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ORIGINAL RESEARCH

Relationship Between Hospital Characteristics and Early Adoption of Angiotensin-Receptor/Neprilysin Inhibitor Among Eligible Patients Hospitalized for Heart Failure

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***Background*—**The angiotensin-receptor/neprilysin inhibitor (ARNI) sacubitril/valsartan reduces hospitalization and mortality for patients with heart failure with reduced ejection fraction. However, adoption of ARNI into clinical practice has been slow. Factors influencing use of ARNI have not been fully elucidated. Using data from the Get With The Guidelines-Heart Failure registry, Hospital Compare, Dartmouth Atlas, and the American Hospital Association Survey, we sought to identify hospital characteristics associated with patient-level receipt of an ARNI prescription.

***Methods and Results*—**We analyzed patients with heart failure with reduced ejection fraction who were eligible for ARNI prescription (ejection fraction≤40%, no contraindications) and hospitalized from October 1, 2015 through December 31, 2016. We used logistic regression to estimate the associations between hospital characteristics and patient ARNI prescription at hospital discharge, accounting for clustering of patients within hospitals using generalized estimating equation methods and adjusting for patient-level covariates. Of 16 674 eligible hospitalizations from 210 hospitals, 1020 patients (6.1%) were prescribed ARNI at discharge. The median hospital-level proportion of patients prescribed ARNI was 3.3% (Q1, Q3: 0%, 12.6%). After adjustment for patient-level covariates, for-profit hospitals had significantly higher odds of ARNI prescription compared with not-for-profit hospitals (odds ratio, 2.53; 95% CI, 1.05–6.10; *P*=0.04), and hospitals located in the Western United States had lower odds of ARNI prescription compared with those in the Northeast (odds ratio, 0.33; 95% CI, 0.13–0.84; *P*=0.02).

***Conclusions*—**Relatively few hospital characteristics were associated with ARNI prescription at hospital discharge, in contrast to what has been observed in early adoption in other disease areas. Additional evaluation of barriers to implementing new evidence into heart failure practice is needed. **(*J Am Heart Assoc*. 2019;8:e010484. DOI: 10.1161/JAHA.118.010484.)**

Key Words: early adoption • implementation science • novel therapy • quality improvement

In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, patients with heart failure (HF) and reduced ejection fraction randomized to the novel angiotensin-receptor/neprilysin inhibitor (ARNI) sacubitril/valsartan had 20% lower risk of cardiovascular death and 16% lower risk of all-cause death compared with those treated with enalapril, with a consistent benefit observed with ARNI therapy across all subgroups.[1] The US Food and Drug Administration (FDA) approved the use of sacubitril/valsartan within 6 months of

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Accompanying Tables S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010484

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Clinical Perspective

What Is New?

- Among hospitalized heart failure patients, angiotensin-receptor/neprilysin inhibitor prescription at discharge was generally low. Discharge from for-profit hospitals was independently associated with higher odds of patient receipt of ARNI prescription.
- There were also regional differences, and a higher score on a composite of non–heart failure-related quality metrics was associated with lower odds of angiotensin-receptor/neprilysin inhibitor prescription.

What Are the Clinical Implications?

- More investigation and understanding of these and other characteristics of early adopters of novel therapy can help reduce variation in future uptake and improve outcomes.

trial publication in July 2015. Within another 12 months, this novel therapy was given a class I recommendation for eligible patients with heart failure and reduced ejection fraction in the May 2016 update to the American College of Cardiology, American Heart Association, and Heart Failure Society of America HF management guidelines.[2] Despite its retail cost, multiple subsequent cost-effectiveness analyses have shown sacubitril/valsartan to be generally below the threshold for cost-effective and high-value therapy based on incremental costs per quality-adjusted life years saved.[3–5] Recent randomized clinical trial results suggest ARNI therapy can be safely initiated in patients hospitalized for acute decompensated heart failure.[6] Even with the substantial potential benefits of optimal use, initial adoption of ARNI therapy has been slow.[7,8] Prior work from other disease areas suggests that variation in care patterns may, in part, be a function of hospital characteristics including teaching status, geographic region, and bed size,[9–12] but whether these factors are associated with early adoption of HF therapies is unknown.

Following the 2001 Institute of Medicine report "Crossing the Quality Chasm," which highlighted the potential gaps in quality attributed to poor implementation of evidence-based care, the efficient application of research findings into practice has received renewed priority.[13] Despite added scrutiny and initiation of quality improvement programs, implementation of clinical trial results into practice has remained sluggish. In the example of mineralocorticoid receptor antagonists, adoption remained only in about a third of adult patients hospitalized with HF almost 8 years after initial publication of results.[14,15] As novel therapies are integrated into routine practice, evaluating the characteristics of early adopters and factors associated with variation in uptake can inform initiatives to improve delivery of guideline-recommended care and reduce variation across providers. Understanding these factors may then help identify targeted opportunities for improvement in healthcare delivery.

