HHS Public Access

Author manuscript

JACC Heart Fail. Author manuscript; available in PMC 2017 February 23.

Published in final edited form as:

JACC Heart Fail. 2013 August ; 1(4): 318–324. doi:10.1016/j.jchf.2013.04.005.

Patterns of Change in Nesiritide Use in Patients with Heart Failure: How Hospitals React to New Information

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Abstract

Objectives—We sought to determine hospital patterns of change in use of nesiritide over a 6-year period following publications of safety concerns in 2005, and to identify hospital characteristics associated with these patterns.

Background—The changing nature of medical evidence often requires a change in practice. Nesiritide was commercialized in 2001 for early relief of dyspnea in patients with decompensated heart failure. In 2005 concerns about its safety led to recommendations to restrict its use. Little is known about how hospitals responded to this information.

Methods—We analyzed data from the Premier database including 403 hospitals contributing 813,783 hospitalizations with heart failure, spanning 2005–2010. We applied a growth mixture modeling approach to hospital-level, risk-standardized, quarterly utilization rates of nesiritide to distinguish hospital groups based on their patterns of change in utilization.

Results—Proportion of hospitalizations using nesiritide declined from 15.4% in 2005 to 1.2% in 2010. The level and speed of change varied markedly among hospitals. After adjusting for differences in patient characteristics across hospitals and years, we identified three distinct groups

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Relationships with Industry: Dr. Krumholz reports that he is the recipient of a research grant from Medtronic, Inc. through Yale University and is chair of a cardiac scientific advisory board for United Health. The other authors report no relationships with industry.

of hospitals: “low utilizers”, “fast de-adopters”, and “slow de-adopters”. In multivariate regression analysis, these groups did not differ in traditional hospital characteristics such as size, urban setting, or teaching status.

Conclusions—We identified three distinct hospital groups characterized by their patterns of change in nesiritide utilization. These trajectory curves can provide hospitals with an important feedback on how fast and effectively they react to new information compared with other hospitals. Uncovering factors that promote organizational learning requires further research.

Keywords

heart failure; drug utilization; hospital; practice patterns; response to new evidence; organizational learning

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The changing nature of medical evidence often requires a change in practice. Studies have described the challenges of translating new information into practice which may take decades, as it did with the beta-Blocker Heart Attack Trial (BHAT).(1) No studies, to our knowledge, have evaluated longitudinal patterns of change in practice at the hospital level. Nesiritide (Natrecor®) provides a good case study of how hospitals changed practices in response to new information. Nesiritide was approved by the Food and Drug Administration (FDA) in 2001 for early relief of dyspnea in patients with acutely decompensated heart failure, but once on the market, it was widely prescribed and used beyond its original indication.(2) In spring 2005, two meta-analyses of small randomized trials raised concerns regarding renal toxicity(3) and higher mortality associated with nesiritide.(4) These publications resulted in an FDA-mandated revision of prescribing information in the “Adverse Reactions/Effects on Mortality” section. A panel of experts recommended in June 2005 that nesiritide be used only in patients with acutely decompensated heart failure who had dyspnea at rest and not to be used for improvement of renal function, enhancement of diuresis, intermittent outpatient infusion, or scheduled repetitive use.(5) To physicians planning the use of nesiritide to relieve symptoms, the panel recommended considering the use of alternative therapies. In 2011, the results of a large randomized trial, i.e., the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), showed that nesiritide had no effect on dyspnea, renal function, mortality or readmission; but was associated with increased rates of hypotension, and it was concluded that nesiritide could not be recommended for routine use in patients with acute heart failure. (6)

Prior work by Hauptman and collaborators has shown that between March and December 2005, the overall use of nesiritide decreased by 66% (from 16.6% to 5.6%).(7) Their study focused on overall change in utilization immediately before and after the publications of safety concerns. Our current study was designed to extend prior work by evaluating the patterns of change among hospitals between 2005 and 2010. We hypothesized that amid a continuing general decrease in nesiritide use, there would be marked heterogeneity in level and speed of de-adoption across hospitals, revealing various institutional responses to new information. We also sought to determine what hospital characteristics would be associated with these distinct hospital groups.

