Heart failure medications prescribed at discharge for patients with left ventricular assist devices

Jacqueline Baras Shreibati, MD,[a] Shubin Sheng, PhD,[b] Gregg C. Fonarow, MD,[c] Adam D. DeVore, MD,[b] Clyde W. Yancy, MD,[d] Deepak L. Bhatt, MD,[e] Phillip Schulte, PhD,[f] Eric D. Peterson, MD,[b] Adrian Hernandez, MD,[b] and Paul A. Heidenreich, MD[a] *Stanford, Los Angeles, CA; Durham, NC; Chicago, IL; Boston, MA; and Rochester, MN*

Background Real-world use of traditional heart failure (HF) medications for patients with left ventricular assist devices (LVADs) is not well known.

Methods We conducted a retrospective, observational analysis of 1,887 advanced HF patients with and without LVADs from 32 LVAD hospitals participating in the Get With The Guidelines–Heart Failure registry from January 2009 to March 2015. We examined HF medication prescription at discharge, temporal trends, and predictors of prescription among patients with an in-hospital (n = 258) or prior (n = 171) LVAD implant, and those with advanced HF but no LVAD, as defined by a left ventricular ejection fraction ≤25% and in-hospital receipt of intravenous inotropes or vasopressin receptor antagonists (n = 1,458).

Results For β-blocker and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB), discharge prescriptions were 58.9% and 53.5% for new LVAD patients, 53.8% and 42.9% for prior LVAD patients, and 73.4% and 63.2% for patients without LVAD support, respectively (both $P < .0001$). Aldosterone antagonist prescription quadrupled among LVAD patients during the study period ($P < .0001$), whereas ACEI/ARB use decreased nearly 20 percentage points (60.0% to 41.4%, $P = .0003$). In the multivariable analysis of LVAD patients, patient age was inversely associated with β-blocker, ACEI/ARB, and aldosterone antagonist prescription.

Conclusions Traditional HF therapies were moderately prescribed at discharge to patients with LVADs and were more frequently prescribed to patients with advanced HF without LVAD support. Moderate prescription rates suggest clinical uncertainty in the use of antiadrenergic medication in this population. Further research is needed on the optimal medical regimen for patients with LVADs. (Am Heart J 2016;179:99-106.)

Left ventricular assist devices (LVADs) are an increasingly common long-term treatment for end-stage systolic heart failure (HF).[1] More than 1,000 devices were implanted as long-term, destination therapy in the United States (US) in 2014.[2] Meanwhile, patients with bridge-to-transplant LVADs receive a median 8.7 months of device support before heart transplantation.[3] The longitudinal success of the LVAD patient may depend on medications to maintain the device, such as antithrombotic agents to prevent pump thrombosis and antihypertensives to reduce risk of stroke.[4–8] Traditional, evidence-based HF medications that promote reverse remodeling in the native heart—such as β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone antagonists—may also be of importance, but in fact, little is known as to what constitutes optimal HF medical therapy in patients with LVADs. To date, there are no prospective trials supporting use or target dosing of outpatient HF-specific therapies in patients with mechanical circulatory support.

Given the lack of data to guide HF medication management in LVAD patients, further understanding of use in real-world practice is of interest. Such data can highlight where research is direly needed for the long-term care of patients with LVADs. Accordingly, we sought to characterize patterns of HF medication prescription using a national, contemporary registry of

From the [a]Stanford University, Stanford, CA, [b]Duke University, Durham, NC, [c]Ronald Reagan-UCLA Medical Center, Los Angeles, CA, [d]Northwestern University, Chicago, IL, [e]Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, and [f]Mayo Clinic, Rochester, MN.

Javed Butler, MD, MPH, served as guest editor for this article.
Submitted February 23, 2016; accepted June 21, 2016.

Reprint requests: Jacqueline Baras Shreibati, MD, Redwood Bldg, T150A, Stanford, CA 94305-5405.
E-mail: jbaras@stanford.edu

