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## Hospital Variation in Intravenous Inotrope Use for Patients Hospitalized with Heart Failure: Insights from Get With The Guidelines

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## Abstract

**Background**—Prior claims analyses suggest that the use of intravenous inotropic therapy for patients hospitalized with heart failure varies substantially by hospital. Whether differences in the clinical characteristics of the patients explain observed differences in the use of inotropic therapy is not known.

**Methods and Results**—We sought to characterize institutional variation in inotrope use among patients hospitalized with heart failure before and after accounting for patients' clinical factors. Hierarchical generalized linear regression models estimated risk-standardized hospital-level rates of inotrope use within 209 hospitals participating in Get With The Guidelines-Heart Failure (GWTG-HF) registry between 2005–2011. The association between risk-standardized rates of inotrope use and clinical outcomes were determined. Overall, an inotropic agent was administered in 7,691 of 126,564 (6.1%) HF hospitalizations: dobutamine 43%, dopamine 24%, milrinone 17%, or a combination 16%. Patterns of inotrope use were stable over the 7-year study period. Use of inotropes varied significantly between hospitals even after accounting for patient and hospital characteristics (median risk-standardized hospital rate 5.9%, IQR 3.7–8.6%, range 1.3–32.9%). After adjusting for case mix and hospital structural differences, model intra-class correlation indicated that 21% of the observed variation in inotrope use was potentially attributable to random hospital effects (i.e. institutional preferences). Hospitals with higher risk-standardized inotrope use had modestly longer risk-standardized length of stay ( $p=0.005$ ) but had no difference in risk-standardized inpatient mortality ( $p=0.12$ ).

**Conclusions**—Use of intravenous inotropic agents during hospitalization for heart failure varies significantly among U.S. hospitals, even after accounting for patient and hospital factors.

### Key Words (MeSH Headings)

Heart failure; cardiotoxic agents [entry term: inotropic agents; positive cardiac]; outcome assessment (health care); physician's practice patterns [entry term: variations; clinical practice]

### Subject Codes

[110] Heart Failure; Congestive; [100] Ethics and Policy; Health policy and outcome research; [33] Other diagnostic testing

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## INTRODUCTION

Pharmacological options for treating acute decompensated heart failure have changed little over the past few decades. Moreover, few positive studies exist of acute treatments for heart failure. As a result, in-hospital management is dictated largely by expert opinion.<sup>1–3</sup> While most patients receive intravenous (IV) loop diuretic therapy to relieve congestion as the primary inpatient intervention<sup>4</sup> followed by transition back to a stable oral regimen, some patients receive more intensive approaches including IV inotropic therapy.

For hemodynamically stable heart failure outpatients, the use of inotropic therapies, other than digoxin, has been associated with increased mortality.<sup>5,6</sup> For hospitalized heart failure patients without evidence of end-organ hypoperfusion, randomized trials of IV milrinone

and levosimendan compared with placebo both found an increased risk of adverse events.<sup>7,8</sup> For unstable heart failure patients, few high-quality data exist to guide care decisions.<sup>9</sup> As would be expected from treatment selection biases, observational data show that patients hospitalized with heart failure who receive an IV inotrope tend to have greater heart failure severity and higher subsequent mortality.<sup>10,11</sup>

Based on these limited data and expert opinion, the American Heart Association/American College of Cardiology (AHA/ACC) clinical practice guidelines provide the following Level IIb recommendation (i.e. may be considered): “Short-term, continuous intravenous inotropic support may be reasonable in those hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance.”<sup>1</sup> The European Society of Cardiology (ESC) guidelines make a similar recommendation, although with at a Level IIa (i.e. it is reasonable to consider).<sup>3</sup> Both guidelines also explicitly state (Level III) that IV inotropic agents are contraindicated in hospitalized patients with heart failure who do not have evidence of decreased organ perfusion.

Analyses of billing data<sup>12</sup> and randomized trial data<sup>11</sup> suggest that inotrope use varies significantly across hospitals. However, billing data lack the clinical detail to enable robust adjustment for case mix and trial data may not adequately reflect non-protocol controlled community practice. Accordingly, we sought to characterize hospital patterns of IV inotrope use using a large contemporary U.S. registry of patients hospitalized with heart failure. The objectives were to 1) quantify current day hospital variation in IV inotropic agent use; 2) determine the phenotypes of the hospitals with high and low use rates; 3) assess whether case mix or structural characteristics explain observed differences; and 4) characterize associations between risk-standardized rates of hospital inotrope use and performance measures, length of stay, and in-hospital mortality.