METHODS

Data Source

We used data from a voluntary, fee-supported database developed by Premier, Inc. Charlotte, NC, for measuring quality and health care utilization. Containing over 330 million discharges from 620 geographically diverse hospitals, the database represents one in every five discharges from U.S. hospitals. In addition to the information available in the standard hospital discharge file, the Premier database contains a date-stamped log of all billed items at the individual patient level including medications and laboratory, diagnostic, and therapeutic services. We used data from calendar years 2005–2010 for our analysis.

Patient data are de-identified in accordance with the Health Insurance Portability and Accountability Act and a random hospital identifier assigned by Premier is used to identify individual hospitals. The Yale University Human Investigation Committee determined that this study is not considered to be Human Subjects Research as defined by the Office of Human Research Protections.

Heart Failure cohort

We included in the study cohort, all hospitalizations from January 1, 2005 to December 31, 2010 with a principal diagnosis of heart failure as defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx or a principal diagnosis of respiratory failure (ICD-9-CM code 518.81) with a secondary diagnosis of congestive heart failure (ICD-9-CM code 428.0). We excluded patients who were less than 18 years of age at the time of admission or those whose physicians were pediatricians, since our focus was not on congenital disease. A patient could contribute more than one hospitalization to the study cohort.

Patient and hospital characteristics

Patient characteristics available in our dataset included age, sex, race/ethnicity, insurance status, and comorbidities. We used the Healthcare Costs and Utilization Project software provided by the Agency for Healthcare Research and Quality (AHRQ) to classify comorbidities from the standard hospital discharge file based on methods described by Elixhauser and Steiner.(8)

For each hospital, Premier database contains information, collected from the American Hospital Association database, on bed count, teaching status, geographic location, and whether it serves an urban or rural population. In addition, we derived the following measures about each hospital's characteristics by pooling its patient-level hospitalization data across 2005–2010: average number of HF hospitalizations each year, proportion of the attending physicians being a cardiologist, proportion of patients with Medicaid as the primary payer, whether the hospital had any cardiology intensive care unit, and capability of performing a number of procedures including ventricular assist device (VAD) or heart transplant, percutaneous coronary intervention (PCI), and implantable cardioverter defibrillator (ICD).

Statistical Analysis

Descriptive statistics (frequencies and percentages) were calculated to assess sample characteristics and drug use. We assessed the proportion of nesiritide use at hospitalization-level (denominator being all hospitalizations with HF across all hospitals) and compared it with the use of potential alternative therapies including other vasodilators (intravenous (IV) nitroglycerin and sodium nitroprusside), and positive inotropic agents (dobutamine, dopamine, and milrinone).

We also assessed nesiritide use at hospital-level (denominator being all hospitalizations with HF in a given hospital). Hierarchical generalized linear modeling (HGLM) was used to calculate hospital-level risk-standardized utilization rates of nesiritide.(9) The model included patient demographic characteristics (age groups, sex, race / ethnicity), comorbidities, and a hospital random effect for each calendar quarter. This model specification takes into account within hospital correlation of utilization patterns while adjusting for differences in case mix both across hospitals and over time. The full list of risk-variables included in the HGLM models with their estimated odds ratios and corresponding 95% confidence intervals are reported in Appendix Table

We applied a growth mixture modeling approach to hospital risk-standardized utilization rates via a SAS macro Proc Traj.(10) This approach assumes there are clusters or groupings of distinctive patterns of change in a population.(11) All hospitals that contributed HF hospitalizations in at least one calendar quarter were included in the analysis. Models with different number of trajectory groups were estimated and the optimal number of distinct trajectory groups was determined by comparing the Bayesian Information Criteria (BIC) index across these models. Our final analysis used a three-group model which had the most favorable BIC index. Each hospital was assigned to a trajectory group based on the estimated posterior probability of its group membership (i.e., following a maximum posterior probability assignment rule).(11)

Chi-square tests and Kruskal-Wallis tests were used to assess whether there were any significant associations between individual hospital characteristics and identified trajectory groups. Multivariate multinomial logistic regression analysis was also performed to examine the association between hospital characteristics and trajectory group membership. Stepwise selection algorithm was used to choose the variables included in the final multivariate model. Estimates with $P<0.05$ were considered statistically significant.

