Published in final edited form as:

Pharmacotherapy. 2018 April ; 38(4): 406–416. doi:10.1002/phar.2091.

Guideline-Directed Medical Therapy and Survival Following Hospitalization in Patients with Heart Failure

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Data from this manuscript have been presented previously:

ACCP 2015 Global Conference, San Francisco, CA, October 17–25, 2015

ACC Scientific Sessions, Chicago, IL, April 2–4, 2016

2016 ACCP Annual Meeting, Hollywood, FL, October 23–26, 2016

Conflict of Interest: Jo E. Rodgers has conflicts to disclose with Novartis (advisory board, research).

Abstract

Background—Modification of guideline-directed medical therapy (GDMT) in hospitalized patients with heart failure (HF) has not been extensively evaluated.

Methods—The community surveillance arm of the Atherosclerosis Risk in Communities Study identified 6959 HF hospitalizations from 2005 to 2011. Predictors of GDMT modification and survival were assessed using multivariable logistic regression and Cox proportional hazards models.

Results—For 5091 hospitalizations, patient mean age was 75 years old, 53% were female, 69% were Caucasian, and 81% had acute decompensated HF (ADHF). Regarding ejection fraction (EF), 31% of patients had HF with reduced EF (HFrEF), 24% had HF with preserved EF (HFpEF), and 44% were missing EF values. At admission, 52% of cases received angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers (ACEI/ARB), 66% β blockers (BB), 9% aldosterone-receptor antagonists, 16% digoxin, 10% hydralazine, and 29% nitrates. Modification of GDMT occurred in up to 23% of hospitalizations. Significant predictors of GDMT initiation included ADHF and HFrEF; discontinuation of medications was observed with select comorbidities. In HFrEF, initiation of any GDMT was associated with reduced 1-year, all-cause mortality (adjusted hazard ratio [HR]: 0.41; 95% confidence interval [CI]: 0.23–0.71) as was initiation of ACEI/ARB, BB, and digoxin. Discontinuation of any therapy versus maintaining GDMT was associated with greater mortality (HR: 1.30; 95% CI: 1.02–1.66). Similar trends were observed in HFpEF.

Conclusions—Our study suggests that GDMT initiation is associated with increased survival and discontinuation of therapy is associated with reduced survival in hospitalized patients with HF. Future studies should be conducted to confirm the impact of GDMT therapy modification in this population.

Keywords

heart failure; predictors; modification; mortality; GDMT

Heart failure (HF) is a chronic disease state that affects 5.8 million Americans (1). Many patients with HF experience at least one episode of acute decompensated HF (ADHF) requiring inpatient care, resulting in more than 1 million hospitalizations annually (2). In the United States, hospitalization for HF has been associated with 20% to 30% 1-year mortality and an annual cost of \$30.7 billion (2–4). Guideline-directed medical therapy (GDMT) is the mainstay of pharmacologic therapy for patients with HF who have reduced ejection fraction (HFrEF) in the absence of any contraindications or intolerance (5, 6). In HFrEF, GDMT includes angiotensin-converting enzyme inhibitors (ACEI) (or angiotensin-receptor blockers (ARB) in ACEI-intolerant patients) and β blockers (BB) in all patients, as well as aldosterone-receptor antagonists (ARA), digoxin, nitrates, and hydralazine in select patients. Unfortunately, no therapy has shown a mortality benefit in patients with HF with preserved ejection fraction (HFpEF) (7).

Few studies have evaluated the frequency of initiating or discontinuing GDMT in hospitalized patients with HF or the effect of GDMT modification on mortality. The most

extensive research conducted in this area to date has been with BB only (8); other studies in other GDMTs have been limited in size and design. Among Medicare beneficiaries (n=3067), BB initiation significantly reduced both short- and long-term mortality in hospitalized Medicare patients with HF (9). Although a small substudy (n=534) observed a reduction in the combined end point of 30-day mortality and HF readmissions with ARA initiation prior to discharge, the Get With the Guidelines Heart Failure Registry (n=5887) found no effect on mortality within 3 years in a subset of patients who received ARAs (10, 11). Digoxin reduced all-cause readmission at both 30 days and 1 year post discharge in patients with HFrEF in the Alabama Heart Failure Project, but not in patients with HFpEF (12). Overall, the potential association of GDMT modification with outcomes has been understudied in hospitalized patients with HFrEF and HFpEF.