## METHODS

### Data Source

We conducted a cross-sectional study using data from the Get With The Guidelines–Heart Failure (GWTG-HF) voluntary quality improvement initiative. The design and validity of this program’s methods and data capture have been published previously.<sup>13–15</sup> Briefly, trained personnel at each site abstract clinical data for all patients admitted with heart failure in compliance with The Joint Commission and Centers for Medicare and Medicaid Services standards for quality indicators. Variables collected include demographic and clinical characteristics, medical history, previous treatments, admission medications, in-hospital treatments, in-hospital outcomes, and discharge medications, including contraindications to evidence-based therapies. The data collection form specifically includes a section on in-hospital “parenteral therapies” including individual yes/no responses for “dobutamine”, “dopamine”, “milrinone”, and “none”. Dopamine, dobutamine, and milrinone are the IV inotropic agents highlighted in the AHA/ACC heart failure guidelines.<sup>1</sup> Clinical data use the point-of-service, interactive, Internet-based Patient Management Tool (Outcome Sciences, Inc, Cambridge, Massachusetts). The Internet-based system performs checks to ensure the completeness of the reported data. Additionally, data quality is monitored independently and

reports are generated to confirm the completeness and accuracy of submitted data. Hospital data elements are collected for all enrolling hospitals from the American Hospital Association database.

Patient data are de-identified in accordance with the Health Insurance Portability and Accountability Act and a random hospital identifier is used to identify the various hospitals. All participating institutions are required to comply with local regulatory and privacy guidelines and to submit the program protocols for review and approval by their institutional review boards. Because data are used primarily at the local site for quality improvement, sites are granted a waiver of informed consent under the common rule. The Duke Clinical Research Institute (Durham, NC) serves as the data analysis center.

### **Patients and Hospitals**

We confined the current analysis to hospital admissions between January 1, 2005 and December 31, 2011 at a hospital fully participating in the GWTG-HF program. Fully participating hospitals were considered to be those with no more than 25% of history panel forms incomplete and no more than 20% of parental therapies data missing. We then excluded hospitalizations for whom discharge data or gender was missing, hospitalizations resulting in transfer to another facility, or hospitalizations that did not have a response for in-patient parental therapies recorded. Finally, we excluded hospitals with less than 25 patients (Appendix 1).

### **Statistical Analysis**

Observed hospital rates of inotrope use were calculated as percent of total patients receiving one or more inotropes during hospitalization. Hospital risk-standardized inotrope use rates were computed as the ratio of predicted to expected rates obtained from hierarchical generalized linear models (HGLMs), with patient and hospital structural characteristics as model fixed effects, multiplied by the overall observed inotrope use rate.<sup>12,16</sup> In the hierarchical model the numerator is what is “predicted” for that hospital based on its rate and sample size if it had the average case mix and the denominator is what is “expected” if its performance was the average for all the hospitals. Patient and hospital-level characteristics were selected based upon previous literature<sup>17</sup> and clinical criteria.<sup>1,3</sup>

Categorical variables with missing observations (all <5% missing) were imputed to the most common category. Insurance status was imputed to Medicare if age $\geq$ 65 and to none otherwise. Race and insurance status were excluded in a sensitivity analysis. For continuous variables, missing observations ranged from 2–16% and were imputed with group-specific medians based on inotrope use. For left ventricular ejection fraction (LVEF) we also considered gender for the imputation. We used cubic spline plots to explore the functional form of continuous variables. As a result, age, systolic blood pressure, LVEF, blood urea nitrogen, hemoglobin, and hospital bed size were modeled as linear continuous, with LVEF truncated at 60% and hemoglobin truncated at 11 g/dL. Heart rate was modeled with 3 linear splines with knots at 75 and 105 beats per minute. Serum creatinine and sodium were modeled with 2 linear splines, with knots at 2.5 mg/dl and 140 mmol/L, respectively.

Patient and hospital characteristics, overall and by quartiles of risk-standardized hospital rates of inotrope use, were summarized using frequencies and proportions for categorical data and medians with inter-quartile ranges (IQRs) for continuous variables. P-values for comparison across quartiles of risk-standardized hospital inotrope rates were computed with Wilcoxon or Kruskal-Wallis test for categorical variables and chi-square rank correlation statistics for continuous variables.

Hierarchical generalized linear models (HGLMs) were also performed to evaluate factors associated with inotrope use. First, patient-level factors were modeled.<sup>16</sup> Subsequently, hospital structural characteristics were added to the model. Odds ratios (OR) and corresponding 95% confidence intervals (95%CI) were reported for all factors in the models. To further assess the contribution of hospital preferences (i.e. random institutional effects) to the variation in use of positive inotropic agents, we calculated the intra-class correlation coefficient for the HGLM model after adding a hospital random effect to the fixed patient and hospital structural effects.<sup>18</sup>

The outcomes of in-hospital mortality and length of stay > 4 days were summarized in the same fashion as patient and hospital characteristics. Risk-standardized hospital mortality and length of stay were calculated using the same methodology to risk-standardized hospital inotrope rates. Performance measures collected by GWTG-HF (discharge to home, documentation of LVEF, use of angiotensin converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB] for left ventricular systolic dysfunction [LVSD], use of beta-blocker for LVSD, and smoking cessation counseling) were reported at the hospital level as percent of eligible patients treated; because all patients deemed eligible for a measure were presumed to merit its application, the performance measures were not risk standardized.

