ORIGINAL RESEARCH

Longitudinal Heart Failure Medication Use and Adherence Following Left Ventricular Assist Device Implantation in Privately Insured Patients

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***Background*—**There are few data describing the longitudinal use of and adherence to heart failure medications following left ventricular assist device (LVAD) implantation.

***Methods and Results*—**Using a large US commercial insurance database, patients who received an LVAD (*International Classification of Diseases, 9th Revision, Clinical Modification* code 37.66) and survived to hospital discharge without heart transplantation between January 1, 2006, and March 31, 2015, were identified. Heart failure medication use from 3 months before 1-year post-LVAD was examined using linked pharmacy claims. Differences in the proportion of patients taking heart failure medications post LVAD compared with pre LVAD were examined using McNemar test. Predictors of post-LVAD medication use and poor medication adherence (proportion of days covered <0.8) were identified via logistic regression. Among 362 patients (mean age, 57.4 years; 75.1% men), compared with pre LVAD, the proportion of patients taking anticoagulants and antiarrhythmics following LVAD increased; mineralocorticoid receptor antagonists, thiazide diuretics, and digoxin decreased; and β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and loop diuretics did not change. Pre-LVAD medication use was associated with post-LVAD use across all medication classes. The proportion of patients with poor medication adherence was 28.8%, 39.0%, and 36.0% for β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and anticoagulants, respectively. Many patients with poor adherence completely discontinued use of the medication.

***Conclusions*—**Neurohormonal antagonist use after LVAD was inconsistent, perhaps reflecting uncertainty of therapeutic benefit in this population. Medication adherence post-LVAD was poor in many patients. Further work is needed to delineate the reasons for nonadherence after LVAD. **(*J Am Heart Assoc*. 2017;6:e005776. DOI: 10.1161/JAHA.117.005776.)**

Key Words: advanced heart failure • left ventricular assist device • medication adherence

The past decade has seen tremendous advances in left ventricular assist device (LVAD) technology.[1,2] As a result, its use in the treatment of advanced heart failure (HF) has expanded over time.[3] Yet, despite the growing use of LVADs, there are few data available to guide the use of HF medications following implantation. The 2013 International Society of Heart and Lung Transplant (ISHLT) mechanical circulatory support guidelines provide only brief recommendations for HF medical therapies in patients with LVAD that were based on insights gleaned from small retrospective studies and/or theoretical knowledge of their biological effects in HF.[4] Furthermore, unlike management of HF with reduced ejection fraction, the use of some medication classes including β-blockers are not universally recommended after LVAD. Nearly all HF medications classes would benefit from further study to define their role in the medical management of patients with LVADs. However, without these further studies, clinicians who manage patients with LVADs are often reliant upon clinical judgment and extrapolation of evidence from other settings in choosing medical therapy. As such, evaluation of observational data can provide meaningful insight into current practice patterns.

A single recent study using Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/6/10/e005776/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- We investigated heart failure medication use before and following left ventricular assist device (LVAD) implantation among 362 commercially insured patients.
- Use of mineralocorticoid receptor antagonists decreased post-LVAD implantation, whereas the use of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and diuretics did not change.
- The only consistent predictor of post-LVAD medication use was use of a medication in the same therapeutic class pre LVAD.
- One fifth of patients were not on anticoagulation after LVAD.
- Many patients had poor adherence to β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers post LVAD, some of whom completely discontinued use of these medications.

What Are the Clinical Implications?

- Evidence to guide the use of neurohormonal antagonists after LVAD is lacking, resulting in variability in treatment across clinical practice.
- Patients are often maintained on the same medications post LVAD that they were taking pre LVAD, and many are not initiated on β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, although these agents may be better tolerated as a result of improved hemodynamics post LVAD.
- Further studies are needed to elucidate the reasons for medication nonadherence following LVAD implantation.

reported that use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and β-blockers was higher post LVAD compared with pre LVAD, whereas use of mineralocorticoid receptor antagonists (MRAs) was lower.[5] However, these data are based on institutional reporting of medications prescribed to patients and do not account for whether patients fill and take their medications as prescribed. Because medication nonadherence is common in patients with cardiovascular diseases such as HF and is significantly associated with differences in outcomes, it is of critical importance to consider adherence when examining patterns of medication use.[6–9] Given the above, we therefore aimed to fill these knowledge gaps by evaluating use of and adherence to HF medications in the year following LVAD implantation in a large commercially insured population.

Methods

We conducted a retrospective analysis of administrative claims data from a large US commercial insurance database, Optum Labs Data Warehouse, which is comprised of privately insured enrollees from geographically diverse regions across the country.[10,11] The database includes professional, facility, and outpatient medication service claims for individuals enrolled in private and Medicare Advantage health plans.[12] Because this study involved analysis of preexisting, de-identified data, it was exempt from institutional review board approval.