The present study utilized abstracted hospital record data from the Atherosclerosis Risk in Communities (ARIC) study community surveillance to investigate the patient characteristics, comorbidities, and exam and laboratory findings that are associated with the initiation or discontinuation of GDMT during hospitalization, as well as the association of GDMT modification with 1-year, all-cause mortality, in hospitalized patients with HF.

METHODS

Study Population

The ARIC study is an ongoing prospective community-based epidemiologic study of cardiovascular disease, conducted since 1987, that is designed to assess risk factors for atherosclerosis and its clinical outcomes. The study has separate prospective cohort and community surveillance components (13). The community surveillance component of the ARIC study conducted continuous and comprehensive retrospective surveillance of hospital discharges for HF since 2005 in Caucasian and African-American men and women, age 55 years and older in four US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Hospitalizations were included in this study if the hospitalization was: (i) due to ADHF (HF as primary diagnosis) or another medical reason with an underlying diagnosis of chronic HF (HF as secondary diagnosis); (ii) the patient was discharged alive but not on hospice; and (iii) information on survival status for 1 year following discharge was available.

Case Identification and Ascertainment

Methods of HF event ascertainment and classification are described previously (14). Briefly, a stratified random sample of hospitalizations from 2005 to 2011 was identified from ARIC community surveillance and were deemed to be eligible for possible abstraction if the patient had any of the following International Classification of Diseases-9th Revision (ICD-9) discharge diagnosis codes in any position: HF (428), rheumatic heart disease (398.91), hypertensive heart disease with congestive HF (402.01, 402.11, 402.91), hypertensive heart disease and renal failure with congestive HF (404.01, 404.03, 404.11, 404.13, 404.91, 404.93), acute cor pulmonale (415.0), chronic pulmonary heart disease, unspecified (416.9), other primary cardiomyopathies (425.4), acute edema of lung, unspecified (518.4), and dyspnea and respiratory abnormalities (786.0). Fully abstracted

cases were independently classified by computer algorithm and/or physicians from the ARIC Mortality and Morbidity Classification Committee. Each abstracted case was classified as ADHF or chronic HF. In addition, based upon current or most recent left ventricular ejection fraction (LVEF), all cases were further classified as HFrEF or HFpEF (LVEF <50% or ≥50%, respectively) or missing LVEF values. Cases with unclassifiable or unlikely HF, hospice discharge, or death during the hospital stay were excluded. Patients may have more than one hospitalization abstracted.

Cases on GDMT were categorized as: “maintain” if the medications were prescribed at any dosage at discharge and either prior to admission or prior to acute decompensation in hospital for in-hospital ADHF events; “initiate” if prescribed only at discharge; “discontinue” if prescribed at admission but not at discharge; or “no therapy” at admission or discharge. These categories were mutually exclusive when defined for individual GDMTs, but not when defined for modification of any therapy. For example, for a patient whose ACEI was initiated and BB was discontinued, these GDMT modifications would be classified as both “initiate” and “discontinue” for the analysis of any therapy. Adherence could not be evaluated, nor was it known if the patient ever picked up the medication at discharge. Vital status after discharge was determined by linkage with the National Death Index.

Statistical Analyses

Patient characteristics and GDMT use were compared using the Pearson χ^2 test for categorical variables and the t-statistic for continuous variables. Logistic regression models were fit to each GDMT to identify the significant predictors of GDMT initiation versus no therapy or GDMT discontinuation versus maintaining therapy, controlling for patient characteristics (age, sex, race, EF, ARIC study site), comorbidities (hypertension, chronic kidney disease [CKD], atrial fibrillation, diabetes, depression, asthma or chronic obstructive pulmonary disease [COPD], coronary heart disease [CHD]), and whether the HF status was acute (ADHF) or chronic. We considered using propensity scores to try to further adjust for possible treatment status selection, but due to the four possible choices (maintain, initiate, discontinue, or no therapy) plus the need to address missing data (discussed below), we chose to simply control for the many potential confounders that were available in the data set. Due to the likelihood of correlation between certain diseases and exam and laboratory values (e.g., serum creatinine and CKD), additional logistic models were estimated to control for exam and laboratory values.