Due to the potential use of low-dose dopamine to theoretically “improve diuresis and better preserve renal function and renal blood flow” (Class IIb, Level of Evidence B)<sup>1</sup> and the absence of dosing data in GWTG, analyses were repeated with hospitalizations involving dopamine alone treated as no inotrope.

A p value 0.05 was considered statistically significant for all tests. All analyses were performed with SAS software version 9.2 (SAS Institute, Cary, NC). The HGLMs were estimated using the GLIMMIX macro in SAS. Figures were created with R (version 2.11.1).<sup>19</sup>

## RESULTS

### Hospital and Patient Characteristics

The final study population consisted of 126,564 patients hospitalized with heart failure at 209 sites (from a starting population of 520,434 patients from 726 sites, Appendix 2). Median annual volume of heart failure admissions per hospital over the 7-year enrollment period was 268 (IQR 94–692; range 25–5995), median hospital size was 240 beds (IQR 121–369), 20% were located in a rural area, 35% were teaching hospitals, and 5.3% performed heart transplants. Summarized at the hospital level, median hospital patient age

was 77 years (IQR of hospital median ages 73–80 years); median hospital gender was 51.0% women (IQR 46.2–56.2%); median hospital race was 82.5% white (IQR 59.4–92.7%) and 6.3% black (IQR 0.9–20.8%); median hospital payer was private insurance 20.7% of patients (IQR 9.7–38.2%), Medicaid 6.0% (IQR 2.7–13.3%), Medicare 55.0% (IQR 29.5–75.1%), and no insurance 1.8% (IQR 0.5–4.2%); median LVEF 44% (IQR 37%–46%), and comorbidities were common (Appendix 2). At the hospital level, median length of stay was 4 days (hospital median IQR 4–5 days) and median in-hospital mortality was 3.1% (hospital median IQR 1.6–4.3%).

### Observed and Risk-Standardized Hospital Use of IV Inotropes

In total, IV inotropes were administered in 7,691 (6.1%) of heart failure hospitalizations. Inotrope use was divided between dobutamine alone in 43% of cases, dopamine alone in 24% of cases, milrinone alone in 17% of cases, and a combination of these agents in 16%.

Among individual hospitals, the observed rate of IV inotrope use ranged from 0–34.4% (median 3.9%, IQR 1.8–7.2%; Table 1). After adjustment for patient-level factors (listed in Table 2) and hospital-level factors (listed in Table 3), variation was observed in institutional risk-standardized rates of IV inotrope use (median rate 5.9%, IQR 3.7–8.6%, range 1.3–32.0%; Table 1, Figure 1).

Overall patterns of inotrope use changed relatively little in absolute terms over the 7-year study period (Figure 2, **Panel A**). Among the 24 hospitals participating continuously from 2005–2011, the risk-standardized hospital median percent of IV inotrope use ranged from 2.0–3.3%, with stable use over time. Dobutamine was the most commonly used agent with stable use over time, whereas dopamine use trended downward and milrinone use trended upward (p for annual trend <0.0001; Figure 2, **Panel B**).

### Patient Characteristics and the Use of Inotropic Agents

We assessed the observed (unadjusted) relationship between patient characteristics and IV inotrope use, showing that patients treated with inotropes were more likely to be male, have prior heart failure, have ischemic etiology, have renal dysfunction, and have lower systolic pressure but notably similar diastolic pressure (difference isolated to pulse pressure) (Appendix 3). Of note, although patients receiving IV inotropes had lower median LVEF, more than a quarter of inotrope-treated patients had a LVEF >35% (Appendix 3). Likewise, although patients receiving IV inotropic agents had lower admission systolic blood pressures, three quarters had an admission SBP >100 mm Hg (noting that blood pressures throughout the course of hospitalization were not available).

In a model accounting for hospital clustering and adjusting for patient-level factors only, the patient factors that were most strongly associated with IV inotrope use were lower systolic blood pressure, followed by lower LVEF, elevated serum creatinine, hyponatremia, advancing age, and elevated blood urea nitrogen (Table 4). The c-statistic for the patient-level model of inotrope use was 0.84.

## Hospital Characteristics and the Use of Inotropic Agents

Although many of the measured hospital characteristics were crudely associated with inotrope use (Table 3), only hospital region and larger hospital size were statistically associated with inotrope use in multivariable HGLM; hospital rural location, academic status, and capacity to perform heart transplantation had no significant association with IV inotrope use after accounting for other patient and hospital factors (Table 4). The addition of hospital-level factors (structural characteristics) to patient-level factors in the HGLM did not improve model discrimination (patient model only c-statistic 0.84; patient and hospital model c-statistic 0.84).

## Variation Attributable to Hospital Preferences

The intra-class correlation was 0.21 after adding a hospital random effect to patient characteristics and hospital structure fixed effects in HGLM models. This suggests that 21% of the observed variation in inotrope use may be explained by individual hospital preferences rather than patient case-mix and hospital structural differences.