In this study, we aim to assess whether hospital-level variation in ARNI prescription exists among patients discharged with acute HF and examine the relationship between hospital characteristics and patient-level receipt of an ARNI prescription in the initial 18 months following FDA approval.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Data Sources

We used data from the GWTG-HF (Get With The Guidelines-Heart Failure) registry, a national, voluntary, ongoing, prospective data collection and quality improvement initiative of hospitalized patients with HF. Details of the program, including its representativeness and validity, have been described elsewhere.[16,17] Briefly, participating hospitals in the registry submitted clinical history including signs and symptoms, medical history, medications, diagnostic test results, and in-hospital outcomes of consecutive eligible HF hospitalizations using an online case report form. Trained personnel abstracted the data using standardized definitions for all data fields. Patients were eligible if they were admitted for an episode of acute HF or developed worsening HF symptoms during a hospitalization for which HF became the primary discharge diagnosis. The Duke Clinical Research Institute served as the data analysis center and analyzed the aggregate de-identified data for research purposes. Data collection on ARNI prescription or contraindication began 1 week after FDA approval in July 2015. Data quality was monitored through an internet-based system to ensure completeness and accuracy. The current analysis was restricted to hospitals submitting aggregated hospitalizations data with >75% completeness of past medical history and >75% of laboratory results. The Duke University institutional review board approved this study.

Study Population

For this analysis, patient hospitalizations were considered eligible if the patient survived to hospital discharge and had heart failure and reduced ejection fraction (documented ejection fraction of ≤40% or qualitative description of moderate/severe ventricular dysfunction) with information on whether ARNI was prescribed or contraindicated. Contraindications to ARNI therapy were submitted to the registry from a prepopulated list that included angiotensin-converting

enzyme inhibitor use within the prior 36 hours, allergy, hyperkalemia, hypotension, other medical reasons, patient reason, renal dysfunction defined as creatinine >2.5 mg/dL in men or >2.0 mg/dL in women, or system reason. We included eligible hospitalizations from October 1, 2015 through December 31, 2016, to allow for a 3-month run-in period after FDA approval of sacubitril/valsartan. Of 40 606 initial hospitalizations from 245 GWTG-HF participating hospitals, there were 18 649 hospitalizations with information on ARNI prescription that additionally reported no ARNI contraindications. A further 1975 hospitalizations from 35 hospitals were excluded because of missing hospital-level data.

Patient and Hospital Characteristics

Patient characteristics from each hospitalization were obtained from the registry, including demographics, public/private insurance status, medical history, results of laboratory tests, information on procedures and therapy performed in the hospital, and discharge medications and contraindications. Because registry patients are not given unique identifiers, multiple hospitalizations from the same patient may be inadvertently included in the analysis population.

Hospital characteristics were ascertained from 3 sources. From the American Hospital Association annual survey, we obtained information on each participating hospital's total number of beds, US census region, membership in the Council of Teaching Hospitals, annual number of Medicaid discharges, availability of adult interventional catheterization and heart transplantation services, and select variables related to hospital financial structure including profit status, membership in a health maintenance organization and/or accountable care organization, and whether the hospital had salaried physicians. We grouped categories available in the American Hospital Association annual survey on profit management structure into "for-profit," "not-for-profit," and "state/county owned." From the Dartmouth Atlas of Health Care, we used the hospital percentage of an ambulatory visit within 14 days of hospital discharge as a measure of healthcare utilization and quality of care.[18] At a hospital service area level (an aggregate of hospitals), we also included proportion of 30-day prescriptions filled with brand name products from the Dartmouth Atlas. We obtained additional hospital-specific performance measures from the Hospital Compare database reported by the Center for Medicare and Medicaid Services. We obtained data on 4 non-HF-related measures related to recommended inpatient medical and surgical care as indicators of overall care quality. These measures included documentation on the following: (1) influenza vaccination; (2) appropriate initial antibiotics for pneumonia; (3) timely prophylactic treatment to prevent blood clots; and (4) preventative antibiotics 1 hour before surgery. A non-HF composite quality score, created by averaging the 4 quality measures per hospital, was used in the analysis to serve as control for assessment of general hospital quality performance.[19] We also obtained the price-standardized, risk-adjusted Medicare spending per beneficiary from Hospital Compare. This ratio measure compares each hospital's Medicare beneficiary spending to a weighted median across all hospitals. We obtained and report risk-adjusted 30-day HF readmission and mortality data, the excess readmission ratio for HF, and emergency department volume from Hospital Compare, but did not include these measures in our statistical models.