Study Population

We identified all patients 18 years and older who underwent LVAD implantation (*International Classification of Diseases, 9th Revision* [*ICD-9*] procedure code 37.66) and survived to hospital discharge without undergoing heart transplantation (*ICD-9* procedure code 37.51) between January 1, 2006, and March 31, 2015. To capture baseline patient medication use and comorbidities, we restricted the analysis to patients who had medical and pharmacy coverage for at least 6 months before LVAD implantation. Furthermore, as our goal was to capture post-LVAD medication use, we also excluded patients with medical and pharmacy coverage for <3 months post-LVAD implantation. Because medication management changes after heart transplantation, we also excluded patients who underwent heart transplantation within 3 months post LVAD.

Patient Characteristics

For each patient, we assessed demographic and clinical characteristics during their baseline period, including age, sex, race, and selected comorbidities. Baseline medical comorbidities (including hypertension, diabetes mellitus, cerebrovascular disease, renal disease, and cardiac arrhythmias) were captured by *ICD-9* codes in one of the first 3 positions on claims taking place within 180 days before LVAD implantation (Table S1).[13–16]

Hospital Characteristics

The American Hospital Association (AHA) data were used to elucidate the characteristics of the hospitals where enrollees had LVADs implanted; 22.7% of patients were missing these data. AHA variables examined included hospital location (rural, micro, metro, or division); bed size; geographic region (Northeast, Midwest, South, and West), and teaching status (ie, those belonging to the Council of Teaching Hospitals of the Association of American Medical Colleges).

Medication Use and Adherence

We examined pharmacy claims from 3 months before 12 months post-LVAD implantation to determine patient

medication use through June 30, 2015. Patients were censored from analysis at the time of heart transplantation (*ICD-9* code 37.51) or at the end of medical/pharmacy coverage. In addition to examining the evidence-based medications shown to improve outcomes in HF with reduced ejection fraction (β-blockers, ACEIs and ARBs, MRAs), we also examined use of commonly prescribed medication classes after LVAD, including loop diuretics; anticoagulants (warfarin, low-molecular-weight heparins, novel oral anticoagulants), antiarrhythmic drugs (AADs), digoxin, thiazide diuretics, and hydralazine/isosorbide dinitrate (Table 1).

Patients were considered to be taking a given medication within a therapeutic class pre LVAD if they filled a medication within 90 days before hospital admission for LVAD surgery. Medication use in the year after LVAD was evaluated in 3-month intervals (0–3, 3–6, 6–9, and 9–12 months) beginning from the date of hospital discharge after LVAD surgery. Patients were considered to be taking a given medication class post LVAD upon filling a prescription for a medication within that therapeutic class. Medication adherence was examined for the most commonly used medication classes after LVAD (β-blockers, ACEI/ARB, loop diuretics, anticoagulants). We considered medications in the same therapeutic class substitutable, therefore we did not double-count the overlapped days for different drugs in the same class. We used pharmacy-based proportion of days covered (PDC) to quantify medication adherence during the 1-year period post LVAD. For each medication class, the PDC was defined as the proportion of days for which the patient had medication available to take (based on all fills) divided by the number of days in their follow-up period. The first day for both the numerator and denominator of the PDC began on the first day that the prescription was filled. A PDC ≥80% was used to define adherence.[17,18] If patients were hospitalized during the follow-up period, hospitalization days were added to the numerator of the PDC calculation. Patients who did not fill a prescription for a particular medication class were not included in the analysis of adherence for that medication class. We performed a continuation analysis to better understand whether patients with poor adherence during follow-up discontinued use of a medication class completely. Discontinuation was defined as failing to refill a given medication class for at least 90 days after the supply ended.

Statistical Analysis

Baseline characteristics were summarized using number (percentage), median (interquartile range), or mean±SD as

Table 1. List of Medications Used for Heart Failure in the Current Study

ACEIs/ARBs	β-Blockers	Loop Diuretics	MRAs	Thiazide Diuretics	Anticoagulants	Antiarrhythmics
Benazepril	Carvedilol	Bumetanide	Spironolactone	Chlorothiazide	Dicumarol	Amiodarone
Captopril	Sotalol	Ethacrynic acid	Eplerenone	Hydrochlorothiazide	Warfarin	Dofetilide
Enalapril	Acebutolol	Furosemide		Indapamide	Dalteparin	Dronedarone
Fosinopril	Atenolol	Torsemide		Metolazone	Enoxaparin	Flecainide
Lisinopril	Bisoprolol				Fondaparinux	Mexiletine
Perindopril Quinapril	Metoprolol succinate				Apixaban Tinzaparin	Procainamide Propafenone
Candesartan Telmisartan	Metoprolol tartrate				Rivaroxoban Danaparoid	Quinidine Sotalol
Ramipril	Nadolol				Dabigatran	
Trandalopril	Nebivolol					
Moexipril	Propanolol					
Valsartan	Labetalol					
Azilsartan	Betaxolol					
Irbesartan	Penbutolol					
Losartan	Pindolol					
Olmesartan	Timolol					
Eprosartan						