## Association between Outcomes and Use of IV Inotropic Agents

When comparing hospitals across quartiles of risk-standardized inotrope use, risk-standardized in-hospital mortality rates were not different between high- and low-use hospitals (Table 5). Length of stay greater than 4 days was statistically more common among high-use hospitals, although absolute differences were small after risk-standardization. Process performance measures were not significantly different between hospitals by inotrope use rates (Table 5).

## Secondary Analysis Excluding Dopamine

When the 1,865 hospitalizations involving dopamine only were redefined as no inotrope, observed median institutional rates of IV inotrope use was 2.3% (IQR 0.7–5.3%, range 0–28.1%) and risk-standardized median rate 4.2% (IQR 2.8–6.8%, range 1.0–40.5%). This change in definition of inotrope use caused 76 hospitals (36%) to reclassify to a different quartile of risk-standardize inotrope use rate, although only 2 hospitals changed more than 1 quartile. With dopamine excluded, model C index was 0.87 (for both the patient only and patient plus hospital factor models) and the intra-class correlation was 0.26. With exclusion of dopamine from the inotrope definition, hospitals in the higher quartiles of risk-standardize inotrope use continued to show a higher adjusted length of stay ( $p=0.29$ ) but no association with adjusted in-hospital mortality ( $p=0.86$ ).

## DISCUSSION

In this large clinical registry of a diverse group of hospitals in the United States, we found marked variation in the rates of use of these agents between hospitals. Using state of the art methods to adjust for patient case mix and hospital structural differences, we found that a substantial portion of variation is attributable to practice patterns at individual hospitals. It is increasingly appreciated that hospital culture can exert a strong influence on discretionary therapies. Although existing data do not clearly define ideal rates of IV inotrope use for patients hospitalized with heart failure, these agents can have negative consequences. The

manifold variation in use even after risk standardization highlights the need for additional research into the optimal use of the agents.

Our findings are consistent with and extend an analysis that was recently conducted with billing data.<sup>12</sup> In that cross-sectional study of 376 hospitals participating in Perspective, a fee-supported database developed by Premier, Inc., the risk-standardized rates of inotrope use ranged across hospitals from 0.9% to 44.6% (median 6.3%, IQR 4.3–9.2%). When adjusting for patient case mix and an individual hospital effect, model c-statistics ranged from 0.77 to 0.88 and intraclass correlation coefficient was 0.113. In that study, hospital rates or patterns of use were not associated with differences in length of stay or risk-standardized mortality rates.

The GWTG-HF registry data include detailed clinical data not present in administrative billing data—in particular LVEF, vital signs and laboratory test results—that guidelines recommend as the basis for deciding when to initiate IV inotropic support (“patients presenting with severe systolic dysfunction, low blood pressure and evidence of low cardiac output”).<sup>1</sup> Despite the addition of this clinical information in the current analysis, we found relatively similar variation in risk-standardized hospital rates of inotrope use and a greater degree to which hospital treatment preferences were responsible for these differences (11% versus 21%). Our study is also consistent with data from the ESCAPE randomized trial which reported that the most significant predictor of inotrope use in multivariable modeling was the study site (hospital).<sup>11</sup> The external validity of findings derived from narrow ESCAPE eligibility criteria within select academic institutions guided by trial treatment protocols had been in question. Additionally, the authors did not quantify the degree to which inotrope use varied across these 26 hospitals nor the proportion of variation that was not explained by differences in patient factors. Therefore, the GWTG-HF analysis reported here provides the most representative analysis of inotropic support in the hospitalized adult with heart failure to include detailed clinical data. Outside the scope of hospitalized adults with heart failure, few data exist looking at rates and variation in inotrope use.<sup>20</sup>

Despite evidence of marked hospital-level variation, it is difficult to determine to what extent hospitals may be over- or under-using inotropic agents. It is known that for hemodynamically stable patients, these agents can increase short and long-term risk. The newest recommendations from the ESC provide the most specific recommendation to date, reserving IV inotropes (and/or intra-aortic balloon pump) for patients with “systolic blood pressure <85 mmHg or shock” evidenced by “reduced peripheral and vital organ perfusion.”<sup>3</sup> Registries suggest that this group, i.e. those with hypotension and shock, represents about 3% of all patients hospitalized with heart failure.<sup>4</sup> Our findings from GWTG-HF and those from other studies suggest that many more patients are being treated with these agents, particularly among certain hospitals, and that a significant portion of this high use is attributable to institutional culture rather than medical indications.<sup>10,12</sup>

A hospital’s propensity to use inotropes was largely independent of outcomes. Risk-standardized hospital inotrope use was not associated with risk-standardized in-hospital mortality rates. A statistically significant but small absolute increase in length of stay at hospitals with higher rates of inotrope use, although may represent incomplete adjustment



for case mix. Due to the nature of GWTG-HF data, we were not able to look at events after discharge.