Statistical Analysis

After applying the eligibility criteria, we reported descriptive statistics on the patients represented in the eligible hospitalization records, including demographics, medical history, medical devices, discharge measurements, and medications at discharge. If discharge measurements were unavailable, admission measurements were substituted if available.

For each hospital, we calculated the observed proportion of eligible hospitalizations that resulted in a discharge prescription of ARNI. We generated descriptive statistics (minimum, maximum, mean, median, first quartile, third quartile) and a distribution plot of observed proportions across hospitals.

We also generated descriptive statistics on the distribution of hospital-level factors and reported these statistics in 2 ways. First, we reported on these distributions at the hospitalization level (n=16 674). Next, we aggregated the information on hospital-level factors so that each hospital was represented only once (n=210); in this version, hospitals are weighted equally regardless of the number of eligible hospitalizations.

We then fit a set of logistic regression models to estimate the odds ratios and 95% CI for the unadjusted and adjusted associations between patient-level and hospital-level characteristics and discharge ARNI prescription. The level of observation in these models was the individual hospitalization. We used generalized estimating equations methods to account for clustering of patients within hospitals. First, we fit a series of univariate models for each of the patient-level and hospital-level factors individually. Next, we fit the final fully adjusted model that included all of the patient-level and hospital-level factors.

After applying standard exclusions above for systematic incompleteness of GWTG-HF data at the hospital and patient level, the rate of missing data in the remaining research-ready data set is minimal (usually <10%). Missing data were handled as follows. For variables that have low rates of missingness

Table 1. Descriptive Statistics on Patient-Level Factors for Eligible Hospitalizations From October 1, 2015 Through December 31, 2016

Variable	Overall
N	16 674
ARNI prescribed at discharge	1020 (6.1%)
Demographics	
Age (y), median (Q1, Q3)	69.0 (58.0, 80.0)
Sex, male	10 772 (64.6%)
Race	
White	10 231 (61.4%)
Black	4602 (27.6%)
Other	1841 (11.0%)
Insurance	
Medicaid	3411 (20.5%)
Medicare	7620 (45.7%)
Other/missing	5643 (33.8%)
Medical history	
Ejection fraction (%), median (Q1, Q3)	25.0 (20.0, 33.0)
Coronary artery disease	9562 (57.3%)
Anemia	2820 (16.9%)
Atrial fibrillation or atrial flutter	5865 (35.2%)
Chronic obstructive pulmonary disease	5447 (32.7%)
Diabetes mellitus	7099 (42.6%)
Hyperlipidemia	8728 (52.3%)
Hypertension	13 583 (81.5%)
Prior CABG	3617 (21.7%)
Renal disease	3115 (18.7%)
Smoking in past 12 mo	3887 (23.3%)
CVA/TIA	2619 (15.7%)
Valvular heart disease	2900 (17.4%)
Devices	
CRT-D	1908 (11.4%)
ICD only	3021 (18.1%)
Discharge measurements	
Heart rate (bpm), median (Q1, Q3)	77.0 (69.0, 88.0)
Systolic blood pressure (mm Hg), median (Q1, Q3)	117.0 (105.0, 130.0)
Creatinine (mg/dL), median (Q1, Q3)	1.2 (1.0, 1.7)
Sodium (mEq/L), median (Q1, Q3)	138.0 (135.0, 140.0)
Medications at discharge	
β-Blocker	14 918 (89.5%)
Mineralocorticoid receptor antagonist	5730 (34.4%)
ACE inhibitor or ARB	15 654 (93.9%)
Additional variables for descriptive purposes only	
Medications before admission	
ACE inhibitor or ARB	
No	5874 (35.2%)
Yes	6011 (36.1%)
Missing	4789 (28.7%)
β-Blockers	
No	3561 (21.4%)
Yes	8324 (49.9%)
Missing	4789 (28.7%)
Admission measurements	
Systolic blood pressure (mm Hg), median (Q1, Q3)	133.0 (116.0, 152.0)
Creatinine (mg/dL), median (Q1, Q3)	1.3 (1.0, 1.7)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ARNI, angiotensin-receptor/neprilysin inhibitor; bpm, beats per minute; CABG, coronary artery bypass graft; CRT-D, cardiac resynchronization therapy defibrillator; CVA, cerebrovascular accident; ICD, implantable cardioverter defibrillator; TIA, transient ischemic attack.