Intravenous and ocular preparations of medications were not included. If a medication was taken as a part of a combination medication (such as amlodipine/benazepril), that was also counted toward angiotensin-converting enzyme inhibitor (ACEI) use. Other medications included in their own categories were (1) digoxin and (2) hydralazine used in combination with isosorbide dinitrate. ARBs indicates angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists.

appropriate. Differences in the proportion of patients taking medications of interest before compared with after LVAD implantation were examined using McNemar test. Predictors of post-LVAD medication use and adherence for the most commonly prescribed medication classes were examined using logistic regression. Post-LVAD medication use was defined as filling a medication in a given therapeutic class within 90 days of hospital discharge after LVAD implantation. Nonadherence to a given medication class was defined as a PDC <80%. Variables were chosen a priori and were limited based on sample size. Results are presented using odds ratios (ORs) and 95% confidence intervals (CIs). Changes in the proportion of patients taking medication classes over time (0–3, 3–6, 6–9, and 9–12 months) post LVAD were examined using linear regression. All analyses were performed using SAS version 9.3. A *P* value cutoff of <0.05 was used to determine statistical significance.

Results

Baseline Characteristics

A total of 1230 patients who underwent LVAD implantation within the study period were identified; 362 patients had medical and pharmacy coverage 6 months prior and 90 days post LVAD, and did not undergo heart transplantation either during their LVAD hospitalization or 3 months post LVAD. The mean age was 57.4 years (SD 12.4), and 75.1% were men (Table 2). In total, 47.2% of patients with LVAD had diabetes mellitus, 70.2% had hypertension, 39.5% had moderate or severe renal disease, 29.6% had cerebrovascular disease, and 46.4% had atrial fibrillation and/or atrial flutter. The majority of LVADs were implanted in hospitals located in "metro" areas (81.4%) with ≥400 beds (89.6%) and that identified themselves as teaching centers (78.9%). In total, 222 (61.3%) had a full year of follow-up after LVAD hospital discharge, whereas the remainder disenrolled or underwent heart transplantation before 1 year post-LVAD.

Medication Use Before and Following LVAD Implantation

Before LVAD implantation, the majority of patients were taking β-blockers (65.5%), loop diuretics (65.5%), and ACEIs/ARBs (56.1%), while about half (48.6%) were taking MRAs (Table 3). Among those taking β-blockers (n=237), the most commonly used were carvedilol (74.3% of patients), metoprolol succinate (19.0%), and metoprolol tartrate (11.4%). Among those taking AADs (n=100), the most commonly used were amiodarone (83.0% of patients), mexiletine (13.0%), and sotalol (13.0%). Of patients taking anticoagulants before LVAD (n=134), the majority were taking warfarin (85.1%); 17 patients were taking novel oral anticoagulants pre LVAD (9 rivaroxaban, 7 dabigatran, and 1 apixaban).

Post LVAD, the proportion of patients using β-blockers (63.3%), loop diuretics (68.2%), and ACEIs/ARBs (53.9%) did not change (*P*=0.56, 0.38, and 0.57, respectively). However, the proportion of patients taking MRAs decreased from 48.6% to 37.6% (*P*=0.002). In comparison, the proportion of patients taking AADs increased from 27.6% to 48.6% following LVAD placement (*P*<0.001). The use of anticoagulants increased from 37.0% pre-LVAD to 82.0% post-LVAD implantation (*P*<0.001). The use of thiazide diuretics and digoxin decreased after LVAD implantation. There were few patients taking hydralazine/isosorbide dinitrate either pre or post LVAD. There were no significant differences in the proportion of patients taking each class of medication by the 3-month time period in the year after LVAD (Figure; *P*>0.05 for each medication class).

Similar to pre LVAD, the most commonly prescribed β-blockers post LVAD were carvedilol (66.4% of 229 patients), metoprolol tartrate (21.4%), and metoprolol succinate (21.0%). Of the 176 patients taking AAD post LVAD, the majority were using amiodarone (89.8%). In alignment with device recommendations, nearly all patients using anticoagulants post LVAD were taking warfarin (294 of 297, 99.0%), although some also filled prescriptions for enoxaparin (n=69, 23.2%) or fondaparinux (n=2, 0.7%). No patients used novel oral anticoagulants after LVAD.