There are several limitations to consider. First, hospitals voluntarily participating in GWTG-HF may not be representative of all hospitals in the United States, although prior study has shown that GWTG-HF hospitals have characteristics similar to hospitals nationwide. We found lower rates of overall IV inotrope use in GWTG-HF registry than in cross-sectional studies, suggesting that, if anything, the general findings here may understate the use and variation that do exist. Second, the GWTG-HF case report form only captured dichotomous use of IV inotropes, without consideration for timing, duration, or dose. Our sensitivity analysis around dopamine use suggest that institutional variation in inotrope use is not explained by low-dose dopamine. Third, physician reasoning and hemodynamic monitoring at the time of inotropic therapy initiation were not available. However, detailed clinical information, including laboratory and vital sign data, that form the foundation of guideline recommendations around inotrope use were available from the time of admission. Fourth, we included many patient and hospital factors during the process of adjustment that are not obviously used in medical decisions around inotrope use. We felt that a liberal approach to covariate inclusion in the process of rate standardization was preferable, but may over-adjust for hospital differences in inotrope use. Fifth, the analysis is at the hospital level, whereas decisions for inotrope use are typically physician driven. We did not have data on prescribing at the physician level. We would expect even greater variation if hospital rates of inotrope use were further divided by individual clinician. Sixth, GWTG collects data by site and hospitalization event, not by patient. The effect of recurrent hospitalizations for individual patients are not specifically accounted for in the analysis. Finally, only the 3 listed inotropes were included, without data on other inotropic agents such as norepinephrine and epinephrine. Although we are not able to provide information on use of these other inotropes, guidelines continue to favor dobutamine, dopamine, and milrinone in their recommendations.<sup>1-3</sup>

## Conclusion

Among U.S. hospitals participating in GWTG-HF, marked differences were observed in the rates of inotrope use for the treatment of patients hospitalized with heart failure. Significant variation persisted even after accounting for measured differences in case mix and hospital type, suggesting that additional data are needed to clarify optimal indications for inotrope use. This study heralds an urgent need for randomized clinical trials to define the proper role of inotropic agents in this high-risk patient population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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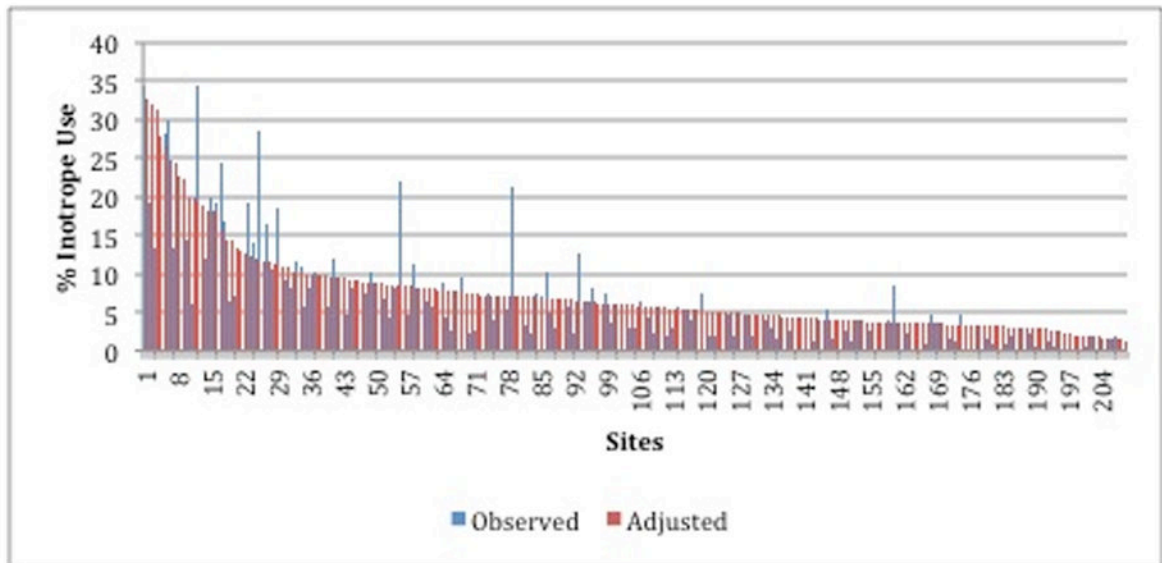
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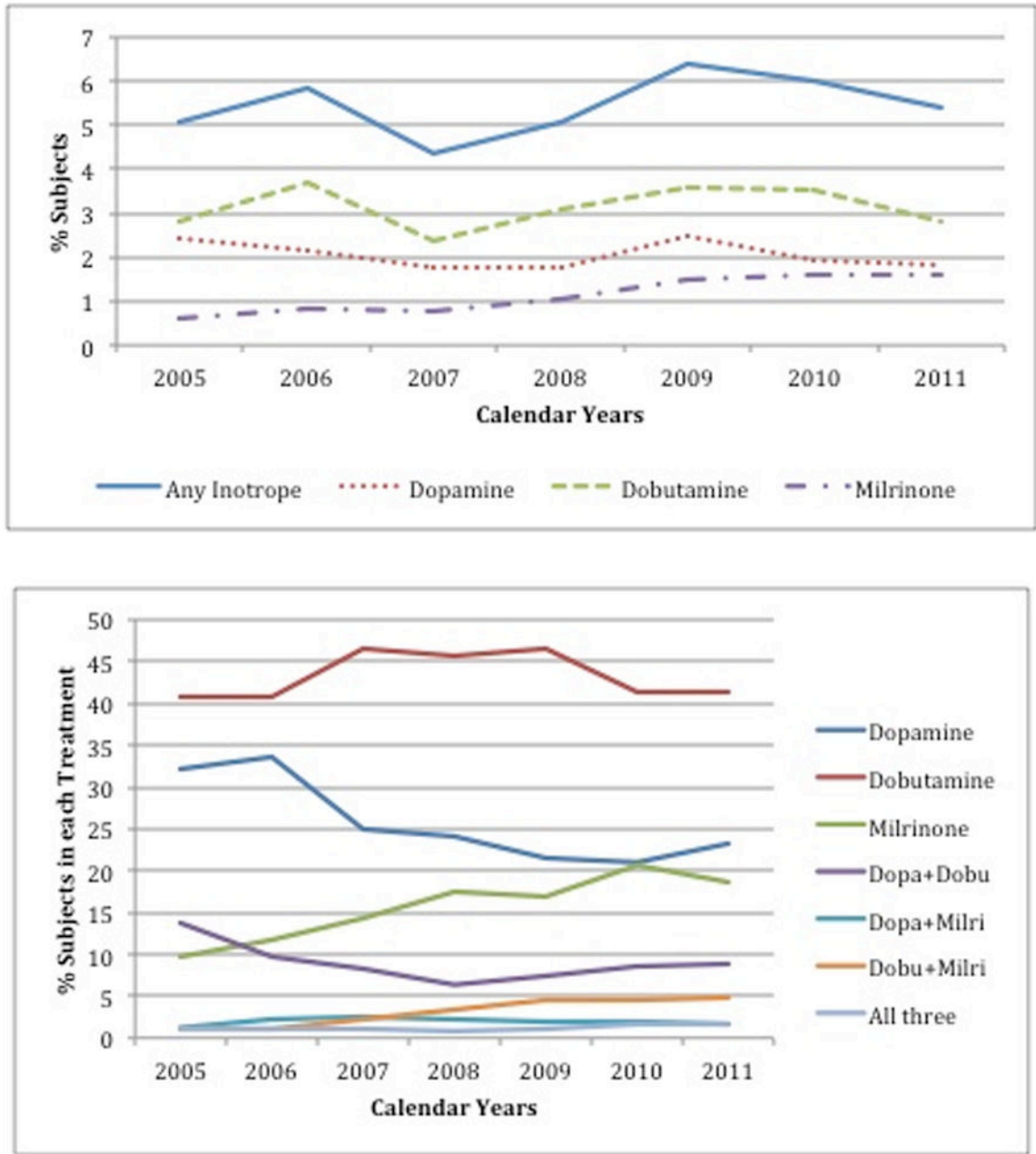
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**Figure 1.** Hospital rates of inotrope use among patients hospitalized with heart failure, with observed (blue) and risk-standardized (red) rates paired for each hospital site. Sites ordered from highest (left) to lowest (right) by hospital risk-standardized rates.