0002-8703

http://dx.doi.org/10.1016/j.ahj.2016.06.011

Table I. Selected patient characteristics

Patient characteristics	Overall (N = 1887)	New LVAD (n = 258)	Prior LVAD (n = 171)	Advanced HF (no LVAD) (n = 1458)	*P* value
Age (y), median (IQR)	60 (50-69)	59 (48-66)	59 (51-67)	60 (50-70)	.0274
Age ≥65 y	706 (37.4)	84 (32.6)	58 (33.9)	564 (38.7)	.11
Male (%)	1345 (71.3)	200 (77.5)	119 (69.6)	1026 (70.4)	.0570
Race/ethnicity (%)					
White	1013 (54.6)	169 (65.8)	106 (62.0)	738 (51.7)	<.0001
African American	685 (37.0)	65 (25.3)	41 (24.0)	579 (40.6)	
Hispanic	80 (4.3)	11 (4.3)	15 (8.8)	54 (3.8)	
Asian	20 (1.1)	1 (0.3)	2 (1.2)	17 (1.2)	
Other	56 (3.0)	11 (4.3)	7 (4.0)	38 (2.7)	
Selected medical history					
Anemia	312 (17.0)	39 (15.1)	42 (24.5)	231 (16.4)	.0185
Atrial fibrillation	632 (34.3)	97 (37.6)	68 (39.8)	467 (33.1)	.11
Atrial flutter	108 (5.9)	14 (5.4)	15 (8.8)	79 (5.6)	.24
COPD or asthma	435 (23.6)	52 (20.2)	51 (29.8)	332 (23.5)	.07
CRT-D	593 (32.2)	107 (41.5)	60 (35.1)	426 (30.2)	.0012
CVA/TIA	267 (14.5)	29 (11.2)	28 (16.4)	210 (14.9)	.24
Diabetes	720 (39.1)	107 (41.5)	70 (40.9)	543 (38.5)	.58
ICD only	713 (38.7)	111 (43.0)	83 (48.5)	519 (36.8)	.0037
Ischemic etiology of HF	994 (54.0)	130 (50.4)	103 (60.2)	761 (53.9)	.13
Renal insufficiency	461 (25.0)	54 (20.9)	39 (22.8)	368 (26.1)	.17
Smoking	352 (19.3)	35 (13.6)	23 (14.5)	294 (20.8)	.0076
Selected medications before admission					
β-Blocker	1046 (69.1)	117 (65.4)	53 (60.2)	876 (70.3)	.0750
ACEI	668 (44.1)	88 (49.2)	39 (44.3)	541 (43.4)	.35
ARB	218 (14.4)	31 (17.3)	10 (11.4)	177 (14.2)	.38
Aldosterone antagonist	571 (37.7)	91 (50.8)	36 (40.9)	444 (35.6)	.0004
Hydralazine	238 (15.7)	29 (16.2)	18 (20.4)	191 (15.3)	.43
Nitrate	281 (18.5)	35 (20.1)	7 (7.9)	238 (19.1)	.0294
Intravenous medications in-hospital					
Inotropes	1645 (91.4)	173 (74.9)	25 (22.5)	1447 (99.2)	<.0001
Vasopressin receptor antagonist	194 (10.8)	68 (29.4)	11 (9.9)	115 (7.9)	<.0001
Vital signs or laboratory tests at admission, median (IQR)					
BMI (kg/m^2)	26.4 (24.1-30.1)	26.4 F (24.5-29.0)	27.0 (26.5-30.5)	26.4 (23.8-30.3)	.0129
Heart rate (beat/min)	88 (76-102)	88 (77-100)	88 (77-99)	88 (76-102)	.84
Creatinine (mg/dL)	1.5 (1.1-2.0)	1.5 (1.1-1.9)	1.3 (1.1-1.7)	1.5 (1.2-2.1)	.0025
Vital signs or laboratory tests at discharge, median (IQR)					
BMI (kg/m^2)	26.7 (22.8-31.6)	26.3 (23.5-30.4)	29.6 (23.7-34.6)	26.5 (22.5-31.6)	.0083
Heart rate (beat/min)	82 (73-92)	85 (77-96)	80 (74-90)	82 (72-92)	.0031
Creatinine (mg/dL)	1.3 (1.0-1.8)	1.1 (0.9-1.5)	1.4 (1.1-1.7)	1.4 (1.0-1.9)	<.001

P values were calculated by comparing nonmissing row values only; these percentages sum to 100%. *COPD*, Chronic obstructive pulmonary disease; *CRT-D*, cardiac resynchronization therapy–defibrillator; *CVA/TIA*, cerebrovascular accident/transient ischemic attack; *ICD*, implantable cardioverter/defibrillator; *IQR*, interquartile range; *BMI*, body mass index.

patients with advanced systolic HF. The objectives were to describe medications prescribed at hospital discharge for patients with advanced HF with and without LVADs between 2009 and 2015 and to examine patient and hospital-level factors associated with prescription to LVAD recipients.