Analyses were conducted with SAS version 9.2 (SAS Institute Inc., Cary, NC), and figures were created with R version 2.11.1.(12)

RESULTS

Use of nesiritide at hospitalization-level

Between 2005 and 2010, there were 813,783 hospitalizations with heart failure. Among these hospitalizations, the proportion using nesiritide decreased from 15.4% (5508/35,769) in the first quarter of 2005 to 1.2% (429/35,872) in the last quarter of 2010 (Figure 1). The sharpest drop in use occurred between second and third quarters of 2005 when the odd ratio

(95% CI) for being treated by nesiritide (compared with the last quarter of 2010) dropped from 15.4 (11.9–19.8) to 8.7 (6.7–11.3) Appendix Table. Over the same period, the proportion of hospitalizations including IV nitroglycerin remained stable between 6% and 8%: 6.5% (2,325/35,769) in the first quarter of 2005, and 7.3% (2,612/35,872) in last quarter of 2010. The proportion of hospitalizations using sodium nitroprusside was less than 1% throughout the 6-year period: 0.6% (208/35,769) in the first quarter of 2005 and 0.4% (136/35,872) at the last quarter of 2010. The proportion of hospitalizations with a positive inotropic agent was 12.1% (4,328/35,769) in the first quarter of 2005, 12.3% (4,787/38,978) in the first quarter of 2006, and then decreased progressively to 9.8% (3,516/35,872) in the last quarter of 2010. (Figure 1)

Use of nesiritide at hospital-level

Between 2005 and 2010, a total of 403 hospitals contributed data on heart failure patients to the database. These were mainly urban, non-teaching, small and medium size hospitals. Key characteristics of these hospitals are summarized in Table 1.

There was a wide variation across hospitals in the proportion of HF patients treated with nesiritide. In the first quarter of 2005, the risk-standardized rates ranged from a minimum of 1.0% to a maximum of 65.9% (median: 11.4%, IQR: 5.6%–20.8%). In the last quarter of 2010, the adjusted rates ranged from a minimum of 0.3% to a maximum of 19.2% (median: 0.7%, IQR: 0.5%–1.0%). (Figure 2)

Hospital groups based on patterns of change in nesiritide use

Application of the growth mixture modeling to hospital risk-standardized utilization rates led to the emergence of three distinct groups of hospitals based on their patterns of change in utilization over time: “low utilizers”, “fast de-adopters” and “slow de-adopters” (Figure 3). The approach took into account both level and speed of change in utilization over the entire 6-year period, however for the sake of simplicity, only the most dominant attribute was used to name the groups. The “low-utilizer” group included 302 hospitals (75% of hospitals, together accounting for 69% of all hospitalizations) with an average risk-standardized rate of 9% in the first quarter of 2005 which decreased to almost 2% at the beginning of 2006 and plateaued at around 1% from 2009. The “fast de-adopter” group included 82 hospitals (20% of hospitals, together accounting for 25% of all hospitalizations) with an average initial risk-standardized utilization rate of 26% that decreased to 10% at the beginning of 2006, 5% at 2009, and 3% at the end of 2010. The remaining 19 hospitals (5% of hospitals, together encompassing 6% of all hospitalizations) were classified as the “slow de-adopters”. They had the highest initial risk-standardized utilization rates and a slower rate of decrease in use over time than the other hospitals. They started with an average utilization rate of 38% which decreased to 26% at the end of 2005, then 20% at 2007 and were still at 10% at the beginning of 2010 (Figure 3).

The average posterior probability of group membership was greater than 0.98 for each of the groups indicating excellent performance of the model in distinguishing the different trajectory patterns.