**Figure 2.** Temporal trends in use of intravenous inotropes. **Panel A** shows the hospital-level mean percent of patients hospitalized with heart failure treated with any inotrope (solid blue line), and treated with individual agents (dashed lines), in each of the years studied. **Panel B** shows a detailed breakdown of the agent(s) used among patients treated with an inotrope.

**Table 1** Hospital-level inotrope use rates, stratified by quartiles of risk-standardized hospital rates of inotrope use.

Variable	Overall	Q1 Low Use Hospitals N=52	Q2 N=52	Q3 N=53	Q4 High Use Hospitals N=52
<b>Inotrope use, OBSERVED, at the hospital level</b>					
Overall:					
median	<b>3.9%</b>	<b>1.0%</b>	<b>2.7%</b>	<b>4.7%</b>	<b>10.4%</b>
IQR	1.8–7.2%	0.0–1.9%	1.6–4.0%	3.2–6.9%	7.1–15.4%
Range	0.0–34.4%	0.0–8.4%	0.0–7.5%	1.7–22.1%	3.6–34.4%
Dopamine:					
median	<b>1.5%</b>	<b>0.6%</b>	<b>1.2%</b>	<b>2.2%</b>	<b>2.9%</b>
IQR	0.6–2.7%	0.0–1.1%	0.1–1.8%	1.1–3.6%	1.9–4.8%
Range	0.0–27.9%	0.0–2.4%	0.0–3.9%	0.0–7.4%	0.0–27.9%
Dobutamine:					
median	<b>1.9%</b>	<b>0.4%</b>	<b>1.4%</b>	<b>2.4%</b>	<b>5.5%</b>
IQR	0.6–4.0%	0.0–0.8%	0.6–2.3%	1.0–3.8%	3.3–10.0%
Range	0.0–28.1%	0.0–3.9%	0.0–5.6%	0.0–15.2%	0.8–28.1%
Milrinone:					
median	<b>0%</b>	<b>0%</b>	<b>0%</b>	<b>0.5%</b>	<b>1.0%</b>
IQR	0.0–1.0%	0.0–0.2%	0.0–0.5%	0.0–1.2%	0.0–2.8%
Range	0.0–21.7%	0.0–5.3%	0.0–3.5%	0.0–11.3%	0.0–21.7%
<b>Inotrope use, RISK-STANDARDIZED for patient and hospital factors, at the hospital level</b>					
Overall:					
median	<b>5.9%</b>	<b>3.1%</b>	<b>4.7%</b>	<b>7.0%</b>	<b>11.5%</b>
IQR	3.7–8.6%	2.3–3.5%	4.1–5.3%	6.6–7.8%	9.8–18.5%
Range	1.3–32.9%	1.3–3.7%	3.7–5.8%	5.9–8.6%	8.6–32.9%