Methods

Data Source

We used data from the Get With The Guidelines–Heart Failure (GWTG-HF) voluntary quality improvement initiative. The details of this registry have been published previously.[9,10] Hospitals submit clinical information for all patients admitted with HF using a point-of-service, interactive, Internet-based Patient Management Tool (Outcome Sciences, Inc, Cambridge, MA). Variables collected include demographic and clinical characteristics; medications before admission; medical history; previous treatments; admission medications; in-hospital treatments, including intravenous medications; in-hospital outcomes; and discharge medications, including contraindications to evidence-based therapies. The data collection form specifically includes a section on new or prior LVAD during the hospitalization of record. Outcome Sciences, Inc, serves as the data collection and coordination center for GWTG. Hospital data elements are collected for all enrolling hospitals from the American

Table II. Hospital characteristics

Hospital characteristics	Overall	New LVAD	Prior LVAD	Advanced HF (no LVAD)	*P* value
Region (%)					
West	395 (20.9)	121 (46.9)	65 (38.1)	209 (14.3)	<.0001
South	893 (47.3)	97 (37.6)	50 (29.2)	746 (51.2)	
Midwest	300 (15.9)	20 (7.7)	3 (1.7)	277 (19.0)	
Northeast	299 (15.9)	20 (7.8)	53 (31.0)	226 (15.5)	
Teaching hospital	1648 (87.6)	240 (93.4)	167 (97.7)	1241 (85.4)	<.0001
Heart transplant hospital	1230 (66.6)	212 (83.8)	144 (84.2)	874 (61.4)	<.0001
No. of beds, median (IQR)	566 (438-657)	556 (524-656)	524 (439-656)	567 (438-657)	.0221
Rural location	35 (1.8)	3 (1.2)	0 (0)	32 (2.2)	.09

Hospital Association database. The GWTG Data Coordinating Center at the Duke Clinical Research Institute serves as the data analysis center and provided institutional review board approval for this project.

Study population

We identified all patients >18 years of age admitted to hospitals fully participating in the American Hospital Association's GWTG-HF national registry from January 1, 2009, to March 16, 2015, who had an implantable LVAD. Patients who received an LVAD during the admission of record were identified by the primary *International Classification of Diseases, Ninth Revision*, procedure code 37.66 ("new LVAD"). This procedure code includes patients with biventricular support (an LVAD and a right ventricular assist device), which, according to national registry data, comprises less than 3% of all implants.[2] Patients with a history of LVAD and without current or prior heart transplantation were also selected ("prior LVAD"). As a comparison group, we also identified advanced HF patients without LVAD support, defined as having a left ventricular ejection fraction ≤25% and in-hospital receipt of medications used in severe acute decompensated HF, including intravenous vasopressin receptor antagonists (conivaptan) for hyponatremia or inotropes (dopamine, dobutamine, or milrinone).[11] We selected an ejection fraction of 25% because this is the recommended cutoff for LVAD implantation.[12]

There may be differences in HF management among institutions that routinely take care of LVAD patients versus those that do not. To reduce this bias, we excluded hospitalizations at centers that did not implant LVADs during the period of analysis. Therefore, the medication prescription rates presented are from centers that took care of both LVAD and non-LVAD patients.

During the study period, there were 6,258 patients with a new or prior LVAD, or with advanced HF without an LVAD. Patients were excluded from the analysis if patients died in-hospital, were discharged to hospice, or received comfort measures (n = 1,280) or if they left against medical advice, were transferred to a different hospital, or had a missing discharge status (n = 398). Eight hundred six patients from 151 sites were excluded because they were admitted to hospitals that did not implant LVADs. The final study population included 1,887 patients from 32 hospitals. Of the 1,458 patients in the advanced HF group without an LVAD, 1,447 (99.2%) received intravenous inotropes.

Outcome measures

The primary outcomes of interest were prescription at discharge of medications that are evidence-based for stage B and stage C systolic HF: β-blockers, ACEI/ARB, aldosterone antagonist, and hydralazine nitrates.[11] Secondary outcomes of interest were prescription of diuretics, lipid-lowering agents, calcium-channel blockers, digoxin, and amiodarone. Prescription of anticoagulation and antiplatelet agents was analyzed separately in the Supplement (Table S1).

Statistical analysis

Baseline patient and hospital characteristics were compared across the new LVAD, prior LVAD, and advanced HF without LVAD groups. Categorical variables were summarized by count and percentages and were compared using the Pearson χ^2 test or, if sample size was insufficient, the Fisher exact test. Continuous variables were summarized by median (25th-75th percentiles) or mean (SD) and compared using Kruskal-Wallis tests. The frequency and proportion of each medication at discharge per year, for each patient group, were examined by Cochran-Armitage tests to test for trends across time. Missing data were excluded from comparison testing.