Time to death analyses were performed using Kaplan-Meier survival curves and Cox proportional hazards modeling. Specifically, to examine the overall likelihood of survival across time between therapy categories for cases with HFrEF, Kaplan-Meier survival curves illustrating the estimated 1-year survival probabilities for each GDMT were first constructed (Figures 1–4). Then a Cox proportional hazards model was fit to estimate the adjusted risk of death within 1 year across GDMT categories between HFrEF and HFpEF, controlling for the predictors described above.

Due to the presence of missing values for some of the examined predictors, particularly LVEF, multiple imputation was used for the Kaplan-Meier survival curves and each model

estimation. For each survival curve and model, 50 multiple imputations by chained equations were used (15). Parameter estimates, standard errors, and estimated survival probabilities were pooled across the 50 imputations to obtain the final results. The Appendix describes details of this multiple imputation approach. The Cox model was used for analysis of time to death due to its amenability to the imputation models used for our approach, as opposed to other nonparametric survival models (16). As a sensitivity analysis, Cox model results using multiple imputation were compared to those obtained using a complete case analysis.

All analyses accounted for stratification in our sampling design and the unequal sampling probabilities in selecting each hospitalization. All statistical tests were conducted at the 0.05 significance level, and the Bonferroni correction was used when appropriate for multiple comparisons. SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for all analyses.

RESULTS

The four communities had 15,654 potentially eligible hospitalizations during 2005 to 2011. Hospitalizations with no validated HF diagnosis (unclassifiable or unlikely HF cases, $n=8152$), discharge to hospice ($n=57$), death during hospitalization ($n=486$), and missing vital status ($n=1868$) were excluded. Patient characteristics for the remaining 5091 hospitalizations are shown in Table 1. Overall, the mean age was 75 ± 10.7 years, and 81% of the hospitalizations were for ADHF. Among HFrEF cases, 45% were female, 64% were Caucasian, and the mean LVEF was 30%. Among those with HFpEF, 65% were female, 70% were Caucasian, and the mean LVEF was 58%. As anticipated, those with HFrEF and HFpEF also differed in medical comorbidities, with higher prevalence of hypertension in HFpEF and higher prevalence of CHD in HFrEF. Clinical features of HF and exam and laboratory values also differed by HF type with higher brain natriuretic peptide (BNP), serum creatinine, and troponin and lower blood pressure in HFrEF cases. At admission, HF cases received ACEI/ARB (52% of hospitalizations), BB (66%), ARA (9%), digoxin (16%), hydralazine (10%), and nitrates (29%). As anticipated, use of GDMT was more common in HFrEF cases than in HFpEF at admission. Modification of GDMT occurred in up to 23% of cases. The percentages of all HF cases maintained, initiated, discontinued or on no therapy are presented in Table 2; the percentages by HFrEF, HFpEF, and missing EF values are presented in Appendix Tables 1a–c. In general, rates of medication modification were similar in HFrEF and HFpEF patient populations.

Predictors of GDMT Modification

The fitted logistic models for each GDMT provide odds ratio estimates for the predictors of initiation versus no GDMT (Table 3) and discontinuation versus maintenance of GDMT (Appendix Table 2). Across all GDMT categories, initiation occurred more commonly in hospitalizations for ADHF than hospitalizations with chronic HF; initiation was also more common in HFrEF compared to HFpEF. In addition, selected comorbidities were associated with less initiation of GDMT. For example, ACEI/ARB were less likely to be initiated for hospitalizations with a diagnosis of CKD, asthma or COPD, and atrial fibrillation. A history of asthma or COPD was associated with a lower rate of BB initiation. Likewise, digoxin was

less likely to be initiated for those with CKD and diabetes but more likely to be initiated in those with atrial fibrillation. Whereas hydralazine and nitrates were each more likely to be initiated for those with CHD, only hydralazine was commonly initiated for those with hypertension. Similarly, GDMT discontinuation tended to correspond inversely with reasons for initiation (e.g., discontinuation of ACEI/ARB occurred more commonly for those with CKD). When specific vital signs and laboratory values were used instead of the corresponding comorbidity category, such as blood pressure and hypertension, results were similar (Appendix Tables 3–4).