(ie, <5% of records), we imputed continuous variables to the overall median value, dichotomous variables to "no," and multichotomous variables to the most frequent categorical value. For variables with >5% missing (including prior HF hospitalization in the past 6 months, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker before admission) we treated the missing values as a separate category. We used a 2-tailed α=0.05 to establish statistical significance and report 95% CI. All analyses were performed in SAS version 9.4 (Cary, NC).

Results

We included 16 674 hospitalizations from October 1, 2015 through December 31, 2016 from 210 hospitals. Median age was 69 years, 64.6% of patients were male, and 27.6% were black. Table 1 shows the baseline patient characteristics of the study population. Patients had a high proportion of comorbid conditions, including coronary artery disease (57%), atrial fibrillation or flutter (35%), and diabetes mellitus (43%). The median ejection fraction was 25% (Q1, Q3; 20%, 33%), and 30% of patients had implantable device therapy. β-Blocker therapy was prescribed at discharge for 90% of patient hospitalizations, and mineralocorticoid receptor antagonists were prescribed in more than a third of discharges. Table S1

Table 2. Descriptive Statistics for Hospital Characteristics at the Patient and Hospital Level

Variable	Hospital Level	Patient Level
N	210	16 674
GWTG-HF variables		
Number of beds, median (Q1, Q3)	333 (211, 508)	456 (297, 679)
Teaching hospital	164 (78.1%)	14 947 (89.6%)
Region		
Northeast	65 (31.0%)	5244 (31.5%)
Midwest	40 (19.0%)	2622 (15.7%)
South	64 (30.5%)	6080 (36.5%)
West	41 (19.5%)	2728 (16.4%)
Percentage Medicaid patients, median (Q1, Q3)	13.2 (3.6, 25.0)	17.2 (8.8, 28.8)
Hospital Compare variables		
Medicare spending per beneficiary, % relative to national weighted median, median (Q1, Q3)	0.0 (−3.0, 3.0)	1.0 (−3.0, 3.0)
Composite of external (non-HF) quality measures, median (Q1, Q3)	95.8 (92.8, 97.3)	95.5 (93.3, 96.8)
Influenza vaccination (%), Median (Q1, Q3)	96.0 (91.0, 99.0)	96.0 (93.0, 98.0)
Antibiotics for pneumonia patients (%), median (Q1, Q3)	97.0 (95.0, 99.0)	98.0 (96.0, 99.0)
Antibiotics for surgery patients (%), median (Q1, Q3)	99.0 (99.0, 100.0)	99.0 (99.0, 100.0)
Blood clots prevention (%), median (Q1, Q3)	91.5 (86.0, 97.0)	89.0 (86.0, 94.0)
Dartmouth atlas of healthcare variables		
Ambulatory visit within 14 d of discharge to home (%), median (Q1, Q3)	62.7 (57.7, 66.9)	62.8 (57.7, 66.9)
30-d prescriptions filled with brand-name products (%), HSA-level, median (Q1, Q3)	26.9 (24.8, 29.0)	27.2 (25.0, 29.3)
American Hospital Association survey (2015) variables		
Heart transplant performed	14 (6.7%)	1514 (9.1%)
Interventional cardiac catheterization at site	175 (83.3%)	15 318 (91.9%)
Integrated salary model	97 (46.2%)	7255 (43.5%)
Profit status		
For-profit	23 (11.0%)	1186 (7.1%)
Not-for-profit	153 (72.9%)	12 466 (74.8%)
Government (state/county/city)	34 (16.2%)	3022 (18.1%)
Health maintenance organizations	16 (7.6%)	1215 (7.3%)
Hospital Compare variables for descriptive analysis only		
Emergency department volume		
Low/medium (0 to <40K patients annually)	63 (30.0%)	2643 (15.9%)
High (40K to <60K patients annually)	50 (23.8%)	3719 (22.3%)
Very high (≥60K patients annually)	97 (46.2%)	10 312 (61.8%)
30-d mortality for HF patients (%), median (Q1, Q3)	11.8 (10.7, 13.1)	11.5 (10.4, 12.8)
30-d readmission for HF patients (%), median (Q1, Q3)	21.6 (20.7, 22.9)	21.7 (20.9, 23.3)
Risk-adjusted excess readmission ratio for HF, % relative to national average, median (Q1, Q3)	−0.8 (−6.8, 5.4)	1.0 (0.9, 1.1)

GWTG-HF indicates Get With The Guidelines-Heart Failure; HF, heart failure; HSA, hospital service area.

compares baseline patient characteristics by ARNI prescription at discharge.