Association between hospital characteristics and distinct hospital groups

We investigated what hospital characteristics were associated with different nesiritide de-adoption trajectory groups. Table 2 shows the hospital characteristics by trajectory group. The three groups differed significantly in hospital size, annual volume of heart failure hospitalizations, regional location, PCI and ICD capability, proportion of cardiologist as attending physician, and proportion of Medicaid patients.(Table 2) However, in multivariate regression analysis, none of the hospitals characteristics differed significantly between the slow de-adopters group and the other two groups. The fast de-adopters were more likely to be located in the Midwest and the South, to have ICD capability and a higher proportion of Medicaid patients in comparison with low utilizers.(Table 3)

DISCUSSION

In this study, we used data from a large network of hospitals to characterize longitudinal patterns of change in nesiritide use following publications raising concerns about its safety. The results showed a continued reduction in the use of this medication between 2005 and 2010, with an initial sharp decrease immediately after the publications followed by a more gradual decrease between 2006 and 2010. The overall average change however, obscures that there was marked variation in nesiritide utilization across hospitals. When taking into account both level and speed of change in utilization over the 6-year period, the hospital trajectories coalesced around some specific patterns leading to the emergence of 3 distinct groups of hospitals. Since the utilization rates already adjusted for differences in case mix across hospitals and across years, these 3 groups depict mainly the heterogeneity of organizational response to new information. These trajectory curves can provide crucial feedback to hospitals about how fast and effectively they react to new information in comparison with other hospitals.

We chose to use hospitals as our unit of analysis for several reasons. First, heart failure patients are usually seen by multiple physicians and it’s not always possible to identify the prescribing physician. Second, revealing variation at the hospital level rather than individual physician level is consistent with an emerging appreciation of team-based care, systems of care, and the impact of hospital internal environment on performance.(13–16) Third, medical decision making is influenced by various organizational characteristics such as team composition (number and type of specialists on the team, inclusion of a pharmacist), internal culture (quality and frequency of communication and collaboration between team members), regulatory context (drug formularies), availability and use of clinical decision support systems for the practice of evidence-based medicine. (13,17,18) However, one of the limitations of our study and the currently available healthcare databases in general is the lack of information on these characteristics.

Our results suggested that there may be common underlying factors among hospitals within each trajectory group. However, when we examined the association between hospital characteristics available in our database and various trajectory groups, none was significantly associated with a hospital’s likelihood of being in the slow de-adopter group compared with the other two groups. This could be due to small number of hospitals in this group, or to the data limitations (i.e., lack of measures reflecting team composition,

communication, internal culture, regulations and restrictions). There is a need for further qualitative and mixed method research to identify additional factors, both internal to the organization and external. For example, one of the unmeasured factors that may explain the significant difference in regional location observed between hospital groups could be the prevalence of pharmaceutical marketing across regions.

Before its safety concerns were published in 2005, nesiritide was widely prescribed.(7,19) The proportion of HF hospitalizations using nesiritide almost doubled those with the main alternative vasodilator, IV nitroglycerin, despite the fact that nesiritide was only approved for very specific indication and was much more expensive. Following the publications, the rate of nesiritide use declined dramatically but we did not observe a “substitution” effect such as a sudden or substantial increase in use of other vasodilators, or of positive inotropic agents. These results could suggest a case of nesiritide overuse before spring 2005.

Our study further revealed that this initial, short-term strong response to new information was followed by a steady decrease in use over subsequent years although at a much more gradual level and speed. This pattern is consistent with what has been observed in many other studies of the adoption of innovations. Those studies have suggested that adoption decisions of organizations are a function of both internal factors as well as external and social factors, but the relative importance of these factors changes over time as information diffuses among potential adopters.(20–22)

There are several limitations to this study. First, hospitals included may not be a representative sample of all hospitals in the United States. Nevertheless, the Premier database contains approximately 20% of annual nationwide acute care hospitalizations. Second, a patient could contribute more than one hospitalization to the study cohort, introducing correlation in data between the multiple hospitalizations. However the impact was likely small since only 9% of patients had more than one hospitalization per quarter, of which the majority had only two hospitalizations (median: 2; IQR: 2–2). Third, our risk-adjustment model relied on claims data only. However, our earlier work of profiling hospital performance for the Centers for Medicare and Medicaid Services has demonstrated that administrative data can provide estimates similar to models employing richer clinical data.(23–24) Finally, as previously mentioned, we lack data on a number of characteristics that might have affected drug utilization such as formularies, other hospital restrictions, and marketing factors.

