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PERSPECTIVES

Early Adoption of Sacubitril/Valsartan for Patients With Heart Failure With Reduced Ejection Fraction

Insights From Get With the Guidelines–Heart Failure (GWTG-HF)

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ABSTRACT

OBJECTIVES The aim of this study was to assess the prevalence and variation in angiotensin receptor/neprilysin inhibitor (ARNI) prescription among a real-world population with heart failure with reduced ejection fraction (HFrEF).

BACKGROUND The U.S. Food and Drug Administration approved sacubitril/valsartan for patients with HFrEF in July 2015. Little is known about the early patterns of use of this novel therapy.

METHODS The study included patients discharged alive from hospitals in Get With the Guidelines–Heart Failure (GWTG-HF), a registry of hospitalized patients with heart failure, between July 2015 and June 2016 who had documentation of whether ARNIs were prescribed at discharge. Patient and hospital characteristics were compared among patients with HFrEF (ejection fraction ≤40%) with and without ARNI prescription at discharge, excluding those with documented contraindications to ARNIs. To evaluate hospital variation, hospitals with at least 10 eligible hospitalizations during the study period were assessed.

RESULTS Of 21,078 patients hospitalized with HFrEF during the study period, 495 (2.3%) were prescribed ARNIs at discharge. Patients prescribed ARNIs were younger (median age 65 years vs. 70 years; $p < 0.001$), had lower ejection fractions (median 23% vs. 25%; $p < 0.001$), and had higher use of aldosterone antagonists (45% vs. 31%; $p < 0.001$) at discharge. At the 241 participating hospitals with 10 or more eligible admissions, 125 (52%) reported no discharge prescriptions of ARNIs.

CONCLUSIONS Approximately 2.3% of patients hospitalized for HFrEF in a national registry were prescribed ARNI therapy in the first 12 months following Food and Drug Administration approval. Further study is needed to identify and overcome barriers to implementing new evidence into practice, such as ARNI use among eligible patients with HFrEF. (J Am Coll Cardiol HF 2017;5:305–9) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor/neprilysin inhibitor

FDA = U.S. Food and Drug Administration

GWTG-HF = Get With the Guidelines-Heart Failure

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

In July 2015, the U.S. Food and Drug Administration (FDA) approved the angiotensin receptor/neprilysin inhibitor (ARNI) sacubitril/valsartan for patients with heart failure (HF) with reduced ejection fraction (HFrEF), on the basis of a 20% reduction in cardiovascular death or hospitalization for HF observed in the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (1). However, few data are currently available on early patterns of use of this novel therapy at the national level. Using data from the American Heart Association's Get With the Guidelines-Heart Failure (GWTG-HF) Registry, we describe contemporary patterns of ARNI prescription at discharge among a real-world hospitalized HFrEF population in the United States. During the 1-year period following FDA approval, we compared characteristics of eligible patients with HFrEF receiving ARNI therapy with those who did not, as well as characteristics of hospitals with any versus no use of ARNI therapy.

METHODS

To describe patterns of early ARNI use, we used data from the GWTG-HF Registry, a national registry of patients hospitalized for HF from 2005 to the present. Trained personnel abstracted data using standardized definitions for all data elements, including demographic and clinical characteristics, medical history, admission laboratory data, therapies on admission, discharge therapies, and in-hospital outcomes. Records from sites not reporting medical history for more than 25% of hospitalizations were excluded, as were individual records that were completely missing the medical history panel. We identified patients with HF with ejection fractions ≤40% who were discharged alive between July 2015 and June 2016 with information on discharge ARNI prescription and ARNI contraindications (n = 31,647). For the present study, we excluded patients with documented contraindications to ARNI therapy (n = 10,569). Contraindications or intolerances included: 1) angiotensin-converting enzyme inhibitor use within the prior 36 h; 2) allergy; 3) hyperkalemia; 4) hypotension; 5) other medical reasons; 6) patient reason; 7) renal dysfunction, defined as creatinine >2.5 mg/dl in men and >2.0 mg/dl in women; and 8) system reason. To evaluate hospital variation in use of ARNI therapy among patients with HF, we calculated observed discharge prescription rates among hospitals with 10 or more eligible hospitalizations.