Table 2 shows the characteristics of included hospitals; the data are shown for both the patient level (n=16 674) and the hospital level (n=210). In the hospital-level data presented, all hospitals were equally weighted, regardless of number of HF hospitalizations. Nearly 80% of hospitals were teaching facilities. In general, hospitals reported >90%

compliance with Hospital Compare measures of non-HF-related patient quality including influenza vaccination and appropriate antibiotic use. Close to half of hospitals (46%) reported an integrated salary model for physicians, and 11% reported for-profit status. Hospitals included in the analysis had a similar risk-adjusted readmission ratio compared with national average.

During the study period, ARNI was prescribed in 1020 of the 16 674 (6.1%) eligible patient hospitalizations. Figure shows the distribution of ARNI prescription rates across hospitals. At the hospital level, the median rate of ARNI prescription was 3.3% (Q1, Q3; 0%, 12.6%). Of the 210 hospitals that met the eligibility criteria, 73 (34.8%, accounting for a total of 3733 individual hospitalizations) provided zero ARNI prescriptions during the entire study period, and only 42 (20.0%) prescribed ARNI to >20% of eligible discharges.

Table 3 (Table S2) shows unadjusted and adjusted associations between hospital characteristics and ARNI prescription. After adjustment for both patient- and hospital-level covariates, for-profit hospitals had significantly higher odds of ARNI prescription (odds ratio 2.53; 95% CI 1.05–6.10) compared with nonprofit hospitals. Hospitals located in the Western United States had lower odds of ARNI prescription (odds ratio: 0.33; 95% CI: 0.13–0.84) compared with the Northeast United States, the reference region. The composite of Hospital Compare non-HF quality measures was inversely associated with ARNI prescription (odds ratio: 0.89; 95% CI: 0.83–0.96). Larger hospital size, teaching status, and higher 30-day prescription of brand-name pharmaceuticals were not significantly associated with ARNI prescription. Rate of ambulatory follow-up visit after hospitalization, a quality measure previously shown to be associated with improved HF outcomes, was not associated with ARNI prescription.[18] Evaluation of the variance inflation factor did not indicate issues of multicollinearity in the final model (not shown).

Discussion

Most patients hospitalized for HF in this study were not prescribed ARNI therapy at discharge. Prescription rate at discharge varied significantly across hospitals, and almost 35% of hospitals did not prescribe ARNI to any of their eligible patients during the study period. At hospitals with no prescription of ARNI, the representative 3733 individual hospitalizations of HF patients highlight just a small proportion of patients who may have received ARNI therapy. Discharge from for-profit hospitals was independently associated with higher odds of patient receipt of ARNI prescription. Regional differences and a higher score on a composite of non-HF-related quality metrics were associated with lower odds of ARNI prescription.

Several factors may have contributed to slow adoption of ARNI since FDA approval, yet empiric data on specific contributors are lacking. Our current analysis uniquely combines data from 3 sources to systemically assess the relationship between hospital-level factors that influence ARNI prescription rates in the initial period following FDA approval. The impact associated with changing the status quo affects both patients and healthcare systems. Particularly salient to HF, where ARNI therapy disrupts patterns of care that have existed for decades, both patients and physicians have been criticized for "therapeutic inertia."[20] However, high retail price, lack of early formulary access, and lengthy prior authorization processes all likely contribute to slow adoption. As select payers have instituted contracts with the pharmaceutical company, adoption may increase in certain regions. In addition, the current healthcare environment emphasizes efficiency and cost-effectiveness and may explain why we observed lower odds of ARNI therapy among hospitals that scored highly on non-HF quality measures. Hospitals emphasizing performance measures selected by the Joint Commission/Centers for Medicare and Medicaid Services may score highly on monitored quality metrics at the expense of noncore performance measures. Systems of care in these hospitals, including admission and discharge order sets and algorithms, may promote efficiency of care over consideration of novel therapies. Our finding that hospitals located in the Western United States were associated with lower odds of ARNI prescription may reflect geographic patterns in payer mix. Patient-level barriers may include high retail and/or copay costs, in addition to the time away from work and financial costs of additional laboratory tests and clinic visits. In our analysis, for-profit hospital status was associated with higher odds of ARNI prescription. While not a perfect proxy for