The univariate predictors of post-LVAD medication use are shown in Table 4. β-Blocker use post LVAD was greater in men compared with women, with an OR of 1.97 (95% CI, 1.21–3.19). ACEI/ARB use was lower among patients with moderate/severe renal disease (OR, 0.49; 95% CI, 0.32–0.75). Past arrhythmias were associated with post-LVAD AAD use (OR, 2.71; 95% CI, 1.55–4.75). Across all medication classes, prior medication use within the same class was associated with post-LVAD medication use.

Anticoagulant use was not significantly associated with a history of cerebrovascular disease or gastrointestinal bleeding. We also examined whether patients who did not fill an anticoagulation prescription had a stroke or gastrointestinal bleed early after LVAD. In the total population, 4 (1.1%) patients had a stroke and 26 (7.2%) had a gastrointestinal bleed between admission for LVAD implantation and 90 days post-LVAD hospital discharge, respectively. Of patients who were not initiated on anticoagulation following LVAD, 1 (1.6%) had a stroke and 7 (10.9%) had gastrointestinal bleeding early after LVAD.

Medication Adherence Post-LVAD Implantation

Poor medication adherence after LVAD was common. In total, 28.8% (66/229), 39.0% (76/195), 36.0% (107/297), and

Table 2. Baseline Characteristics of 362 Patients With LVAD

Characteristic (Total, N=362)	Value
Age, mean (SD), y	57.4 (12.4)
Age group, No. (%), y	
18–34	21 (5.8)
35–44	31 (8.6)
45–54	71 (19.6)
55–64	138 (38.1)
65+	101 (27.9)
Sex, No. (%)	
Female	90 (24.9)
Male	272 (75.1)
Race, No. (%)	
White	236 (65.2)
Black	77 (21.3)
Asian	8 (2.2)
Hispanic	28 (7.7)
Unknown/missing	13 (3.6)
Year of LVAD implantation, No. (%)	
2006	6 (1.7)
2007	15 (4.1)
2008	18 (5.0)
2009	25 (6.9)
2010	37 (10.2)
2011	58 (16.0)
2012	55 (15.2)
2013	63 (17.4)
2014	68 (18.8)
2015	17 (4.7)
LVAD hospitalization length of stay, mean (SD)	41.4 (29.8)
Length of follow-up, mean (SD), d	486.2 (409.7)
Charlson index, mean (SD)	4.5 (2.5)
Medical comorbidities, No. (%)	
Diabetes mellitus	171 (47.2)
Hypertension	254 (70.2)
Myocardial infarction	122 (33.7)
Cerebrovascular disease	107 (29.6)
Moderate/severe renal disease	143 (39.5)
Chronic obstructive pulmonary disease	187 (51.7)
Gastrointestinal bleeding	32 (8.8)
Cardiac arrhythmias	291 (80.4)
Hospital location, No. (%)	
Division	52 (18.6)
Metro	228 (81.4)
Bed size, No. (%)	
50–199	3 (1.1)
200–399	26 (9.3)
400+	251 (89.6)
Teaching status, No. (%)	
Teaching	221 (78.9)
Nonteaching	59 (21.1)
Geographic region	
Northeast	19 (6.5)
South	122 (43.6)
Midwest	113 (40.4)
West	26 (9.3)

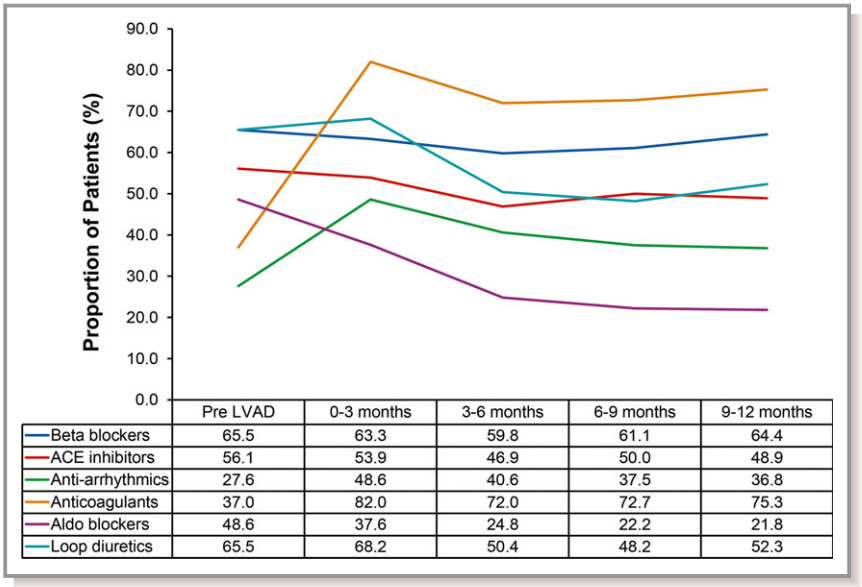
LVAD indicates left ventricular assist device.