Multivariable logistic regression analyses were performed to examine the association of patient and hospital factors with discharge medication prescription (yes/no) for patients with new and prior LVADs. Generalized estimating equations were used to account for within-hospital clustering. Because of small sample size and risk of overfitting models, the variables included in the models were selected based upon expert opinion before analysis and included admission year; age; sex; history of atrial fibrillation or atrial flutter, coronary artery disease, hypertension, diabetes, and chronic obstructive pulmonary disease; serum creatinine and potassium at

Table III. Heart failure medications prescribed at discharge

Discharge medication	Overall	New LVAD	Prior LVAD	Advanced HF (no LVAD)	*P* value
β-Blocker (%)					
Yes, prescribed	1313 (69.6)	152 (58.9)	92 (53.8)	1069 (73.4)	
No, contraindicated	503 (26.7)	84 (32.6)	60 (35.1)	359 (24.6)	
Not prescribed	70 (3.7)	22 (8.5)	19 (11.1)	29 (2.0)	<.0001
ACEI/ARB					
Yes, prescribed	1130 (60.0)	138 (53.5)	73 (42.9)	919 (63.2)	
No, contraindicated	693 (36.8)	102 (39.5)	75 (44.2)	516 (35.4)	
Not prescribed	61 (3.2)	18 (7.0)	22 (12.9)	21 (1.4)	<.0001
Aldosterone antagonist					
Yes, prescribed	902 (48.5)	124 (49.2)	77 (45.6)	701 (48.7)	
No, contraindicated	385 (20.7)	53 (21.0)	35 (20.7)	297 (20.6)	
Not prescribed	573 (30.8)	75 (29.8)	57 (33.7)	441 (30.7)	.92
Hydralazine nitrate					
Yes, prescribed	400 (21.6)	50 (19.8)	21 (13.4)	329 (22.8)	
No, contraindicated	192 (10.4)	17 (6.8)	21 (13.4)	154 (10.7)	.0108
Not prescribed	1260 (68.0)	185 (73.4)	115 (73.2)	960 (66.5)	

discharge; and hospital region, teaching status, and bed count.

For the outcomes of interest, prescription of HF medications at discharge, there were <1% missing data. However, 20% of admissions had missing data for medications, laboratory tests, and vital signs before admission. In the multivariable models, if a patient had missing medical history, it was imputed to no. When other patient or hospital characteristics were missing, multiple imputations with 25 imputed data sets generated using fully conditional specification methods were used. Final estimates presented represented the combined results over 25 imputations.

All *P* values were 2 sided, with $P < .05$ considered statistically significant. All analyses were performed with SAS software version 9.2 (SAS Institute, Cary, NC).

Funding from the American Heart Association (Young Investigator Seed Grant Spring 2014) was used to support the research and creation of the paper. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

Patient and hospital characteristics

Patient characteristics at admission and discharge are displayed in Table I. Overall, patients were predominately male (71.3%) and white (54.6%). The median age was 59 years for new and prior LVAD patients and 60 years for advanced HF patients without an LVAD ($P = .0274$). Approximately one-quarter (25.3%) of new LVAD recipients were African American versus 24.0% of prior LVAD recipients and 40.6% of advanced HF patients without an LVAD ($P < .0001$). Comorbidities were mostly similar across the 3 patient groups. New LVAD recipients, however, were more likely to have a medical history of cardiac resynchronization therapy–defibrillator and less likely to have a history of smoking or anemia. Median creatinine was lowest among prior LVAD patients at admission ($P = .0025$) and was lowest among new LVAD patients at discharge ($P < .0001$).

The facilities represented among the study cohort were all sites of LVAD implants during the study period. Hence, they were predominately large, urban teaching hospitals (Table II). LVAD patients were more often admitted to hospitals that performed heart transplantation.

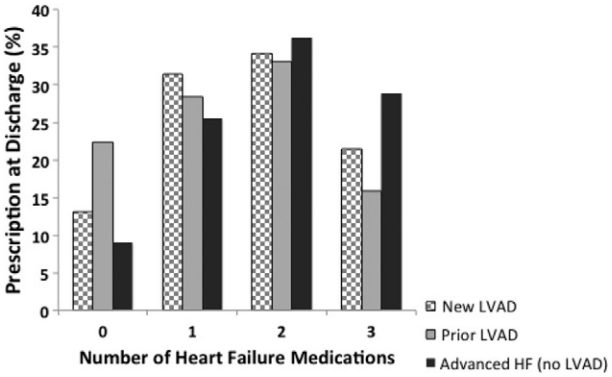
HF discharge medications

The prescription of HF medications at discharge was lower among LVAD recipients compared with advanced HF patients without LVAD support (Table III). Approximately 58.9% of new LVAD patients and 53.8% of prior LVAD patients were prescribed an evidence-based β-blocker at the time of discharge compared with 73.4% of advanced HF patients ($P < .0001$). Prior LVAD patients were least likely to be prescribed ACEI/ARB at discharge (42.9%) compared with new LVAD patients (53.5%) and advanced HF patients without an LVAD (63.2%) ($P < .0001$). When patients with documented contraindications to standard HF therapy were excluded, β-blockers and ACEI/ARB were prescribed to 87.3% and 88.4% of new LVAD patients, 82.9% and 76.8% of prior LVAD patients, and 97.3% and 97.7% of patients without LVADs, respectively (both $P < .0001$).