GDMT Modification and Mortality

The survival probability curves for a hospitalized patient with HFrEF initiated, maintained, discontinued, or receiving no therapy for any GDMT, ACEI/ARB, BB, and digoxin are shown in Figures 1–4. Among those with HFrEF, cases that initiated any GDMT therapy had a reduced risk (hazard) of death, relative to those with no therapy (adjusted hazard ratio [HR]: 0.41; 95% confidence interval [CI]: 0.23–0.71). In addition, the initiation of ACEI/ARB (HR: 0.63; 95% CI: 0.44–0.92), BB (HR: 0.52; 95% CI: 0.35–0.79), and digoxin (HR: 0.56; 95% CI: 0.31–0.99) had a reduced risk of death, relative to cases with no therapy. In contrast, discontinuation of any GDMT therapy (HR: 1.30; 95% CI: 1.02–1.66) was associated with an increased risk of death, relative to maintaining any GDMT therapy. Those initiated on ARA, nitrates, and hydralazine had a lower risk of mortality, relative to those with no therapy. Discontinuation of any therapy increased the risk of mortality, relative to maintaining these therapies. In cases with HFpEF, the initiation of ACEI/ARB (HR: 0.54; 95% CI: 0.31–0.94) was associated with a reduced risk of death, compared with using no therapy. In contrast, HFpEF cases discontinuing ACEI/ARB (HR: 1.81; 95% CI: 1.25–2.61) and BB (HR: 1.52; 95% CI: 1.02–2.28) were associated with an increased risk of death, relative to maintaining the respective therapies (Table 4).

DISCUSSION

This study demonstrates that up to a quarter of hospitalized patients with HF may undergo GDMT modification. In this comprehensive analysis of GDMT, initiation of any GDMT at discharge in hospitalizations with HFrEF was associated with a substantially lower risk of mortality. Individual assessment of initiation of ACEI/ARB, BB, and digoxin also demonstrated significant reductions in mortality, whereas initiation of ARA, nitrates, and hydralazine only trended towards a reduction in mortality likely due to small sample size. Similarly, discontinuation of any GDMT was associated with a significant increase in mortality.

Putting these findings in context, existing evidence on the effects of GDMT modification and mortality in hospitalized patients with HF is limited to BB and ACEI/ARB only. A prospective, randomized trial found hospitalized patients with HF randomized to continuing BB experienced greater dyspnea improvement and overall well-being compared to patients discontinuing therapy (17). A retrospective study assessed the impact of both initiation and discontinuation of BB in hospitalized patients with HF. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) database

found that patients recently initiated on a BB had a significant reduction in all-cause mortality and rehospitalization rates (HR: 0.61; 95% CI: 0.44–0.83, $p=0.002$) compared to those who were not treated (8). In addition, a meta-analysis ($n=7319$ patients) including these two studies along with two additional small observational studies from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations (OPTIME) in chronic HF and Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trials demonstrated an increased risk for combined short-term rehospitalization or death when BB was discontinued in patients with ADHF (relative risk [RR]: 1.59; 95% CI: 1.03–2.45) (18). Finally, a recently published analysis using the Get with the Guidelines-Heart Failure Registry ($n=16,052$ patients) found that compared with continuation, withdrawal of ACEI/ARB during HF hospitalization was associated with higher rates of postdischarge mortality and readmission (19).

Although our findings suggest a reduction in mortality with digoxin initiation, this estimated observational association differs from that of the Digitalis Investigation Group (DIG) Trial (20), which showed digoxin only reduced the rate of hospitalization, but not mortality, in patients with HF. Other clinical analyses have demonstrated mortality benefit with digoxin when it is dosed to achieve lower serum digoxin concentrations (SDCs), 0.5 to 0.9 ng/mL (21). Our analysis was performed in a time period (2005–2011) when prescribers likely were dosing digoxin to maintain lower serum concentrations. In addition, we adjusted for predictors of higher SDC including age, gender, body weight, and serum creatinine. Regarding the lack of benefit with ARA initiation, small sample size may have contributed to lack of a significant finding; however, the direction of association suggests benefit. Moreover, although ARAs have demonstrated benefit in patients with New York Heart Association (NYHA) class III-IV HF in the Randomized Aldactone Evaluation Study (RALES) trial, this study was in a stable community-based population (22). The efficacy and, perhaps more importantly, safety of ARAs in patients with ADHF has not been assessed. Similarly, findings with hydralazine/isosorbide dinitrate in patients with HF were limited by small sample size, which precluded a subanalysis of African Americans alone.