We compared baseline characteristics of patients who received ARNI therapy with those who did not using chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. A similar approach was used to compare characteristics of hospitals with at least 1 patient prescribed an ARNI at discharge during the study period versus those with no patients prescribed ARNIs at discharge. We used a 2-sided $\alpha = 0.05$ to establish statistical significance and used SAS version 9.4 (SAS Institute, Cary, North Carolina) for all analyses. The Institutional Review Board of the Duke University Health System approved the study and granted a waiver of consent.

RESULTS

Our final study population included 21,078 HFrEF hospitalizations from 347 participating hospitals. During the year following FDA approval, ARNI therapy was prescribed at discharge in 495 hospitalizations (2.3%; 1.0% from July to December 2015 and 3.6% from January to June 2016). Compared with patients with HFrEF not receiving ARNIs, patients prescribed ARNIs were younger (median age 65 years vs. 70 years; $p < 0.001$), had lower ejection fractions (median 23% vs. 25%; $p < 0.001$), and more often had ischemic disease (65% vs. 58%; $p = 0.004$) (**Table 1**). Insurance was not associated with ARNI discharge prescription ($p = 0.21$). Compared with patients not receiving ARNIs, those prescribed ARNIs at discharge were also more likely to be prescribed mineralocorticoid receptor antagonists (45% vs. 31%; $p < 0.001$), but beta-blocker prescription at discharge was similar.

Of the 241 hospitals with 10 or more eligible hospitalizations included in this analysis, the majority

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(52%) reported no discharge prescriptions of ARNI therapy during the 1-year period following approval (Table 2). Among those hospitals with at least 1 ARNI prescription, the percentage of hospitalized patients with HFrEF prescribed ARNI therapy varied substantially, from a low of 0.13% to a high of 90%. The median prescription rate among hospitals with any ARNI use was 3.8% of eligible patients. Hospitals prescribing ARNI therapy to eligible patients with HFrEF were, on average, more likely to be located in the southern United States compared with those that reported no discharge prescriptions for ARNI therapy (Table 2). No differences were observed in teaching status or urban location in hospitals with any versus no ARNI use. Between July 2015 and June 2016, the average monthly discharge ARNI prescription rate at discharge increased from 0.32% in July 2015 to 5.3% in June 2016 (Figure 1).

DISCUSSION

In the PARADIGM-HF trial, the ARNI sacubitril/valsartan reduced cardiovascular mortality or HF hospitalization in patients with HFrEF by 20% (1), leading to FDA approval in July 2015. We evaluated patterns of early ARNI use in a national registry of patients with HF during the year following FDA approval. Our major findings include the following: 1) approximately 2% of patients with HFrEF without documented contraindications were prescribed ARNI therapy at hospital discharge; 2) patients prescribed ARNI therapy were younger; 3) among hospitals prescribing ARNI therapy, the median prescription rate was 3.8% but varied substantially, from a low of 0.13% to a high of 90%; and 4) monthly prescription of ARNI therapy at discharge has increased overall in the 12 months after FDA approval.

Prior work has demonstrated substantial delays in the integration of new evidence into clinical practice and variation in the delivery of guideline-directed care, with the landmark Institute of Medicine report underscoring an average 17-year delay from publication of trial results to widespread uptake (2). Several obstacles to the adoption of ARNI therapy specifically include formulary approval, prior authorization requirements, and high out-of-pocket cost for patients. In fact, the rate increase seen in the latter 6 months of the study period may reflect greater access and easing of formulary restrictions. However, questions regarding real-world tolerability, optimal timing for initiation, and potential concerns regarding an increased risk for macular degeneration and dementia will require further