In conclusion, this study establishes that amid a general decrease in nesiritide use, there were important variations across hospitals revealing distinct hospital groups based on their patterns of change in practice in response to new information. These trajectory curves can provide hospitals with an important feedback on their “learning rates” or how fast and effectively they react to new information. The study also highlights the need for additional mixed-methods research to uncover the factors that foster or impede organizational learning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by grant DF10-301 from the Patrick and Catherine Weldon Donaghue Medical Research Foundation in West Hartford, Connecticut and by grant UL1 RR024139-06S1 from the National Center for Advancing Translational Sciences in Bethesda, Maryland. Dr. Krumholz is supported by grant U01 HL105270-02 (Center for Cardiovascular Outcomes Research at Yale University).

ABBREVIATIONS AND ACRONYMS

FDA	Food and Drug Administration
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
AHRQ	Agency for Healthcare Research and Quality
VAD	Ventricular Assist Device
PCI	Percutaneous Coronary Intervention
ICD	Implantable Cardioverter Defibrillator
HGLM	Hierarchical Generalized Linear Model
BIC	Bayesian Information Criteria
OR	Odds Ratio
IQR	Inter-quartile Range

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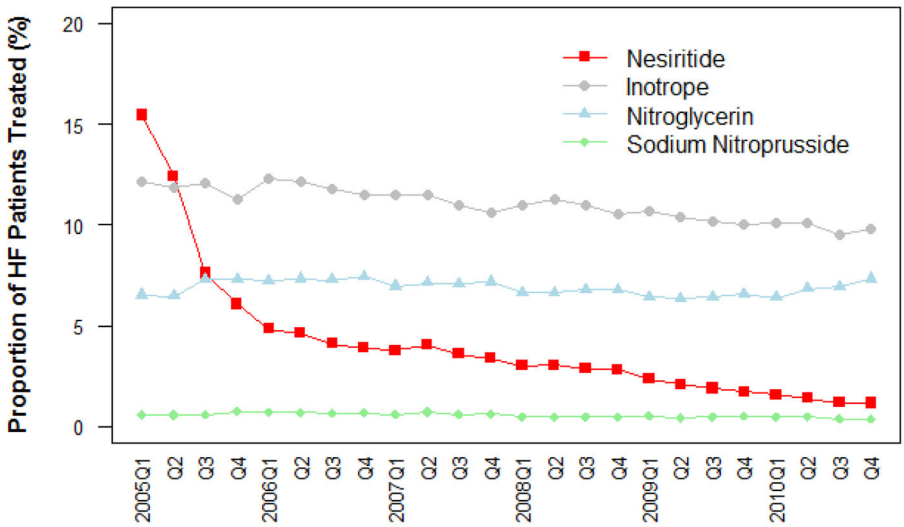

Figure 1. Trends in use of IV vasodilators and inotropes among patients hospitalized with heart failure

The figure shows the proportion of hospitalizations including an IV vasodilator (nesiritide, nitroglycerin, sodium nitroprusside) or a positive inotropic agent among all heart failure hospitalizations between the first quarter of 2005 and the last quarter of 2010.