Hydralazine nitrates were prescribed to 13.4% of prior LVAD patients, 19.8% of new LVAD patients, and 22.8% of advanced HF patients without LVADs ($P = .0108$). There were no significant differences in aldosterone antagonist prescription across the 3 groups ($P = .92$); it was prescribed to 48.5% of all patients.

Altogether, 21.4% of new LVAD patients, 15.9% of prior LVAD patients, and 28.9% of advanced HF patients without an LVAD were prescribed a combined regimen

Figure 1



Number of HF medications prescribed at discharge.Heart failure medications include β-blocker, ACEI/ARB, and aldosterone antagonist. $P < .0001$ across all groups by Pearson χ^2 test.

of β-blocker, ACEI/ARB, and aldosterone antagonist ($P < .0001$) (Figure 1). Patients without an LVAD were least likely to be prescribed none of these medications (9.2%) compared with new LVAD patients (13.1%) or prior LVAD patients (22.5%).

Other discharge medications

Diuretic prescription at discharge was highest among advanced HF patients without an LVAD (80.1%), followed by new (65.9%) and prior LVAD (47.4%) patients ($P < .0001$) (Table IV). Similarly, digoxin use was highest among non-LVAD patients (35.3%) and lowest among prior LVAD patients (10.5%) ($P < .0001$). Amiodarone was more often prescribed at discharge to new LVAD recipients (31.4%) than prior LVAD patients (14.0%) or patients without an LVAD (21.7%) ($P < .0001$).

Temporal trends in HF discharge medication

Figure 2, *A* shows unadjusted HF medication prescription trends among LVAD recipients (n = 429) from 2009 through 2014. Overall, β-blocker prescription did not change over the 6-year period (overall use: 56.8%) ($P = .19$). ACEI/ARB prescription decreased from a peak of 66.7% in 2010 to 41.4% in 2014 (overall use: 49.3%) ($P = .0003$). Aldosterone antagonist use increased from 13.3% in 2009 to 55.8% in 2014 (overall use: 47.7%) ($P < .0001$). Hydralazine nitrate use decreased from 33.3% in 2009 to 12.9% in 2014 (overall use 17.4%) ($P = .0056$). For advanced HF patients without LVAD support, β-blocker and ACEI/ARB prescription decreased, but aldosterone antagonist and hydralazine-nitrates prescription did not significantly change (Figure 2, *B*).

Regression analysis

Table V presents the patient and hospital characteristics significantly associated with prescription of HF medications at discharge for all LVAD patients; the Supplement (Table S2) provides the full list of covariates and associated odds ratios (ORs). There were no hospital characteristics significantly associated with HF medication prescription. Patient age, per 10 years, was inversely associated with β-blocker (adjusted OR 0.23, 95% CI 0.12-0.42, $P < .0001$), ACEI/ARB (OR 0.75, 95% CI 0.57-0.99, $P = .04$), and aldosterone antagonist (OR 0.77, 95% CI 0.66-0.90, $P < .0001$) prescription. Admission year was positively associated with aldosterone antagonist prescription (OR per year 1.44, 95% CI 1.06-1.97, $P = .02$).

Discussion

Since 2006, >15,000 individuals with advanced HF have received an LVAD in the United States. For these patients, there are no clinical trials to guide the medical management of their HF. It is common practice to use β-blockers, ACEI/ARB, and aldosterone antagonists for blood pressure control after device implantation,[6–8,13] but there remains significant controversy as to the use of these antiadrenergic agents for the myocardium itself. We used the national GWTG-HF registry to describe contemporary discharge prescription patterns of HF medications among advanced HF patients with and without LVADs. We found a moderate level of use among patients admitted for LVAD implant and LVAD patients readmitted to the hospital: 56.8% were prescribed an evidence-based β-blocker, 49.3% were prescribed an ACEI/ARB, and 47.7% were prescribed aldosterone antagonist therapy. In comparison, advanced HF patients without the hemodynamic support of LVADs were prescribed β-blockers (73.4%), ACEI/ARB (63.1%), and aldosterone antagonists (48.7%) more frequently. We also found that aldosterone antagonist prescription to LVAD patients nearly quadrupled from 13.3% in 2009 to 55.8% in 2014, whereas ACEI/ARB prescription use decreased >20 percentage points over the period of analysis. Altogether, these findings characterize profound clinical uncertainty of the optimal medication regimen for the LVAD patient.