TABLE 1 Baseline Characteristics of Eligible Hospitalizations

	ARNI Prescribed at Discharge		
	No (n = 20,583)	Yes (n = 495)	p Value
Demographics			
Age (yrs)	70 (58–81)	65 (55–77)	<0.001
Male	13,203 (64.1%)	337 (68.1%)	0.07
Race			<0.001
White	12,435 (60.4%)	286 (57.8%)	
Black or African American	5,055 (24.6%)	155 (31.3%)	
Other	3,093 (15.0%)	54 (10.9%)	
Insurance			0.21
Medicaid	3,838 (18.6%)	99 (20.0%)	
Medicare	9,392 (45.6%)	206 (41.6%)	
Other/missing	7,353 (35.7%)	190 (38.4%)	
Medical history			
Ejection fraction (%)	25.0 (20.0–33.0)	23.0 (19.0–30.0)	<0.001
Ischemic etiology	11,988 (58.2%)	320 (64.6%)	0.004
Atrial fibrillation	6,966 (33.8%)	188 (38.0%)	0.05
Diabetes mellitus	8,879 (43.1%)	255 (51.5%)	<0.001
Renal disease	4,401 (21.4%)	100 (20.2%)	0.53
Stroke/TIA	3,191 (15.5%)	64 (12.9%)	0.12
Discharge measurements			
Systolic blood pressure (mm Hg)*	117.0 (104.0–131.0)	112.0 (101.0–127.0)	<0.001
Creatinine (mg/dl)†	1.3 (1.0–1.7)	1.2 (0.9–1.6)	0.04
Potassium (mEq/l)‡	4.0 (3.8–4.4)	4.0 (3.7–4.4)	0.26
Medications at discharge			
Beta-blockers	18,301 (88.9%)	452 (91.3%)	0.09
Mineralocorticoid receptor antagonists	6,457 (31.4%)	222 (44.8%)	<0.001

Values are median (interquartile range) or n (%). *Information on systolic blood pressure was available for 12,999 discharges without ARNIs and 318 with ARNIs. †Information on creatinine was available for 13,375 discharges without ARNIs and 330 with ARNIs. ‡Information on potassium was available for 9,344 discharges without ARNIs and 179 with ARNIs.

ARNI = angiotensin receptor/neprilysin inhibitor; TIA = transient ischemic attack.

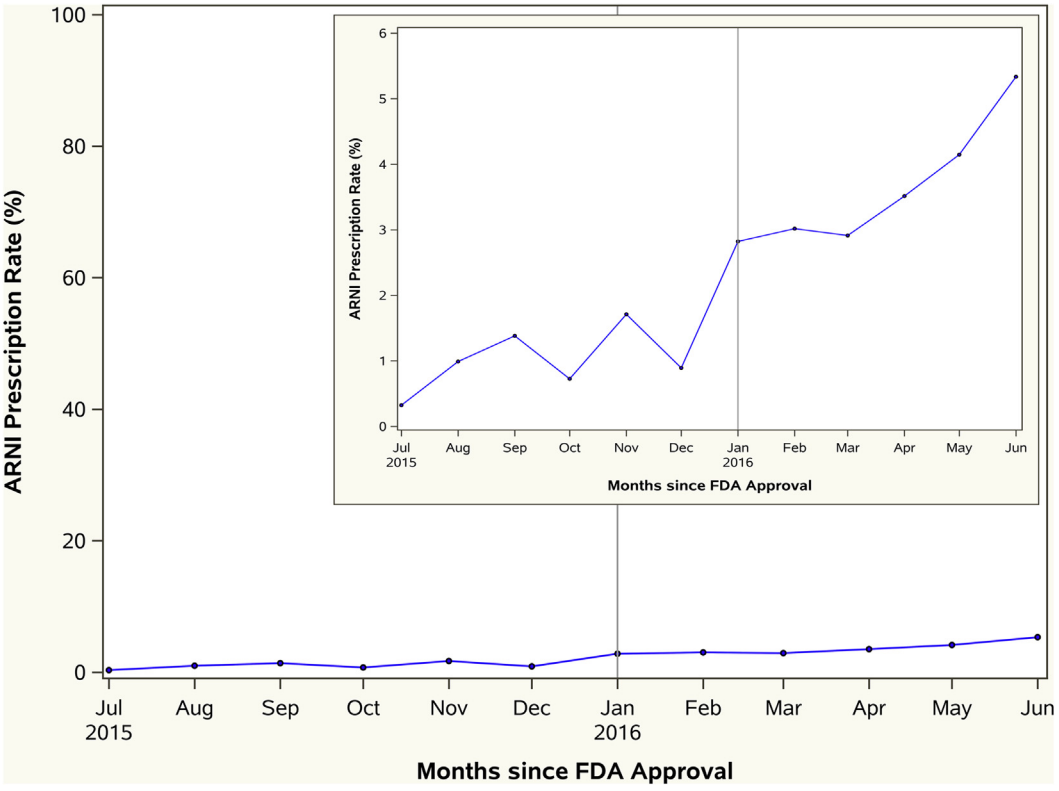
TABLE 2 Hospital Characteristics by Hospital-Level Angiotensin Receptor/Neprilysin Inhibitor Prescription Rates