55.9% (138/247) of patients were nonadherent to β-blockers, ACEIs/ARBs, anticoagulants, and loop diuretics, respectively. On univariate analysis, pre-LVAD use was associated with decreased odds of nonadherence for β-blockers and loop diuretics, with ORs of 0.44 (95% CI, 0.24–0.81) and 0.39 (95% CI, 0.21–0.75), respectively. A Charlson comorbidity index of 5 or more was associated with increased odds of nonadherence to anticoagulants (OR, 2.80; 95% CI, 1.00–7.88); however, no evidence of an association between comorbidity burden and adherence to β-blockers, ACEIs/ARBs, and loop

Table 3. Medication Use Pre and Post LVAD

Medication Class	Pre LVAD	Post LVAD	*P* Value
β-Blocker	237 (65.5)	195 (53.9)	0.56
ACEI/ARB	203 (56.1)	229 (63.3)	0.57
Antiarrhythmic	100 (27.6)	176 (48.6)	<0.001
Anticoagulant	134 (37.0)	297 (82.0)	<0.001
MRA	176 (48.6)	136 (37.6)	0.002
Loop diuretic	237 (65.5)	247 (68.2)	0.38
Thiazide diuretic	91 (25.1)	33 (9.1)	<0.001
Hydralazine and isosorbide dinitrate	3 (0.8)	9 (2.5)	0.65
Digoxin	111 (30.7)	70 (19.3)	<0.001

All values are shown as number (percentage). ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonist.



	Pre LVAD	0-3 months	3-6 months	6-9 months	9-12 months
Beta blockers	65.5	63.3	59.8	61.1	64.4
ACE inhibitors	56.1	53.9	46.9	50.0	48.9
Anti-arrhythmics	27.6	48.6	40.6	37.5	36.8
Anticoagulants	37.0	82.0	72.0	72.7	75.3
Aldo blockers	48.6	37.6	24.8	22.2	21.8
Loop diuretics	65.5	68.2	50.4	48.2	52.3

Figure. Trends in medication use before and after left ventricular assist device (LVAD) implantation. The proportions of patients taking classes of medications pre LVAD and in the year post LVAD are shown. AAD indicates antiarrhythmic drugs; ACE/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists.

diuretics was detected. Age, sex, and race/ethnicity were not significantly associated with adherence to any of the medication classes (Table 5).

Many patients who were nonadherent completely discontinued use of β-blockers (18/66, 27.3% of nonadherent), ACEIs/ARBs (34/76, 44.7%), anticoagulants (28/107, 26.2%), and loop diuretics (62/138, 44.9%) during follow-up.

Discussion

In this study, we examined the longitudinal use of HF medications before and following LVAD implantation in a large group of individuals enrolled in private and Medicare Advantage health plans. There were a number of important findings from our analysis. First, many patients were not taking neurohormonal medications before LVAD implantation. Second, the only consistent predictor of post-LVAD medication use was pre-LVAD use of a medication in the same therapeutic class. Third, use of some classes of medications changed after LVAD. In particular, AAD and anticoagulant use increased, whereas use of MRAs decreased. Furthermore, there was no use of novel oral anticoagulants after LVAD, although many patients received low-molecular-weight heparin. Finally, some patients had poor medication adherence following LVAD implantation, many of whom discontinued use of medications such as β-blockers and ACEIs/ARBs completely.

With the advent of continuous-flow device technology, the number of LVAD implantations being performed across the United States, particularly in the context of destination therapy, has continued to rise.[1,19] These devices provide a means of mechanically unloading the heart, with consequent restoration of cardiac output and correction of the left-sided volume-mediated neurohormonal axis.[20,21] However, little is known about how to optimally medically manage patients with LVADs. While a wealth of clinical trial data exist to guide the use of traditional HF medications (such as β-blockers and ACEIs/ARBs) in patients with HF with reduced ejection fraction, similar data to guide the management of patients with LVADs are not available. Accordingly, the most recent ISHLT LVAD guidelines recommended use of these HF medications in patients with LVADs based only on consensus agreement (level of evidence C).[4]As a result of the lack of outcomes data to guide therapy, the use of HF medications after LVAD may vary. Understanding the current medical management of patients on LVAD support is hence an important first step toward defining best practices.