Our study suggests that up to a quarter of HF hospitalizations may have GDMT modification, and modification is predicted by disease acuity and selected comorbidities. Although the observational nature of this study risks potential confounding by indication (e.g., discontinuation may be appropriate in a patient with extremely poor prognosis), the potential impact of GDMT modification on patient outcomes is substantial. These findings from ARIC community surveillance provide new insights into the frequency and predictors of GDMT modification and the association between GDMT modification and mortality among hospitalized HF patients.

In addition to expanding the evidence supporting use of GDMT for hospitalized patients with HF, our findings further strengthen current evidence for GDMT use by assessing a diverse community of patients. For instance, our study population is of older age with larger representation of African Americans, greater disease severity, and more frequent comorbidities compared to the hospitalized patients in the OPTIMIZE-HF Registry (23). Beyond demonstrating benefit for patients with HFrEF, hospitalized patients with HFpEF may potentially benefit from select GDMT despite no data to support use of these therapies

in ambulatory patients with HFpEF. Hospitalized patients with HFpEF may differ from ambulatory patients with HFpEF such that they derive benefit from GDMT, whereas ambulatory patients with HFpEF do not. Although the underlying mechanism for this difference is not clear, hospitalized patients may experience greater neurohormonal activation warranting intervention with GDMT and may have more comorbid conditions that also benefit from these same therapies.

This study was unique as it assessed predictors of initiating or discontinuing GDMT in hospitalized patients with HF. Patients hospitalized for ADHF were more likely to be initiated on any GDMT relative to those hospitalized for other reasons with chronic HF as a comorbid condition. This finding may indicate that during hospitalizations, providers focus on appropriately managing acute conditions and defer chronic conditions to ambulatory care providers. Although this tendency to focus only on acute illnesses may be suitable when patients are already receiving optimal HF therapy, hospital stays may in many cases present an opportune time to initiate appropriate GDMT in patients who are not receiving optimal therapy for HF. Several studies have reported improved outcomes in hospitalized patients with HF who were initiated on select GDMT (10–12). Furthermore, many patients may not be receiving an optimal GDMT regimen based on current HF guidelines. Another recent subanalysis of the Get With the Guidelines-Heart Failure Registry observed that among patients hospitalized with HF, nearly half warranted starting at least one new HF-related medication at discharge to comply with current guidelines for optimal therapy. Additionally, 25% of patients warranted more than one new HF medication and at least one out of every ten merited at least three or more medications (24).

Our study suggests that patients with HFrEF were more likely to be initiated on GDMT compared to those with HFpEF. This finding is not surprising considering the lack of evidence supporting GDMT in patients with HFpEF (7). A retrospective analysis of elderly patients with HFpEF enrolled in the OPTIMIZE-HF study reported no improvement in mortality or rehospitalization with newly started BB therapy (25). With the exception of OPTIMIZE-HF, no other trial has assessed modification of GDMT in either the HFrEF or HFpEF populations. In addition, our findings suggest that select comorbidities serve as a reason for discontinuing GDMT in hospitalized patients with HF. For instance, patients presenting with worsening renal function or established CKD may require discontinuation of ACEI/ARB for concerns of hyperkalemia. However, in the absence of contraindications, GDMT should be continued during hospitalization or initiated/re-initiated once the patient is stable prior to discharge.

Study Limitations

Use of GDMT based on observational data for hospitalized patients in four community settings was low relative to findings from prospective HF clinical trials as well as the Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) registry (26). In addition, the rationale for initiating, maintaining, or discontinuing therapy during hospitalization was not collected in ARIC community surveillance. Bias in the estimates could result from confounding by indication or unobserved variables. Despite covariate adjustment, the improvements in mortality

associated with the initiation of GDMT may have been influenced by unobserved associations with both GDMT modification and survival. For example, both HF Stage and NYHA class were not available and these variables could not be controlled for in the model. In particular, medications may have been discontinued for patients with very poor prognosis even though they were not discharged directly to hospice, which would cause an overestimation of the effect for discontinuation. Likewise, those with an expected survival of greater than 1 year may have been more likely to initiate therapy due to the time to benefit for GDMT, which would inflate the benefit of initiation.