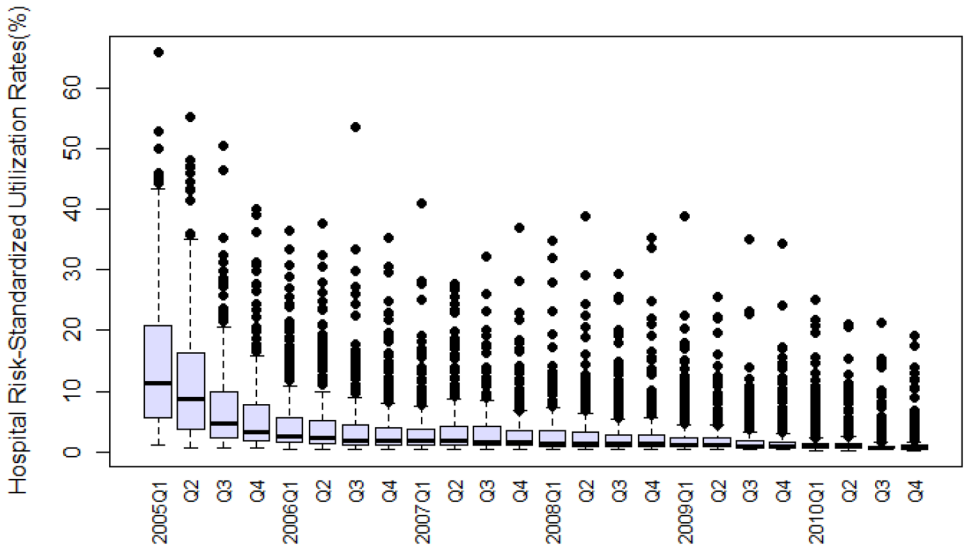

Figure 2. Distributions of hospital risk-standardized rates of nesiritide utilization

The figure shows the distribution across hospitals of nesiritide risk-standardized utilization rates for each quarter of calendar year from 2005 through 2010.

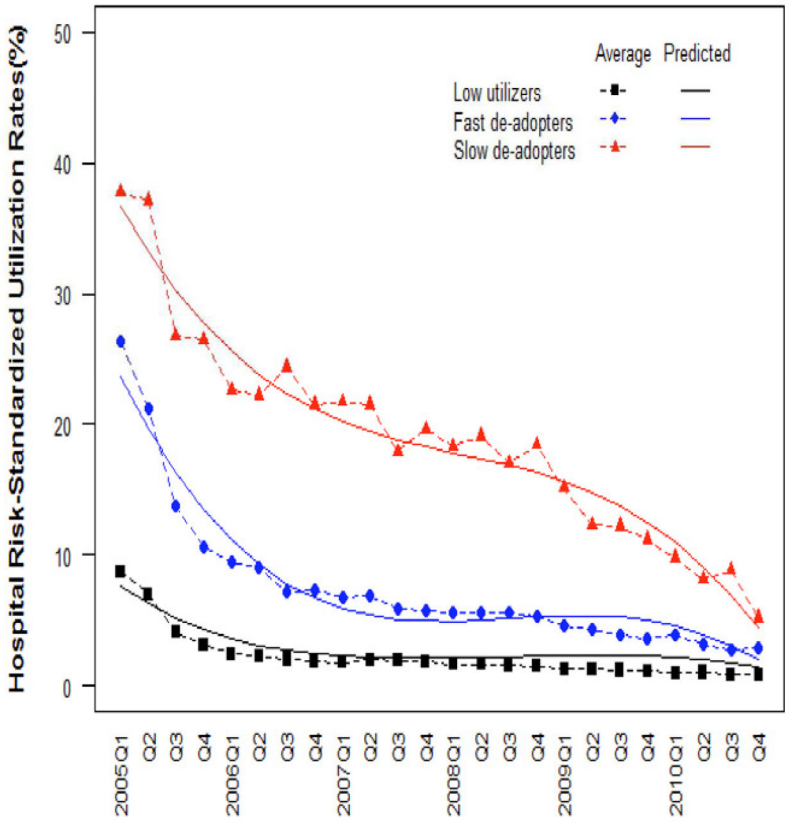

Figure 3. Distinct groups of hospitals based on their patterns of change in nesiritide use over the 6-year period 2005–2010

Three distinct groups of hospitals were identified. The figure shows the average and predicted group trajectories using hospital-level risk-standardized rates of nesiritide utilization between the first quarter of 2005 and the last quarter of 2010.

Table 1

Sample characteristics

	Hospitals N (%)	Hospitalizations N (%)
Total	403 *	813,783
Number of beds		
<200	146 (36)	120,033 (15)
200 – 400	155 (38)	303,521 (37)
> 400	100 (25)	390,229 (48)
Teaching status		
NO	292 (73)	491,719 (60)
YES	109 (27)	321,500 (40)
Region		
Midwest	88 (22)	166,989 (21)
Northeast	63 (16)	169,392 (21)
South	169 (42)	365,294 (45)
West	81 (20)	111,544 (14)
Population served		
Rural	86 (21)	89,642 (11)
Urban	315 (79)	723,577 (89)
Average annual HF volume		
< 25	9 (2)	336 (0)
26 – 200	128 (32)	67,638 (8)
201 – 500	152 (38)	261,071 (32)
501 – 1000	91 (23)	330,976 (41)
1001 – 1500	23 (6)	153,762 (19)

*: 2 hospitals were missing general characteristics including number of beds, teaching status, area served, and geographic location.