Q=quartile; IQR=interquartile range.

**Table 2** Patient characteristics summarized at the hospital level and stratified by quartiles of risk-standardized hospital rates of inotrope use.

Patient Variable summarized at Hospital Level	Q1	Q2	Q3	Q4	P-value
	Low Use Hospitals N=52 (Patients 29,336)	N=52 (Patients 31,582)	N=53 (Patients 34,551)	High Use Hospitals N=52 (Patients 31,095)	
<b>Patient Demographics</b>					
Age, hospital median of mean years (IQR)	77 (73-80)	77 (73-80)	78 (74-81)	75 (72-78)	0.11
Female, median hospital percent (IQR)	52.0% (48.5-58.9)	51.8% (47.3-58.2)	51.2% (46.2-55.2)	48.4% (43.3-52.0)%	0.0021
Race, hospital median percent (IQR)					
White	85.6% (59.2-95.8)%	85.1% (61.6-93.8)	82.5% (57.7-93.7)	74.7% (57.8-86.6)	0.081
Black	4.6% (1.2-30.5)	8.5% (0.8-19.7)	4.4% (0.9-12.0)	8.6% (1.0-26.6)	0.77
Other	3.6% (1.5-11.2)	2.9% (0.9-7.0)	5.2% (1.2-15.6)	6.5% (1.6-14.4)	0.15
Health Insurance Status, median hospital percent (IQR)					
Medicare	56.3% (29.7-79.6)	53.4% (35.9-74.5)	48.9% (20.6-67.6)	59.3% (26.2-76.7)	0.64
Medicaid	5.3% (1.9-11.4)	7.0% (2.8-14.6)	6.0% (3.0-14.0)	5.4% (3.3-12.6)	0.89
Private/other	21.4% (8.1-41.1)	19.1% (8.3-38.9)	20.8% (12.0-32.4)	20.8% (10.3-35.7)	0.98
None or undetermined	2.1% (0.5-4.2)	1.7% (0.3-4.6)	1.8% (0.5-3.6)	1.9% (0.8-5.1)	0.82
<b>Cardiac History, median hospital percent (IQR)</b>					
Heart failure, prior diagnosis	55.5% (32.3-66.2)	62.2% (43.4-73.7)	58.9% (36.5-70.3)	63.7% (45.9-74.2)	0.34
Ischemic heart disease	52.8% (45.4-58.0)	55.0% (47.5-66.5)	55.4% (50.4-60.9)	54.6% (47.5-59.6)	0.47
Valve disease	5.4% (3.2-15.0)	10.2% (4.0-17.0)	12.4% (6.7-21.4)	12.3% (4.7-19.5)	0.018
ICD or CRT-D	7.4% (4.6-14.2)	9.3% (5.5-12.6)	10.6% (5.2-14.4)	11.1% (7.3-17.9)	0.087
Atrial fibrillation or flutter	28.3% (22.6-39.2)	35.5% (24.8-42.2)	36.1% (27.5-41.2)	33.2% (23.2-42.9)	0.31
Beta-blocker at admission	38.8% (0.0-57.6)	49.6% (11.0-66.3)	49.0% (20.8-66.0)	56.6% (10.8-67.6)	0.34
<b>Medical History, median hospital percent (IQR)</b>					
Diabetes	41.5% (36.9-47.9)	43.0% (37.3-47.7)	40.7% (38.1-45.4)	41.0% (34.5-45.2)	0.81
Hypertension	71.7% (66.9-77.7)	76.1% (69.7-81.5)	76.8% (65.4-81.5)	72.0% (63.4-78.6)	0.084
Hyperlipidemia	36.5% (27.4-44.4)	43.2% (33.5-52.7)	41.7% (34.6-49.1)	38.8% (25.3-47.4)	0.065
Peripheral vascular disease	8.7% (4.3-12.9)	13.0% (7.9-18.2)	12.1% (7.7-17.2)	9.1% (5.2-13.2)	0.0059
CVA/TIA	13.4% (9.7-16.2)	15.3% (10.6-19.4)	13.8% (10.7-16.2)	12.2% (7.8-15.3)	0.054