The effects of mechanical unloading from an LVAD are complex and include the regression of myocyte hypertrophy and, potentially, the progression of cell atrophy.[14–16] It has been proposed that antiadrenergic HF medications, combined with LVAD support, may enhance LVAD-induced positive remodeling and reduce LVAD-induced negative remodeling.[17] To date, however, there are very few human studies demonstrating the cellular or clinical benefits of antiadrenergic HF pharmacotherapy in LVAD recipients.[18,19] Because of the lack of clinical evidence, the International Society for Heart and Lung Transplant guidelines do not recommend HF pharmacotherapy in LVAD patients to reverse left ventricular remodeling. Rather, they recommend β-blockers for hypertension and tachyarrhythmia control,

Table IV. Other medications prescribed at discharge

Discharge medication	Overall	New LVAD	Prior LVAD	Advanced HF (no LVAD)	*P* value
Diuretic (%)	1419 (75.2)	170 (65.9)	81 (47.4)	1168 (80.1)	<.0001
Lipid lowering	953 (59.6)	113 (53.8)	66 (64.1)	774 (60.2)	.30
Calcium-channel blocker	54 (2.9)	13 (5.0)	12 (7.0)	29 (2.0)	<.0001
Digoxin	588 (31.2)	55 (21.3)	18 (10.5)	515 (35.3)	<.0001
Amiodarone	422 (22.4)	81 (31.4)	24 (14.0)	317 (21.7)	<.0001

ACEI/ARBs for hypertension and risk reduction in patients with vascular disease and diabetes, and mineralocorticoid receptor antagonists for potassium repletion and antifibrotic effects (class I, all level of evidence C).[13]

The paucity of evidence to support HF medication in LVAD recipients helps explain why HF medications in our study were prescribed less frequently to patients with LVADs than to advanced HF patients without LVADs. The difference in prescription is likely also explained by the fact that LVAD patients had higher rates of reported contraindications to β-blockers and ACEI/ARB than non-LVAD patients; for instance, >44% of prior LVAD patients, versus 35.4% of non-LVAD patients, had a contraindication to ACEI/ARB prescription at discharge. We suspect that many of the prior LVAD patients were readmitted for device-related adverse events, such as bleeding or infection,[20] and therefore may not have tolerated these medications. Many advanced HF patients without LVAD support likely also had contraindications to these medications possibly because of severe decompensation, advanced age, hypotension, frailty, or other comorbidities.

We found that older age was significantly associated with a decrease in likelihood of β-blocker, ACEI/ARB, and aldosterone antagonist prescription to LVAD recipients. Decreased use of HF-specific medications among older patients with mild to moderate HF has been shown previously in the GWTG-HF registry[21,22] and among Medicare patients with coronary artery disease.[23] Older age is likely confounded by an increased risk of comorbidities that lowers tolerance for HF medications.

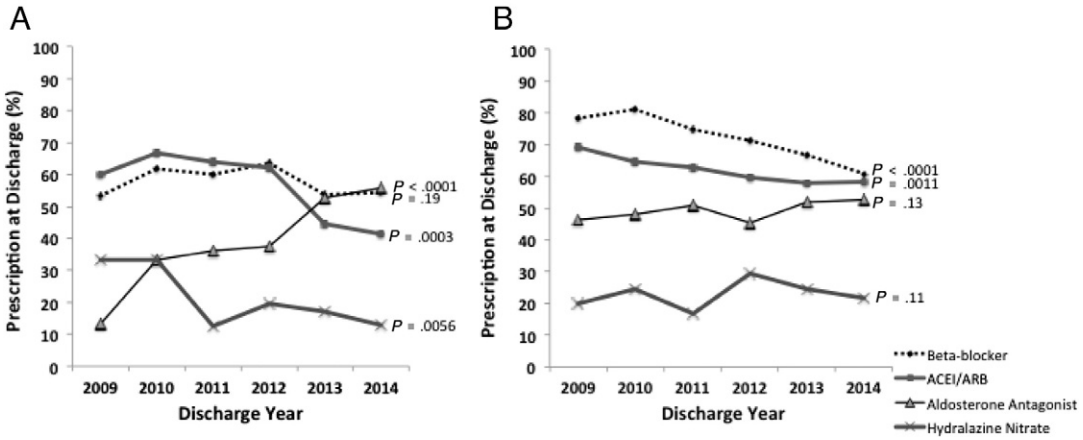
The use of HF medications after LVAD implantation was recently described using data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry.[24] The study did not report medication use among LVAD recipients after readmissions. Among 9,359 patients, use of β-blockers by 1 month after implant was 55.6%, use of ACEI/ARB was 39.2%, and use of aldosterone antagonists was 31.4%. In comparison, we report >10 percentage points higher prescription of ACEI/ARB and aldosterone antagonists at discharge among new LVAD recipients. As the patient characteristics in the INTERMACS registry are similar to patient characteristics in the GWTG-HF registry, we suspect that some of the difference in medication use can be explained by differences in the hospitals included in each study. Hospitals enrolled in the GWTG-HF program are known to demonstrate better processes of care than other hospitals not enrolled in GWTG-HF, including higher HF medication prescription at discharge.[25] It is crucial that future research examine whether differences in LVAD medication use—at the individual and hospital level—translate into clinically important differences in outcomes.

