[5] and are associated with significant increase in

the risk of all-cause mortality. Therefore, it is essential to identify patients with a high risk for recurrent HF admissions and intensify their follow-up and treatment.

Previous studies have shown baseline patient characteristics to be associated with significant risk of HF readmission, although there is a relative lack of consensus between studies.[6–8] Furthermore, data are scarce on predictors of recurrent HF hospitalization, especially in patients with mild HF and an implanted ICD or CRT-D. The present study therefore provides relevant information for the clinician with important clinical implications.

First, we found that prior HF hospitalization is a strong predictor for recurrent HF hospitalizations. This is consistent with prior studies showing history of a prior HF hospitalization is perhaps the strongest, most consistent risk factor for HF rehospitalization.[9]

Our study also found LVEDV to be a significant predictor of recurrent HF hospitalization. This is in agreement with prior studies showing a higher LVEDV to be associated with worse outcomes in HF patients, including death and HF hospitalization.[10,11] It is likely that increased dilation of the left ventricle correlates with more advanced stages of myocardial

Table 4 Symptoms and clinical presentation at the time of first heart failure hospitalization by the presence of recurrent heart failure hospitalization after the first heart failure admission

Clinical presentation	No recurrent HF	Recurrent HF	*P*-value
Paroxysmal nocturnal dyspnoea (*n*, %)	59 (44)	47 (41)	0.541
Orthopnea (*n*, %)	67 (46)	71 (55)	0.130
Presence of rales at admission (*n*, %)	0.8 ± 0.7	0.8 ± 0.7	0.276
Pulmonary congestion (*n*, %)	1.0 ± 0.9	1.2 ± 0.9	0.190
Oedema (*n*, %)	1.0 ± 1.0	0.9 ± 1.0	0.468
Weight before admission (kg)	87.2 ± 18.1	88.3 ± 19.2	0.876
Weight after admission (kg)	84.0 ± 17.6	82.6 ± 17.4	0.781

HF, heart failure.

Table 5 Medical and mechanical therapy during the first heart failure hospitalization by the presence of recurrent heart failure hospitalization after the first heart failure admission

Medical therapy	No recurrent HF	Recurrent HF	*P*-value
Oral diuretics (*n*, %)	104 (56)	88 (58)	0.757
Iv. diuretics (*n*, %)	171 (92)	142 (92)	0.914
Oral beta-blocker (*n*, %)	40 (22)	30 (20)	0.702
Oral ACE inhibitor (*n*, %)	23 (13)	25 (17)	0.282
Oral ARB (*n*, %)	7 (4)	7 (5)	0.688
Oral aldosterone antagonist (*n*, %)	9 (5)	11 (7)	0.358
Iv. inotrope therapy (*n*, %)	18 (10)	22 (15)	0.199
Mechanical respirator support (*n*, %)	21 (11)	15 (10)	0.699

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Iv., intravenous therapy.

remodelling, and thus with a more tenuous haemodynamic state at baseline and a consequently increased predisposition to recurrent decompensation. Conversely, our study did not show LVEF to be a significant predictor of recurrent HF admission. Indeed, LVEF has only inconsistently been associated with HF outcomes, with only a few studies to our knowledge demonstrating a significant association between lower LVEF and HF re-admission.[11,12]

We also revealed a significant association between baseline digitalis therapy and risk of HF re-admission. Although prior data have shown that digoxin therapy is associated with a decreased risk of HF re-admission in patients in sinus rhythm,[13] it is plausible that in our population of mildly symptomatic HF patients, digitalis treatment serves as a surrogate marker for sicker patients.

Furthermore, we investigated left ventricular reverse remodelling in patients with or without recurrent HF hospitalization. We found that patients implanted with CRT-D presenting with no recurrent HF hospitalization had better echocardiographic reverse remodelling as compared with patients with recurrent HF events. This finding further emphasizes the role of post CRT-D implantation echocardiography in the clinical management of such patients.

Interestingly, in our study, there was no association between presenting signs or symptoms at first HF admission and risk of recurrent re-admission. To our knowledge, there has only been sparse evidence linking such presenting factors to risk of recurrent HF re-admission.[8] One potential explanation for this finding is that the signs and symptoms of a HF exacerbation at the time of hospital presentation, such as dyspnoea, peripheral oedema, and pulmonary rales, tend to be relatively ubiquitous.

While we have previously investigated the role of CRT in first and recurrent HF events in patients enrolled in MADIT-CRT,[1] we did not specifically assess predictors for recurrent HF events. The current study further extends our prior findings and may help guiding the clinician to identify patients at particularly high risk for recurrent HF hospitalization.

Our study was limited primarily by the fact that our population was a composite of patients with two different device therapies, CRT-D and ICD. Thus, the identified risk factors for the population as a whole may not necessarily apply to both treatment arms. Additionally, the relatively small number of patients with a recurrent HF event during the study follow-up period may have resulted in limited statistical power to detect further differences.

Limitations

Our sub-study has some certain limitations: first, as we were focusing on CRT-D induced reverse remodelling and its relation with recurrent HF admissions, patients on ICD arm were excluded from the current analysis. Second, there was brain natriuretic peptide measurement only at index hospitalization at baseline, no cardiac troponin or brain natriuretic peptide levels were detected during the rehospitalization events, which could provide more information about the severity of the event. Third, the concomitant medications were shown only during the first HF events, while changes in medical treatment between the first and second HF events were not specifically analysed in this study because of lack of detailed data.

Conclusions

Clinical presentation at initial HF hospitalization does not predict risk for recurrent HF admission in patients with mild systolic HF and an implanted ICD or CRT-D. Prior HF hospitalization, larger LV volumes, and digitalis therapy at baseline were associated with an increased risk for recurrent HF admissions. Patients implanted with CRT-D presenting with recurrent HF events had less favourable echocardiographic reverse remodelling.

Acknowledgements

Conflict of interest

None declared.

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Supporting information

Supporting information may be found in the online version of this article.

Table S1. Predictors for recurrent HF hospitalization considering baseline parameters, and clinical presentation and management of patients at first HF hospitalization including digitalis therapy at baseline.

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