The pre-LVAD use of HF medications in our study appeared lower compared with rates previously documented in patients with clinically stable HF.[22] This was not surprising given that patients with advanced HF are apt to be less tolerant of neurohormonal antagonists. In addition, the overall comorbidity burden of our study population was high, with a significant proportion experiencing concomitant renal, vascular, and pulmonary diseases, which may limit use of HF medications. The pre-LVAD medication use we observed also differed somewhat from that reported in the INTERMACS registry. Use of ACEIs/ARBs (56% versus 38%), β-blockers

Table 4. Univariate Predictors of Post-LVAD Medication Use

Variable	Odds Ratio (95% CI)					
	β-Blockers	ACEIs/ARBs	AADs	Anticoagulants	MRAs	Loop Diuretics
Age group, y						
18–34	REF	REF	REF	REF	REF	REF
35–44	0.80 (0.26–2.44)	1.42 (0.47–4.34)	0.79 (0.26–2.42)	0.48 (0.11–2.07)	0.47 (0.15–1.46)	0.41 (0.10–1.73)
45–54	2.05 (0.75–5.64)	2.61 (0.97–7.06)	1.13 (0.43–3.00)	0.82 (0.21–3.23)	0.41 (0.15–1.10)	0.29 (0.08–1.07)
55–64	1.60 (0.63–4.08)	2.01 (0.80–5.10)	1.31 (0.52–3.28)	1.11 (0.30–4.16)	0.53 (0.21–1.34)	0.41 (0.11–1.46)
65+	0.90 (0.35–2.32)	0.87 (0.34–2.27)	0.78 (0.31–2.01)	0.54 (0.15–1.97)	0.32 (0.12–0.83)	0.29 (0.08–1.05)
Sex						
Female	REF	REF	REF	REF	REF	REF
Male	1.97 (1.21–3.19)*	0.81 (0.50–1.31)	1.18 (0.73–1.90)	1.20 (0.65–2.19)	0.87 (0.54–1.42)	0.90 (0.53–1.50)
Race						
White	REF	REF	REF	REF	REF	REF
Asian	0.99 (0.23–4.25)	2.76 (0.55–13.94)	1.11 (0.27–4.53)	. . .	0.57 (0.11–2.89)	3.13 (0.38–25.93)
Black	1.17 (0.68–2.00)	1.10 (0.66–1.85)	1.14 (0.68–1.90)	0.89 (0.45–1.75)	0.87 (0.51–1.50)	1.05 (0.60–1.84)
Hispanic	1.07 (0.47–2.42)	1.94 (0.84–4.46)	1.48 (0.67–3.26)	0.73 (0.28–1.91)	2.65 (1.19–5.91)*	0.81 (0.36–1.83)
Unknown/missing	0.69 (0.23–2.13)	0.57 (0.18–1.81)	0.69 (0.22–2.18)	0.23 (0.07–0.73)*	0.76 (0.23–2.55)	0.28 (0.09–0.89)
Pre-LVAD use	1.78 (1.14–2.77)*	1.95 (1.28–2.96)*	3.66 (2.23–6.02)*	3.47 (1.74–6.91)*	1.76 (1.14–2.70)*	4.55 (2.83–7.30)*
Myocardial infarction	0.94 (0.60–1.47)	1.24 (0.80–1.92)	1.39 (0.90–2.16)	0.84 (0.48–1.47)	0.86 (0.55–1.35)	1.11 (0.69–1.77)
Diabetes mellitus	1.34 (0.87–2.06)	1.14 (0.75–1.73)	1.04 (0.69–1.57)	0.95 (0.56–1.63)	1.02 (0.67–1.57)	1.15 (0.74–1.79)
Hypertension	1.21 (0.76–1.92)	0.96 (0.61–1.50)	1.49 (0.95–2.35)	1.37 (0.78–2.41)	0.83 (0.52–1.31)	1.32 (0.82–2.13)
Cardiac arrhythmias	0.62 (0.35–1.09)	. . .	2.71 (1.55–4.75)*	. . .		
Renal disease	. . .	0.49 (0.32–0.75)*	. . .	. . .	0.73 (0.48–1.13)	1.37 (0.87–2.14)
CVD	. . .	. . .	. . .	1.02 (0.57–1.84)		
GIB	. . .	. . .	. . .	2.24 (0.66–7.58)		

. . . indicates not performed. AAD indicates antiarrhythmic drugs; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CI, confidence interval; CVD, cerebrovascular disease; GIB, gastrointestinal bleeding; LVAD, left ventricular assist device; MRAs, mineralocorticoid receptor antagonists; REF, reference category.
*$P<0.05$.

(66% versus 55%), MRAs (49% versus 40%), and warfarin (34% versus 22%) was higher pre LVAD in our population compared with in the INTERMACS registry.[5] In the INTERMACS registry, medications are entered into a case report form based on current or prior use as documented in the patient's medical record, which can include patient report and/or prescriptions ordered. It does not take into account whether prescriptions were ever filled by patients.[23] Thus, it is unclear whether our findings reflect actual differences in medication use in the populations studied versus failure to capture pre-LVAD medication use accurately in the INTERMACS registry.