Limitations

This study has several limitations. We attempted to identify a comparison group of advanced HF patients without LVAD support using ejection fraction and in-hospital use of intravenous medications. However, identifying patients with refractory, advanced HF (stage D) is challenging because HF progression is highly variable and the exact course is uncertain.[26] It is possible that we included patients in the non-LVAD group that recovered and would no longer be considered as appropriate comparisons. Alternatively, patients in the non-LVAD group may be sicker or frailer than the patients who qualified for LVAD support. Ultimately, we chose a definition that attempted but could not definitively characterize a group of patients with progressive signs and symptoms of HF.

We were unable to ascertain the specific reasons for contraindication to prescription, such as hypotension for β-blockers and ACEI/ARB; furthermore, it is possible that contraindications may have been underreported. Third, we were unable to account for repeat hospitalizations in our study; advanced HF patients are at high risk for readmission due to acute decompensated HF[27] and/or LVAD complications.[28] Rates of prescription at discharge may be lower than expected if patients were already prescribed those medications during a previous hospitalization. Fourth, we were unable to determine whether patients received LVADs as bridge-to-transplant or destination therapy: medication management may be influenced by the expected duration of LVAD support. We also did not have information on the severity of disease, such as the INTERMACS clinical profile, at the time of implantation. Fifth, we did not have information on the reasons for admission, in addition to HF; admissions for LVAD adverse events, such as bleeding, would help explain patterns of lower medication use. We also did not have information on associated clinical outcomes, such as

Figure 2



Temporal trends in HF medications prescribed at discharge to (**A**) patients with LVADs and (**B**) advanced HF patients without LVADs. The LVAD patients included 429 patients with an LVAD implant in-hospital or a medical history of LVAD. *P* values were based on Cochran-Armitage tests for trend.

Table V. Select factors associated with HF medication prescription at discharge to patients with LVADs

Model and variable	Adjusted OR (95% CI)	*P* value
β-Blocker		
Age, per 10 y	0.23 (0.12-0.42)	<.0001
ACEI/ARB		
Age, per 10 y	0.75 (0.57-0.99)	.04
Aldosterone antagonist		
Age, per 10 y	0.77 (0.66-0.90)	<.0001
Admission year	1.44 (1.06-1.97)	.02
Hydralazine nitrate		
Female	4.04 (1.45-11.26)	.01

See Supplement for nonsignificant factors in models.

stroke, bleeding, or death. Sixth, the sample size of LVAD patients was small, and power was limited to fully examine factors that affected discharge prescription patterns. Unmeasured confounding may influence these findings. Finally, the 32 LVAD centers represented in GWTG-HF may not be representative of all hospitals that treat LVAD and advanced HF patients in the United States.

Conclusion

In summary, our multicenter registry analysis highlights the clinical uncertainty that surrounds prescription of β-blockers, ACEI/ARB, and aldosterone antagonists in LVAD recipients. Prescription of these antiadrenergic medications was highly variable between 2009 and 2015. They were not prescribed as frequently for LVAD recipients as they were for advanced HF patients without LVAD support. We hypothesize that the moderate use of HF medications in LVAD patients was due to medication intolerance and the lack of evidence to support their use. Further research is needed on the benefit of antiadrenergic therapy in patients with LVADs.

Acknowledgements

The GWTG-HF program is provided by the American Heart Association. The GWTG-HF program is supported in part by Medtronic, Ortho-McNeil, and the American Heart Association Pharmaceutical Roundtable. GWTG-HF has been funded in the past through support from GlaxoSmithKline.

Disclosures

J. Baras Shreibati: none.

S. Sheng: none.

G. C. Fonarow: Consultant/Advisory Board: Amgen, Bayer, Janssen, Novartis, Medtronic.

A. D. DeVore: research grant: American Heart Association, Amgen, Maquet, Novartis, Thoratec. Consultant/Advisory Board: Maquet.

C. W. Yancy: none.

D. L. Bhatt: research grant: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company.

E. D. Peterson: research grant: Janssen. Consultant/Advisory Board: Janssen, Boehringer Ingelheim, Sanofi, Merck, Astra Zeneca, Bayer.

A. Hernandez: research grant: Amgen, Astra Zeneca, Bayer, Bristol-Myers Squibb, Glaxo SmithKline, Merck & Co., Portola. Consultant/Advisory Board: Amgen, Astra Zeneca, Bayer, Eli Lilly, Gilead, Glaxo SmithKline,

Janssen, Merck & Co., MyoKardia, Pfizer, Pluristem, Novartis.

P. A. Heidenreich: none.

Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2016.06.011.