Table 2

Hospital characteristics by nesiritide use trajectory groups

	Low Utilizers (N=302)	Fast De-adopters (N=82)	Slow De-adopters (N=19)	p-value
Number of beds				
< 200	41.4	20.7	31.6	0.0048
200–400	37.4	43.9	31.6	
> 400	21.2	35.4	36.8	
Teaching status				
NO	72.4	72	83.3	0.5886
YES	27.6	28.1	16.7	
Region				
MIDWEST	20.9	28.1	11.1	<0.0001
NORTHEAST	18.3	7.3	11.1	
SOUTH	36.2	58.5	66.7	
WEST	24.6	6.1	11.1	
Population served				
RURAL	23.9	12.2	22.2	0.0719
URBAN	76.1	87.8	77.8	
Heart failure volume				
< 25	3	0	0	0.0005
26 – 200	37.1	17.1	10.5	
201 – 500	33.8	48.8	52.6	
501 – 1000	20.2	31.7	21.1	
1001 – 1500	6	2.4	15.8	
Procedure performed				
LVAD/Transplant	8.6	10.8	15.8	0.5638
PCI	55	76.8	84.2	0.0002
ICD	61.9	86.6	84.2	<0.0001
Use of CCU	47.4	48.8	63.2	0.4076
Percent (%) of Medicaid patients, median (IQR)	3.2 (1.6–6.0)	4.5 (2.8–6.6)	3.3 (2.1–6.6)	0.0066
Percent (%) of cardiologist as attending, median (IQR)	7.7 (0.4–19.1)	16.5 (6.1–29.6)	17.5 (3.1–31.8)	0.0075

Table 3

Relationship between hospital characteristics and patterns of nesiritide use

	Fast de-adopters vs. Low utilizers			Slow de-adopters vs. Low utilizers			Slow de-adopters vs. Fast de-adopters		
Hospital characteristics	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Midwest vs. West	7.2	2.4–22.4	0.0005	1.4	0.2–19.6	0.7720	0.2	0.0–1.8	0.1465
Northeast vs. West	2.8	0.7–10.8	0.1246	1.9	0.2–15.6	0.5441	0.7	0.1–7.5	0.7462
South vs. West	9.5	3.3–27.4	<0.0001	5.0	1.0–24.9	0.0518	0.5	0.1–3.4	0.4976
Percent (%) of Medicaid patients[1]	2.2	1.3–3.8	0.0036	1.7	0.6–4.7	0.3164	0.8	0.3–2.2	0.6126
ICD performed (yes vs. no)	3.6	1.8–7.2	0.0003	3.1	0.9–11.0	0.0839	0.9	0.2–3.5	0.8298

[1]:The unit for OR effect is 10%.

ICD: Implantable Cardioverter Defibrillator

JACC Heart Fail. Author manuscript; available in PMC 2017 February 23.

Appendix Table

Fixed effects estimates of the hierarchical logistic regression model used for calculating hospital risk-standardized utilization rates of nesiritide