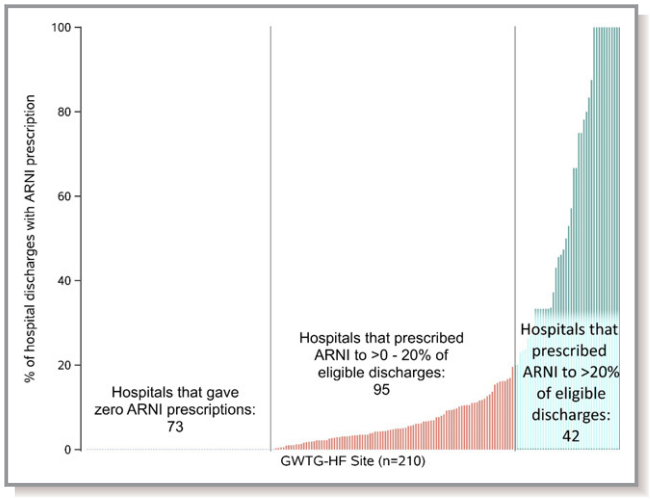

Figure. Distribution of unadjusted angiotensin-receptor/neprilysin inhibitor (ARNI) prescription proportions across hospitals. GWTG-HF indicates Get With The Guidelines-Heart Failure.

Table 3. Unadjusted and Adjusted Odds Ratios for the Association Between Hospital-Level Factors and ARNI Prescription at Discharge

Variable	Unadjusted*		Adjusted†	
	Odds Ratios (95% CI)	*P* Value	Odds Ratios (95% CI)	*P* Value
GWTG-HF Registry				
Number of beds, per 50-bed increment	1.00 (0.96–1.04)	0.99	0.98 (0.93–1.03)	0.33
Teaching hospital	0.79 (0.43–1.45)	0.44	0.58 (0.30–1.14)	0.12
Region				
Northeast	REF		REF	
Midwest	0.99 (0.47–2.06)	0.97	0.96 (0.44–2.07)	0.91
South	1.09 (0.57–2.07)	0.80	1.05 (0.56–1.98)	0.88
West	0.44 (0.17–1.11)	0.08	0.33 (0.13–0.84)	0.02
Percentage Medicaid patients, per 5%	0.98 (0.88–1.10)	0.71	0.95 (0.85–1.08)	0.45
Hospital Compare				
Medicare spending per beneficiary, % relative to national median	1.03 (0.99–1.08)	0.15	1.00 (0.96–1.05)	0.85
Composite of external (non-HF) quality measures, per 1% increment‡	0.94 (0.87–1.02)	0.14	0.89 (0.83–0.96)	0.003
Dartmouth Atlas of Health Care				
Ambulatory visit within 14 d of hospital discharge, per 5%	0.92 (0.81–1.04)	0.18	1.03 (0.89–1.19)	0.72
30-d prescriptions filled with brand-name products, per 5%	1.57 (1.11–2.21)	0.01	1.26 (0.78–2.05)	0.35
American Hospital Association Survey				
Heart transplants performed at hospital	0.97 (0.35–2.68)	0.95	0.76 (0.33–1.74)	0.52
Integrated salary model	1.26 (0.75–2.12)	0.38	1.52 (0.87–2.65)	0.14
Interventional cardiac catheterization performed at hospital	1.32 (0.60–2.91)	0.49	1.32 (0.59–2.94)	0.50
Profit status				
Not-for-profit	REF		REF	
For-profit	1.86 (0.83–4.16)	0.13	2.53 (1.05–6.10)	0.04
Government (State/County/City)	1.32 (0.62–2.80)	0.47	1.51 (0.56–4.05)	0.41
Health maintenance organization (HMO)	1.00 (0.42–2.39)	0.99	1.05 (0.45–2.46)	0.90

ARNI indicates angiotensin-receptor neprilysin inhibitor; GWTG-HF, Get With The Guidelines-Heart Failure; HF, heart failure.
*Unadjusted estimates are from univariate models containing only that variable.
†Adjusted estimates are derived from a fully adjusted model that includes all of the patient- and hospital-level factors. Patient-level factors used in the model are included in Table S2.
‡These measures included documentation on the following: (1) influenza vaccination, (2) appropriate initial antibiotics for pneumonia, (3) timely prophylactic treatment to prevent blood clots, and (4) preventative antibiotics 1 h before surgery. A noncardiac composite quality score, created by averaging the 4 quality measures per hospital, was used in the analysis to serve as control for assessment of general hospital quality performance.

patient-level socioeconomic status, for-profit hospital status may be associated with availability of economic and social resources at the patient level, which may reduce barriers to uptake. Future work examining the independent effect of socioeconomic status and use of novel therapies is needed.