While the use of some medication classes changed after LVAD, the proportion of patients using β-blockers and ACEIs/ARBs post-LVAD implantation did not. In theory, patients may better tolerate β-blockers and ACEIs/ARBs given the hemodynamic stabilization conferred by mechanical circulatory support. However, similar use of these medications post LVAD as compared with pre LVAD may reflect the uncertainty and lack of clear guidance that clinicians have in medically managing patients post LVAD, resulting in a tendency to simply continue pre LVAD therapies. As evidence of this phenomenon, the only consistent predictor of post-LVAD medication use observed in this study was use of a medication in the same therapeutic class pre LVAD. On the other hand, MRA use declined following LVAD implantation. In the pivotal RALES (Randomized Aldactone Evaluation Study), spironolactone showed mortality benefit as an adjunctive therapy to β-blockers and ACEIs/ARBs.[24] Whether there is therapeutic benefit associated with MRA use in patients with LVADs is a question that has not been studied. As such, providers may discontinue them in an effort to simplify medical regimens. Other factors such as hypotension and renal insufficiency may also contribute to the decreased use of MRAs post LVAD.

Table 5. Univariate Predictors of Medication Nonadherence

	β-Blockers		ACEIs/ARBs		Anticoagulants		Loop Diuretics	
	No.*	Odds Ratio (95% CI)	No.*	Odds Ratio (95% CI)	No.*	Odds Ratio (95% CI)	No.*	Odds Ratio (95% CI)
Age group, y								
18–34	6	REF	5	REF	5	REF	11	REF
35–44	3	0.23 (0.04–1.25)	6	0.48 (0.09–2.52)	12	2.84 (0.76–10.58)	10	0.53 (0.15–1.88)
45–54	11	0.27 (0.07–1.00)	15	0.38 (0.09–1.60)	16	0.97 (0.30–3.15)	25	0.80 (0.26–2.43)
55–64	24	0.34 (0.10–1.17)	28	0.41 (0.10–1.64)	43	1.45 (0.49–4.35)	49	0.64 (0.23–1.78)
65+	22	0.67 (0.19–2.34)	22	0.98 (0.23–4.19)	31	1.75 (0.57–5.41)	43	1.30 (0.44–3.84)
Sex								
Female	14	REF	20	REF	19	REF	36	REF
Male	52		56		88		102	
Race								
White	46	REF	48	REF	73	REF	99	REF
Black	12	0.56 (0.06–5.10)	16	0.78 (0.14–4.43)	24	1.02 (0.24–4.39)	26	0.49 (0.11–2.24)
Hispanic	4	0.68 (0.33–1.42)	7	0.96 (0.47–1.98)	4	1.05 (0.58–1.88)	8	0.60 (0.32–1.12)
Asian	3	0.63 (0.20–2.03)	2	0.91 (0.34–2.48)	3	0.38 (0.12–1.16)	3	0.52 (0.19–1.38)
Unknown/missing	1	1.66 (0.36–7.74)	3	2.34 (0.38–14.54)	3	1.27 (0.28–5.85)	2	0.43 (0.07–2.65)
Charlson comorbidity index								
0 or 1	3	REF	7	REF	5	REF	13	REF
2	15	3.25 (0.78–13.48)	12	1.21 (0.37–3.98)	15	2.44 (0.77–7.78)	17	0.44 (0.14–1.34)
3	7	1.01 (0.23–4.54)	14	0.96 (0.31–3.00)	20	2.93 (0.95–9.03)	25	1.04 (0.33–3.23)
4	13	1.88 (0.46–7.72)	13	1.39 (0.43–4.56)	18	2.33 (0.76–7.19)	26	0.70 (0.24–2.08)
≥ 5	28	1.73 (0.46–6.55)	30	1.05 (0.37–2.96)	49	2.80 (1.00–7.88)†	57	0.64 (0.24–1.73)
Pre-LVAD use								
No	28	REF	33	REF	57	REF	42	REF
Yes	38	0.44 (0.24–0.81)†	43	0.61 (0.34–1.11)	50	1.41 (0.87–2.27)	96	0.39 (0.21–0.75)†

ACEIs/ARBs indicates angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CI, confidence interval; LVAD, left ventricular assist device; REF, reference category.
*Number of nonadherent patients in each category.
†$P<0.05$.