References

1. Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. J Heart Lung Transplant 2014;33:555-64.
2. Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant 2015;34:1495-504.
3. U.S. Department of Health & Human Services. OPTN/SRTR 2012 annual data report: heart. http://srtr.transplant.hrsa.gov/annual_reports/2012/pdf/05_heart_13.pdf. [Accessed on Jan 5, 2016].
4. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007;357:885-96.
5. Boyle AJ, Russell SD, Teuteberg JJ, et al. Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anti-coagulation. J Heart Lung Transplant 2009;28:881-7.
6. Lampert BC, Eckert C, Weaver S, et al. Blood pressure control in continuous flow left ventricular assist devices: efficacy and impact on adverse events. Ann Thorac Surg 2014;97:139-46.
7. Nassif ME, Tibrewala A, Raymer DS, et al. Systolic blood pressure on discharge after left ventricular assist device insertion is associated with subsequent stroke. J Heart Lung Transplant 2015;34:503-8.
8. Saeed O, Jermyn R, Kargoli F, et al. Blood pressure and adverse events during continuous flow left ventricular assist device support. Circ Heart Fail 2015;8:551-6.
9. LaBresh KA, Ellrodt AG, Gliklich R, et al. Get with the guidelines for cardiovascular secondary prevention: pilot results. Arch Intern Med 2004;164:203-9.
10. Smaha LA, American Heart A. The American Heart Association Get With The Guidelines program. Am Heart J 2004;148:S46-8.
11. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.
12. Department of Health and Human Services. Food and Drug Administration device approvals and clearances. HeartMate® SNAP-VE LVAS - P920014/S016. http://www.accessdata.fda.gov/cdrh_docs/pdf/p920014s016a.pdf. [Accessed on Jan 5, 2016].
13. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 2013;32:157-87.
14. Ambardekar AV, Buttrick PM. Reverse remodeling with left ventricular assist devices: a review of clinical, cellular, and molecular effects. Circ Heart Fail 2011;4:224-33.
15. Brinks H, Tevaearai H, Muhlfeld C, et al. Contractile function is preserved in unloaded hearts despite atrophic remodeling. J Thorac Cardiovasc Surg 2009;137:742-6.
16. Drakos SG, Wever-Pinzon O, Selzman CH, et al. Magnitude and time course of changes induced by continuous-flow left ventricular assist device unloading in chronic heart failure: insights into cardiac recovery. J Am Coll Cardiol 2013;61:1985-94.
17. Yacoub MH, Tansley P, Birks EJ, et al. A novel combination therapy to reverse end-stage heart failure. Transplant Proc 2001;33:2762-4.
18. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med 2006;355:1873-84.
19. Klotz S, Danser AH, Foronjy RF, et al. The impact of angiotensin-converting enzyme inhibitor therapy on the extracellular collagen matrix during left ventricular assist device support in patients with end-stage heart failure. J Am Coll Cardiol 2007;49:1166-74.
20. Hasin T, Marmor Y, Kremers W, et al. Readmissions after implantation of axial flow left ventricular assist device. J Am Coll Cardiol 2013;61:153-63.
21. Forman DE, Cannon CP, Hernandez AF, et al. Influence of age on the management of heart failure: findings from Get With the Guidelines–Heart Failure (GWTG-HF). Am Heart J 2009;157:1010-7.
22. Golwala HB, Thadani U, Liang L, et al. Use of hydralazine-isosorbide dinitrate combination in African American and other race/ethnic group patients with heart failure and reduced left ventricular ejection fraction. J Am Heart Assoc 2013;2:e000214.
23. Krumholz HM, Vaccarino V, Ellerbeck EF, et al. Determinants of appropriate use of angiotensin-converting enzyme inhibitors after acute myocardial infarction in persons > or = 65 years of age. Am J Cardiol 1997;79:581-6.
24. Khazanie P, Hammill BG, Patel CB, et al. Use of heart failure medical therapies among patients with left ventricular assist devices: insights from INTERMACS. J Card Fail 2016, http://dx.doi.org/10.1016/j.cardfail.2016.02.004. [pii: S1071-9164(16)00064-6, Epub ahead of print].
25. Heidenreich PA, Hernandez AF, Yancy CW, et al. Get With The Guidelines program participation, process of care, and outcome for Medicare patients hospitalized with heart failure. Circ Cardiovasc Qual Outcomes 2012;5:37-43.
26. Fang JC, Ewald GA, Allen LA, et al. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. J Card Fail 2015;21:519-34.
27. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med 2009;360:1418-28.
28. Smedira NG, Hoercher KJ, Lima B, et al. Unplanned hospital readmissions after HeartMate II implantation: frequency, risk factors, and impact on resource use and survival. JACC Heart Fail 2013;1:31-9.