Continued work is also necessary to further understand barriers outside the scope of our current analysis. In the context of our analysis, clinicians may have been reticent to institute novel therapeutic changes during a hospitalization for HF. There remain theoretical unknowns regarding real-world tolerability and optimal timing for initiation necessitating thoughtful consideration. In PARADIGM-HF, sacubitril/valsartan was initiated in outpatients with heart failure and reduced ejection fraction rather than in patients hospitalized with HF. However, recent randomized clinical trial results suggest that ARNI initiation during a hospitalization for acute HF resulted in greater reductions in N-terminal pro-brain natriuretic peptide concentration than enalapril therapy with no associated differences in side effects such as symptomatic hypotension and renal insufficiency.[6] Additionally, within PARADIGM-HF patients who were hospitalized for HF during the trial, sacubitril/valsartan treatment was associated with significantly lower risk of all-cause and HF-specific hospital readmission compared with enalapril.[21] Medication prescription at the time of discharge can be a strong predictor of long-term patient drug adherence in cardiovascular disease.[22,23] More efforts are

necessary to characterize long-term outcomes in these and other special populations receiving ARNI. Widespread registries for populations not studied in PARADIGM-HF in addition to other initiatives may provide additional data to support the implementation of novel evidence-based medicines.

Limitations

Our study has several key limitations. First, data on inpatient ARNI adjustments and tolerability, postdischarge initiation, and adherence to ARNI therapy were not available. Contraindications to ARNI therapy were abstracted based on documentation in the medical record, so some patients may have had undocumented contraindications or intolerances that precluded prescription. Second, the registry is a voluntary initiative, and data may not be representative of all US hospitals. However, prior study has shown that GWTG-HF hospitals have characteristics similar to hospitals nationwide.[17]

Conclusions

Among patients hospitalized for HF, ARNI prescription varied substantially across hospitals. In contrast to what has been observed in other disease areas, few key hospital characteristics were associated with patterns of care after adjustment for patient factors. Further study is needed to understand and minimize additional system- and provider-level barriers to implementing new evidence-based therapies into practice.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics by ARNI prescription at discharge.

Variable	Not Prescribed ARNI	Prescribed ARNI	p-value
N	15,654	1,020	
Demographics			
Age (years), Median (Q1, Q3)	69.0 (58.0, 81.0)	67.0 (57.0, 76.5)	< .001
Sex, Male	10,114 (64.6%)	658 (64.5%)	.95
Race			.001
White	9,635 (61.5%)	596 (58.4%)	
Black or African American	4,272 (27.3%)	330 (32.4%)	
Other	1,747 (11.2%)	94 (9.2%)	
Insurance			.48
Medicaid	3,209 (20.5%)	202 (19.8%)	
Medicare	7,165 (45.8%)	455 (44.6%)	
Other/Missing	5,280 (33.7%)	363 (35.6%)	
Medical History			
Ejection fraction (%), Median (Q1, Q3)	25.0 (20.0, 33.0)	22.5 (18.0, 28.5)	< .001
Ischemic etiology	8,913 (56.9%)	649 (63.6%)	< .001
Anemia	2,656 (17.0%)	164 (16.1%)	.46
Atrial fibrillation or atrial flutter	5,492 (35.1%)	373 (36.6%)	.34
Chronic obstructive pulmonary disease	5,101 (32.6%)	346 (33.9%)	.38
Diabetes mellitus	6,615 (42.3%)	484 (47.5%)	.001
Heart failure hospitalization in prior 6 months			.07
No	3,505 (22.4%)	212 (20.8%)	
Yes	3,186 (20.4%)	237 (23.2%)	
Missing	8,963 (57.3%)	571 (56.0%)	
Hyperlipidemia	8,142 (52.0%)	586 (57.5%)	< .001
Hypertension	12,719 (81.3%)	864 (84.7%)	.006
Prior CABG	3,365 (21.5%)	252 (24.7%)	.02
Renal disease	2,960 (18.9%)	155 (15.2%)	.003
Smoking in past 12 months	3,687 (23.6%)	200 (19.6%)	.004
CVA/TIA	2,450 (15.7%)	169 (16.6%)	.44
Valvular heart disease	2,687 (17.2%)	213 (20.9%)	.002
Devices			
CRT-D	1,660 (10.6%)	248 (24.3%)	< .001
ICD only	2,710 (17.3%)	311 (30.5%)	< .001
Discharge measurements			
Heart rate (bpm), Median (Q1, Q3)	77.0 (69.0, 88.0)	76.0 (69.0, 86.0)	.006
Systolic blood pressure (mmHg), Median (Q1, Q3)	117.0 (105.0, 131.0)	112.0 (101.0, 125.0)	< .001