	ARNI Prescription Rate		
	0 (n = 125)	>0 (n = 116)	p Value
Number of beds	279 (203–425)	345 (227–507)	0.09
Teaching hospital	76 (60.8%)	67 (57.8%)	0.63
Region			0.006
Northeast	29 (23.2%)	31 (26.7%)	
Midwest	35 (28.0%)	20 (17.2%)	
South	33 (26.4%)	51 (44.0%)	
West	28 (22.4%)	14 (12.1%)	
Urban	110 (88.0%)	109 (94.0%)	0.11
Heart transplantation performed	5 (6.4%)	10 (12.2%)	0.21
Primary PCI performed	75 (81.5%)	85 (89.5%)	0.12
Percentage Medicaid patients	12.2 (6.5–21.7)	11.8 (5.7–22.3)	0.70

Values are median (interquartile range) or n (%). The table includes hospitals with 10 or more eligible hospitalizations during the study period. ARNI prescription rates among hospitals with any use: mean 7.3%, median 3.8% (interquartile range: 2.0% to 7.0%), minimum 0.13%, maximum 90.0%. Information for number of beds was available for 124 sites with no ARNI use and 113 sites with ARNI use. Information for heart transplantation was available for 78 sites with no ARNI use and 82 sites with ARNI use. Information for PCI was available for 92 sites with no ARNI use and 95 sites with ARNI use.

ARNI = angiotensin receptor/neprilysin inhibitor; PCI = percutaneous coronary intervention.

FIGURE 1 Angiotensin Receptor/Neprilysin Inhibitor Prescription Rate at Hospital Discharge From July 2015 to June 2016



Among eligible Get With the Guidelines-Heart Failure hospitalizations for heart failure with reduced ejection fraction (ejection fraction ≤40%), the angiotensin receptor/neprilysin inhibitor (ARNI) prescription rate at hospital discharge is low but has increased since U.S. Food and Drug Administration (FDA) approval. The **gray line** defines the 6-month mark since FDA approval (January 1, 2016).

study (3). Despite these barriers, however, ARNI therapy received a Class I recommendation in the American College of Cardiology, American Heart Association, and Heart Failure Society of America guidelines in May 2016, and the benefits of optimal implementation could be substantial (4,5).

STUDY LIMITATIONS. First, data on post-discharge ARNI initiation and adherence to ARNI therapy were not available. Sacubitril/valsartan was not explicitly tested in patients with HFrEF hospitalized with acute HF, and ongoing studies will evaluate patients who initiate this drug during and immediately following hospitalization for decompensated HF (NCT02554890 and NCT02661217). Second, estimates of hospital variation are less precise for sites with fewer patients and are likely to evolve as additional eligible hospitalizations accrue. Finally, the registry is a voluntary initiative, and data may not be representative of all U.S. hospitals.

CONCLUSIONS

We found that ARNI therapy was prescribed in approximately 2 of 100 patients hospitalized for HFrEF during the year following FDA approval. There was substantial variation among participating hospitals in ARNI use and in characteristics of patients receiving ARNI therapy. Further research on barriers to successful implementation of evidence-based therapy into clinical practice is needed.

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