Variables	OR (95% CI)	p-value
Time points (quarter)		
1	21.1 (16.4–27.1)	<.0001
2	15.4 (11.9–19.8)	<.0001
3	8.7 (6.7–11.3)	<.0001
4	6.3 (4.8–8.1)	<.0001
5	4.8 (3.7–6.2)	<.0001
6	4.6 (3.5–5.9)	<.0001
7	3.8 (2.9–4.9)	<.0001
8	3.6 (2.7–4.6)	<.0001
9	3.3 (2.6–4.3)	<.0001
10	3.5 (2.7–4.6)	<.0001
11	3.2 (2.5–4.2)	<.0001
12	3.1 (2.4–4.1)	<.0001
13	2.6 (2.0–3.4)	<.0001
14	2.6 (2.0–3.4)	<.0001
15	2.5 (1.9–3.2)	<.0001
16	2.4 (1.8–3.1)	<.0001
17	1.9 (1.5–2.5)	<.0001
18	1.8 (1.4–2.4)	<.0001
19	1.6 (1.2–2.2)	0.0006
20	1.4 (1.1–1.9)	0.01
21	1.3 (1.0–1.8)	0.0424
22	1.3 (1.0–1.7)	0.101
23	1.0 (0.8–1.4)	0.7969
24	1.0 (.–.)	.
Age Group		
18 – 24	2.1 (1.6–2.6)	<.0001
25 – 34	1.5 (1.3–1.7)	<.0001
35 – 44	1.4 (1.3–1.5)	<.0001
45 – 54	1.3 (1.2–1.3)	<.0001
55 – 64	1.3 (1.2–1.3)	<.0001
65 – 74	1.2 (1.1–1.2)	<.0001
75 – 99	1.0 (.–.)	.
Gender		
Female	0.8 (0.8–0.8)	<.0001
Male	1.0 (.–.)	.
Race		
White	1.1 (1.1–1.2)	0.0001

Variables	OR (95% CI)	p-value
Black	1.2 (1.2–1.3)	<.0001
Hispanic	1.1 (1.0–1.2)	0.1077
Other	1.0 (.–.)	.
Elixhauser Comorbidity		
Valvular disease	1.2 (1.1–1.3)	0.0002
Pulmonary circulation disease	0.8 (0.8–0.9)	0.0005
Peripheral vascular disease	1.0 (0.9–1.1)	0.3963
Hypertension	0.9 (0.8–0.9)	<.0001
Paralysis	0.8 (0.7–0.9)	<.0001
Other neurological disorders	0.8 (0.7–0.8)	<.0001
Chronic pulmonary disease	0.9 (0.9–1.0)	<.0001
Diabetes w/o chronic complications	1.2 (1.1–1.2)	<.0001
Diabetes w/chronic complications	1.2 (1.2–1.3)	<.0001
Hypothyroidism	1.1 (1.0–1.1)	0.001
Renal failure	1.4 (1.3–1.4)	<.0001
Liver disease	1.0 (0.9–1.1)	0.9721
Peptic ulcer Disease x bleeding	0.7 (0.4–1.4)	0.361
Acquired immune deficiency syndrome	0.6 (0.4–0.8)	0.0002
Lymphoma	0.9 (0.8–1.1)	0.3999
Metastatic cancer	0.7 (0.6–0.8)	<.0001
Solid tumor w/out metastasis	0.8 (0.7–0.9)	<.0001
Rheumatoid arthritis/collagen vas	0.9 (0.8–1.0)	0.0095
Coagulopthy	1.2 (1.2–1.3)	<.0001
Obesity	1.1 (1.0–1.1)	<.0001
Weight loss	1.2 (1.1–1.3)	<.0001
Fluid and electrolyte disorders	1.4 (1.3–1.4)	<.0001
Chronic blood loss anemia	0.9 (0.8–1.0)	0.0686
Deficiency Anemias	1.0 (1.0–1.1)	0.0256
Alcohol abuse	1.1 (1.0–1.1)	0.1291
Drug abuse	1.0 (0.9–1.1)	0.6205
Psychoses	0.8 (0.8–0.9)	<.0001
Depression	0.9 (0.8–0.9)	<.0001
Other AHRQ Comorbidity		
Disorders of lipid metabolism	1.0 (1.0–1.1)	0.0003
Coronary atherosclerosis and other heart disease	1.4 (1.4–1.5)	<.0001
Acute myocardial infarction	1.4 (1.3–1.5)	<.0001
Peripheral and visceral atherosclerosis	1.1 (1.0–1.3)	0.0307
Aortic; peripheral; and visceral artery aneurysms	1.1 (1.0–1.2)	0.1274
Aortic and peripheral arterial embolism or thrombosis	1.1 (0.9–1.4)	0.254
Transient cerebral ischemia	0.8 (0.6–1.0)	0.0568
Cardiac dysrhythmias	1.3 (1.3–1.3)	<.0001
Cardiac arrest and ventricular fibrillation	1.1 (1.0–1.3)	0.0023