Furthermore, the abstraction process only recorded medication uses at two time points during the hospital stay: approximately at admission and at discharge. The follow-up period of 1 year was limited to ascertaining mortality events. Adherence and tolerability were not assessed, and patients discharged without GDMT may have started therapy post discharge. It has been proposed that early follow-up of patients after hospitalization can reduce readmissions rates and subsequently, morbidity and mortality. A study among Medicare beneficiaries hospitalized for HF observed a significant relationship between early follow-up and a reduction in 30-day readmission rates (27). However, a substantial amount of variation existed in rates of early follow-up between institutions. Discontinuation of therapy due to intolerance or lack of adherence to therapy post discharge would bias the effect size toward the null, meaning these results underestimate the effect if these occurred. The limitations inherent within our registry resonate with the conclusions from a recent study that reviewed hospitalized HF registries and concluded that there is a significant need to standardize the data collected in future registry studies (28). Most notably, the prevalence of inpatient therapies is frequently characterized but less is known about the route, dose, duration, and modifications made to therapies throughout hospitalization and post discharge. In this study, we note that a clinically significant portion of patients have modification of GDMT during hospitalization, however, rationale for these changes was not recorded. Future studies should query this information as part of data collection (28).

Given the considerable percentage of missing EF values, limiting the analysis to those with complete case analysis may introduce bias; thus, multiple imputation was utilized. Our sample of HF cases with missing EF values had some characteristics similar to the known HFrEF cases and other characteristics similar to the known HFpEF cases. Results from complete case analysis were similar in magnitude but less likely to be statistically significant when these 2262 cases with missing data were excluded (Appendix Table 5).

Due to the retrospective and observational nature of the data, causality should not be implied or assumed. The findings presented here identify the associations between therapy modification and mortality while adjusting for patient characteristics. Finally, the results we report may not be generalizable to a population that differs in patient characteristics from the four communities of the ARIC study.

CONCLUSIONS

Data from this cohort of hospitalized patients with HF suggest that the initiation and maintenance of GDMT during hospitalization is associated with improved outcomes,

whereas discontinuation and lack of initiation are associated with worsened outcomes. Despite the well-established role of GDMT for chronic HF management, many patients with HF require hospitalization. Given this is an observational, nonrandomized, hypothesis-generating study, additional research is warranted to determine if patients with HF should continue or be initiated on GDMT to improve long-term outcomes.

Acknowledgments

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors thank the staff and participants of the ARIC study for their important contribution.

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Figure 1.
Survival Probabilities at 1 Year for a Hospitalized Patient with HFrEF on Any Therapy
(n=2,757)

Figure 2.
Survival Probabilities at 1 Year for a Hospitalized Patient with HFrEF on ACEI/ARB
(n=2,704)

Figure 3.
Survival Probabilities at 1 Year for a Hospitalized Patient with HFrEF on β Blockers
(n=2,616)

Figure 4.
Survival Probabilities at 1 Year for a Hospitalized Patient with HFrEF on Digoxin (n=2,578)
^aHFrEF=Heart failure with reduced ejection fraction, ACEI/ARB = angiotensin-converting enzyme inhibitor and/or receptor blocker

Characteristics of Validated Hospitalized Heart Failure Cases: Atherosclerosis Risk in Communities Heart Failure Community Surveillance 2005–2011