Variable	Not Prescribed ARNI	Prescribed ARNI	p-value
Creatinine (mg/dL), Median (Q1, Q3)	1.3 (1.0, 1.7)	1.2 (1.0, 1.5)	.002
Sodium (mEq/L), Median (Q1, Q3)	138.0 (135.0, 140.0)	138.0 (136.0, 140.0)	.04
Medications at discharge			
Beta blocker	13,987 (89.4%)	931 (91.3%)	.05
Mineralocorticoid receptor antagonist	5,238 (33.5%)	492 (48.2%)	< .001
Additional variables for descriptive purposes only:			
Medications prior to admission			
ACE or ARB			< .001
No	5,503 (35.2%)	371 (36.4%)	
Yes	5,779 (36.9%)	232 (22.7%)	
Missing	4,372 (27.9%)	417 (40.9%)	
Beta blockers			< .001
No	3,449 (22.0%)	112 (11.0%)	
Yes	7,833 (50.0%)	491 (48.1%)	
Missing	4,372 (27.9%)	417 (40.9%)	
Admission measurements			
Systolic blood pressure (mmHg), Median (Q1, Q3)	133.0 (116.0, 152.0)	132.0 (114.0, 147.0)	< .001
Creatinine (mg/dL), Median (Q1, Q3)	1.3 (1.0, 1.7)	1.3 (1.0, 1.5)	.04

Table S2. Unadjusted and adjusted odds ratios for the association between patient-level factors and angiotensin-receptor/neprilysin inhibitor (ARNI) prescription at discharge.

	Unadjusted[a]		Adjusted[b]	
Variable	**Odds Ratios (95% CI)**	**p-value**	**Odds Ratios (95% CI)**	**p-value**
Patient-Level Factors				
Demographics				
Age (years), per 10 year increment	0.90 (0.87–0.93)	<0.001	0.90 (0.86–0.95)	<0.001
Sex, Male	1.03 (0.95–1.11)	046	0.93 (0.85–1.03)	0.15
Race				
White	REF		REF	
Black or African-American	1.29 (1.14–1.46)	<0.001	1.14 (1.00–1.31)	0.05
Other	1.19 (1.08–1.32)	<0.001	1.12 (0.96–1.30)	0.16
Insurance				
Medicare	REF		REF	
Medicaid	1.16 (1.04–1.30)	0.009	0.98 (0.87–1.12)	0.81
Other/Unknown	1.05 (0.96–1.16)	0.27	1.00 (0.90–1.11)	0.98
Medical history				.
Ejection fraction (%), per 5% increment	0.86 (0.84–0.89)	<0.001	0.90 (0.88–0.92)	<0.001
Ischemic etiology	1.08 (1.01–1.15)	0.03	1.07 (0.98–1.18)	0.14
Anemia	0.96 (0.87–1.06)	0.40	0.99 (0.88–1.11)	0.86
Atrial fibrillation or atrial flutter	0.98 (0.92–1.05)	0.54	0.97 (0.89–1.06)	0.46
Chronic obstructive pulmonary disease	1.02 (0.95–1.09)	0.57	0.99 (0.91–1.08)	0.83
Diabetes mellitus	1.12 (1.06–1.19)	<0.001	1.15 (1.07–1.24)	<0.001
Hyperlipidemia	1.09 (1.01–1.18)	0.03	1.08 (0.97–1.19)	0.14
Hypertension	1.07 (1.00–1.15)	0.04	1.11 (1.01–1.22)	0.03
Prior CABG	1.04 (0.96–1.12)	0.32	1.02 (0.92–1.13)	0.73
Renal disease	0.80 (0.73–0.88)	<0.001	0.79 (0.70–0.88)	<0.001
Smoking in past 12 months	0.99 (0.91–1.07)	0.73	0.89 (0.80–1.00)	0.04
CVA/TIA	1.03 (0.94–1.13)	0.53	1.03 (0.92–1.16)	0.58
Valvular heart disease	1.14 (1.03–1.27)	0.01	1.17 (1.03–1.33)	0.01
Devices				
None	REF		REF	
ICD only	1.65 (1.48–1.84)	<0.001	1.50 (1.33–1.69)	<0.001
CRT-D	2.07 (1.78–2.40)	<0.001	1.97 (1.69–2.30)	<0.001
Discharge measurements				
Heart rate (bpm)	1.00 (1.00–1.00)	0.48	1.00 (0.99–1.00)	0.06
Systolic blood pressure, per 5mmHg increment	0.96 (0.95–0.97)	<0.001	0.98 (0.96–0.99)	<0.001
Serum creatinine (mg/dL)	0.98 (0.92–1.04)	0.55	1.00 (0.96–1.04)	0.93
Sodium (mEq/L)	1.00 (1.00–1.00)	0.34	1.00 (1.00–1.01)	0.27
Medications at discharge				
Beta blocker	1.26 (1.12–1.42)	<0.001	1.25 (1.09–1.43)	0.002
Mineralocorticoid receptor antagonist	1.44 (1.31–1.59)	<0.001	1.25 (1.12–1.40)	<0.001