In the absence of severe recurrent bleeding, use of anticoagulants is required after LVAD to maintain pump patency, thus it is not surprising that their use increased post LVAD. Even so, almost 20% of patients did not have pharmacy claims for anticoagulation in the 90 days after LVAD. A small number of patients had a stroke or gastrointestinal bleeding early after LVAD, which could partially account for the results observed. However, it is also plausible that, given the cost of warfarin, some patients might have elected to pay out-of-pocket without involving insurance coverage. However, even in INTERMACS, ≈10% to 15% of patients were not documented as taking warfarin after LVAD.[5] We also found that nearly one quarter of patients used enoxaparin in the year after LVAD. While no guidelines exist to support its use after LVAD, it has been shown to have biologic efficacy in the LVAD population.[25] Although there has been interest in understanding whether it is safe to use novel oral anticoagulants as an alternative to warfarin post-LVAD implantation,[26] we saw no evidence of their use in our study. Finally, AAD use was also significantly increased following LVAD placement. Ventricular arrhythmias occur in approximately one third of patients with LVAD, with the highest incidence observed during the first 2 weeks of mechanical support,[27,28] thereby providing a plausible explanation for the observed increase in use.

To the best of our knowledge, this is the first study to examine medication adherence after LVAD. We found that a substantial proportion of patients had poor adherence to medications such as β-blockers and ACEIs/ARBs following LVAD implantation. However, many patients with poor adherence discontinued use of medications in that class completely. We cannot determine whether patients discontinued use after discussing with their physician, and whether discontinuation was caused by intolerance or other reasons. Pre-LVAD medication use was significantly associated with

better adherence for β-blockers and loop diuretics; familiarity with and tolerance of these medications before LVAD placement may have contributed to better adherence post-LVAD. Studies have demonstrated that nonadherence to HF treatments is associated with increased risk of hospital readmission and death, and that interventions to improve adherence can improve these outcomes.[6,22,29] Further work is needed to delineate the reasons for nonadherence after LVAD and examine the associations of nonadherence and outcomes.

Study Limitations

First, the Optum Labs Data Warehouse includes individuals enrolled in private and Medicare Advantage health plans, and findings may not be generalizable to populations with other health insurance types. Second, medications purchased out-of-pocket (without submitting to insurance) would not be captured in our analysis. Third, we do not have information on the LVAD models used or their indication (bridge-to-transplant or destination therapy). Fourth, as with any claims-based study, there is potential for misclassification when relying on billing codes to identify comorbidities. Finally, as with all research conducted using pharmacy claims, we were unable to distinguish whether patients stopped a medication based on physician instruction or of their own accord. Reasons for poor adherence could not be determined and would be of interest to examine in future studies.

Conclusions

The use of β-blockers and ACEIs/ARBs, the cornerstones of HF medical therapy, did not increase following LVAD implantation. Medication adherence post LVAD was suboptimal in many patients. Further studies are needed to determine the optimal use of HF medications after LVAD.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Variable Definitions

Variable	Baseline Comorbidity or Outcome	ICD Codes
Diabetes mellitus[1, 2]	Comorbidity	250.XX, 253.5
Hypertension[1, 2]	Comorbidity	401.X, 402.XX, 403.XX, 404.00, 404.10, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.XX, 437.2
Cerebrovascular Disease[1, 2]	Comorbidity	430, 431, 432.1, 432.9, 433.00, 433.1, 433.10, 433.11, 433.20, 433.21, 433.30, 433.31, 433.91, 434.0, 434.00, 434.01, 434.10, 434.11, 434.9, 434.90, 434.91, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437.0, 437.1, 437.3, 437.4, 437.5, 437.7, 437.8, 437.9, 438, 438.0, 438.10, 438.11, 438.12, 438.19, 438.20, 438.21, 438.22, 438.50, 438.6, 438.7, 438.81, 438.82, 438.83, 438.84, 438.85, 438.89, 438.9
Chronic pulmonary disease[3]	Comorbidity	416.8, 416.9, 490.x- 505.x, 506.4, 508.1, 508.8
Moderate/Severe Renal Disease[3]	Comorbidity	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92. 404.93, 582.x, 538-583.7, 585.x, 586.x, 588.x, V42.0, V45.1, V56.x Added 584.X (acute kidney failure)
Cardiac Arrhythmias	Comorbidity	427.x
Gastrointestinal Bleeding[4]	Comorbidity and Post-left ventricular assist device outcome	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x
Myocardial Infarction[3]	Comorbidity	410.X, 412.X
Stroke/ transient ischemic attack[4]	Post-left ventricular assist device outcome	430, 431, 433.x1, 434.x1, 435.x, 436

Baseline comorbidities were identified by examining diagnosis codes in position 1-3 in the inpatient or outpatient setting. Outcomes (GI bleeding, stroke/ TIA) occurring post-LVAD were examined using at inpatient codes in the first and second position. When assessing stroke, events with a primary discharge diagnosis of rehabilitation (ICD-9-CM code V57) or any additional diagnoses of trauma (ICD-9-CM codes 800-804 and 850-854) were excluded. When assessing gastrointestinal bleeding, we excluded the events that had a primary discharge diagnosis of rehabilitation (ICD-9-CM code V57)

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