Table 1

Characteristic	All (n=5091)	HF+EF (n=1585)	HFpEF (n=1244)	Missing EF (n=2262)	p-value ^a
Age – Years	75 (0.11)	74 (0.28)	76 (0.31)	75 (0.21)	<0.001
Female Sex	53%	45%	65%	52%	<0.001
Race or Ethnic Group					
Caucasian	69%	64%	70%	72%	<0.001
African American	28%	33%	27%	25%	<0.001
Other	4%	4%	3%	4%	0.66
Clinical Features of Heart Failure					
LVEF % ^b	43	30	58	-	<0.001
BNP (pg/mL) ^c	1242 (39)	1598 (100)	866 (38)	1,197 (47)	-
Pro-BNP (pg/mL) ^c	9674 (577)	12,801 (1008)	7315 (798)	9421 (1028)	-
ADHF	81%	88%	90%	72%	0.15
Exam/Laboratory Values					
Blood Pressure (mmHg) ^d	141 (0.5)	139 (1.0)	148 (1.1)	138 (0.8)	<0.001
Heart Rate (bpm) ^d	88 (0.4)	92 (0.8)	87 (0.8)	87 (0.5)	<0.001
BUN (mg/dL) ^c	40 (0.4)	40 (0.74)	38 (0.75)	40 (0.6)	0.08
Serum Creatinine (mg/dL) ^c	2.1 (0.03)	2.1 (0.05)	2.02 (0.05)	2.14 (0.04)	0.28
Hemoglobin (g/dL) ^b	11 (0.03)	11 (0.07)	11 (0.07)	11 (0.05)	<0.001
Sodium (mEq/L) ^b	136 (0.08)	136 (0.13)	136 (0.14)	136 (0.13)	0.06
Troponin T (ng/mL) ^c	0.19 (0.03)	0.30 (0.06)	0.13 (0.05)	0.15 (0.06)	-
Medical Comorbidities					
Hypertension	84%	81%	87%	84%	<0.001
Coronary Heart Disease	67%	71%	56%	69%	<0.001
Chronic Kidney Disease	69%	65%	68%	71%	0.13
Diabetes	48%	46%	46%	50%	0.96
Asthma/COPD	36%	27%	33%	43%	0.003

Characteristic	All (n=5091)	HFrEF (n=1585)	HFpEF (n=1244)	Missing EF (n=2262)	p-value ^a
Treatments at Admission					
Atrial Fibrillation	38%	33%	37%	42%	0.04
Diuretic	71%	64%	67%	77%	0.15
ACEI/ARB	52%	54%	49%	53%	0.04
BB	66%	64%	63%	69%	0.48
ARA	9%	11%	5%	10%	<0.001
Digoxin	16%	16%	11%	19%	0.003
Hydralazine	10%	8%	9%	11%	0.37
Nitrates	29%	29%	22%	34%	<0.001

Data presented as mean (standard error) or percent unless otherwise indicated;

^a p-value for the comparison of HFrEF versus HFpEF

ACEI/ARB = angiotensin-converting enzyme inhibitor and/or receptor blocker, ADHF = acute decompensated heart failure, ARA = aldosterone-receptor antagonist, BB = β blocker, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, COPD = chronic obstructive pulmonary disease, EF = ejection fraction, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, LVEF = left ventricular ejection fraction, pro-BNP = N-terminal pro b-type natriuretic peptide

^b Worst value: lowest value obtained during hospitalization;

^c Worst value: highest value obtained during hospitalization;

^d Value obtained on admission

Table 2
Guideline-Directed Medical Therapy Modification of All Heart Failure Cases (n=5091)

	Any ^a	Diuretic	ACEI/ARB	BB	ARA	Digoxin	Hydralazine	Nitrate
Initiate	13%	13%	12%	12%	4%	5%	4%	9%
Maintain	70%	62%	42%	60%	7%	12%	7%	25%
Discontinue	23%	9%	10%	6%	2%	4%	3%	5%
No Therapy	6%	16%	36%	22%	87%	79%	86%	61%

^aGuideline directed medical therapy modification is not mutually exclusive for “Any”. Percentages for the “Any” column were created without adjustment for the sampling weights, other columns were created with adjustment for sampling weights and have been rounded to 100.

ACEI/ARB = angiotensin-converting enzyme inhibitor and/or receptor blocker, ARA = aldosterone-receptor antagonist, BB = β blocker

Table 3

Predictors of Initiating Guideline-Directed Medical Therapy Based on Heart Failure Characteristics and Common Comorbidities for Cases Not on Therapy at Admission

Predictor	ACEI/ARB n=2404	BB n=1781	ARA n=4630	Digoxin n=4303	Hydralazine n=4543	Nitrates n=3584
ADHF versus Chronic HF	2.18 (1.54–3.08)	2.78 (1.92–4.00)	1.88 (1.08–3.28)	2.06 (1.30–3.28)	2.17 (1.31–3.61)	2.39 (1.63–3.50)
HFpEF versus HFpEF	2.44 (1.80–3.31)	2.97 (2.19–4.04)	2.35 (1.51–3.65)	3.38 (2.21–5.15)	1.79 (1.16–2.76)	1.51 (1.11–2.05)
Hypertension	1.23 (0.92–1.64)	1.23 (0.90–1.69)	1.06 (0.68–1.64)	0.69 (0.46–1.03)	2.32 (1.38–3.89)	0.97 (0.69–1.37)
Coronary Heart Disease	0.90 (0.71–1.15)	0.88 (0.68–1.14)	1.33 (0.93–1.91)	0.79 (0.57–1.08)	1.44 (1.03–2.03)	2.26 (1.74–2.95)
Chronic Kidney Disease	0.53 (0.41–0.67)	0.87 (0.67–1.14)	0.77 (0.54–1.09)	0.62 (0.44–0.89)	2.52 (1.67–3.79)	1.31 (1.00–1.72)
Diabetes	0.85 (0.66–1.08)	1.01 (0.78–1.32)	0.67 (0.47–0.95)	0.53 (0.37–0.74)	0.94 (0.68–1.31)	1.17 (0.92–1.49)
Asthma/COPD	0.73 (0.57–0.94)	0.65 (0.51–0.85)	0.79 (0.56–1.12)	1.04 (0.76–1.44)	1.02 (0.72–1.44)	0.98 (0.77–1.26)
Atrial Fibrillation	0.69 (0.54–0.89)	0.83 (0.63–1.09)	0.88 (0.62–1.26)	3.35 (2.45–4.58)	1.00 (0.69–1.45)	0.82 (0.63–1.06)
Depression	0.69 (0.49–0.98)	0.79 (0.57–1.11)	0.52 (0.31–0.89)	0.82 (0.51–1.34)	1.38 (0.88–2.18)	0.86 (0.62–1.21)

Data are presented as odds ratio (95% CI)

ACEI/ARB = angiotensin-converting enzyme inhibitor and/or receptor blocker, ADHF = acute decompensated heart failure, ARA = aldosterone-receptor antagonist, BB = β blocker, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HFpEF = heart failure with preserved ejection fraction, HFpEF = heart failure with reduced ejection fraction, OR = odds ratio

Table 4
Association of Guideline Directed Medical Therapy Modification with Time to Death (n=5091)

	HFrEF		HFpEF	
	Initiate versus No Therapy	Discontinue versus Maintain	Initiate versus No Therapy	Discontinue versus Maintain
Any	0.41 (0.23–0.71)	1.30 (1.02–1.66)	0.70 (0.46–1.06)	1.24 (0.83–1.85)
ACEI/ARB	0.63 (0.44–0.92)	1.30 (0.83–2.03)	0.54 (0.31–0.94)	1.81 (1.25–2.61)
BB	0.52 (0.35–0.79)	1.45 (0.73–2.91)	0.94 (0.57–1.55)	1.52 (1.02–2.28)
ARA	0.66 (0.37–1.16)	1.62 (0.70–3.71)	0.89 (0.51–1.54)	1.25 (0.64–2.44)
Digoxin	0.56 (0.31–0.99)	0.70 (0.33–1.49)	0.91 (0.52–1.62)	1.37 (0.81–2.30)
Nitrates	0.81 (0.50–1.32)	0.80 (0.42–1.53)	1.04 (0.71–1.53)	1.22 (0.77–1.95)
Hydralazine	0.97 (0.55–1.71)	1.38 (0.44–4.37)	1.25 (0.76–2.04)	1.65 (0.95–2.89)

Data are presented as hazard ratio (95% CI)

ACEI/ARB = angiotensin-converting enzyme inhibitor and/or receptor blocker, ARA = aldosterone-receptor antagonist, BB = β blocker, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction

Models were adjusted for age, sex, ejection fraction, field center, comorbidities and heart failure status (acute decompensated heart failure or chronic)