Patient Variable summarized at Hospital Level	Q1	Q2	Q3	Q4	P-value
	Low Use Hospitals N=52 (Patients 29,336)	N=52 (Patients 31,582)	N=53 (Patients 34,551)	High Use Hospitals N=52 (Patients 31,095)	
Renal insufficiency, no dialysis	16.3% (12.4–21.0)	16.5% (12.5–22.3)	19.1% (15.6–23.0)	16.3% (11.4–22.5)	0.33
Renal insufficiency, dialysis	2.3% (0.3–4.0)	1.8% (0.0–4.2)	2.2% (0.0–4.4)	2.2% (1.1–3.5)	0.94
Anemia	15.7% (7.5–23.2)	21.0% (13.4–28.0)	16.1% (11.1–24.1)	16.2% (10.1–21.8)	0.071
COPD or asthma	28.3% (23.7–32.4)	32.2% (25.8–36.3)	29.2% (22.4–36.6)	29.4% (22.1–24.9)	0.25
Smoking	14.6% (11.4–19.7)	16.8% (10.7–19.9)	12.3% (7.7–17.7)	16.7% (10.5–18.7)	0.062
Depression	7.3% (4.3–13.7)	10.7% (6.5–15.8)	9.1% (4.9–12.3)	7.8% (3.9–11.3)	0.042
<b>Measurements Closest to Admission, median hospital median (IQR)</b>					
Systolic blood pressure, mmHg	138 (135–142)	139 (135–142)	139 (134–140)	138 (133–140)	0.59
Heart rate, bpm	83 (80–85)	82 (80–85)	82 (80–84)	82 (80–85)	0.83
Body mass index, kg/m <sup>2</sup>	28.3 (24.0–34.3)	28.3 (24.0–34.0)	28.2 (24.0–34.0)	28.3 (24.2–34.3)	0.024
Left ventricular ejection fraction	0.45 (0.36–0.50)	0.45 (0.40–0.45)	0.45 (0.38–0.47)	0.40 (0.35–0.45)	0.80
Serum sodium, mmol/L	138 (138–139)	138 (137–139)	138 (138–139)	138 (137–139)	0.26
Serum creatinine, mg/dL	1.3 (1.2–1.4)	1.3 (1.3–1.4)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	0.99
Blood urea nitrogen, mg/dL	25 (23–26)	25 (23–26)	26 (24–28)	26 (23–27)	0.0058
Hemoglobin, g/dL	11.9 (11.7–12.2)	11.8 (11.6–12.3)	11.9 (11.7–12.1)	12.0 (11.6–12.3)	0.89

Q=quartile; IQR=interquartile range; ICD=implantable cardioverter-defibrillator; CRT-D=cardiac resynchronization therapy with implantable cardioverter-defibrillator; CVA=cerebrovascular accident; TIA=transient ischemic attack; COPD=chronic obstructive pulmonary disease; mmHg=millimeters mercury; bpm=beats per minute; BNP=b-type natriuretic peptide.

P-values calculated by comparing only non-missing values. All tests treat the column variable as ordinal.

Missing data: body mass index 18.9%; left ventricular ejection fraction 4.1%; sodium 15.2%; Cr 13.6%; BUN 15.0%; HgB 16.2%; BNP 31.8%.



**Table 3**  
Hospital characteristics stratified by quartiles of risk-standardized hospital rates of inotrope use.

Hospital Variable	Q1	Q2	Q3	Q4	P-value
	Low Use Hospitals N=52	N=52	N=53	High Use Hospitals N=52	
Number of heart failure hospitalizations 2005–2011, median (IQR)	255 (97–634)	195 (77–606)	269 (72–788)	344 (116–732)	0.83
Hospital size, inpatient beds, median (IQR)	219 (128–369)	227 (61–83)	258 (107–326)	286 (174–359)	0.31
Region					0.88
West	15.4%	7.7%	13.2%	15.4%	
South	44.2%	34.6%	37.7%	42.3%	
Midwest	22.1%	30.8%	24.5%	23.1%	
Northeast	19.2%	26.9%	24.5%	19.2%	
Rural location	15.4%	23.1%	28.3%	13.5%	0.21
Teaching hospital	36.5%	38.5%	24.5%	42.3%	0.26
Heart transplants performed	7.7%	1.9%	5.7%	5.8%	0.61

Q=quartile; IQR=interquartile range.

All tests treat the column variable as ordinal.

**Table 4**

Predictors of inotrope use as determined by hierarchical generalized linear regression.

Variable	Model Fixed Effects: Patient + Hospital Characteristics C Index=0.8428						Model Fixed Effects: ONLY Patient Characteristics C Index=0.8427						
	Adjusted OR	Lower 95% CI	Upper 95% CI	T-Value	P-value	Global Test Chi-Sq	Adjusted OR	Lower 95% CI	Upper 95% CI	T-Value	P-value	Global Test Hi-Sq	P-Value Chi-Sq
Age, per 5 year	0.92	0.91	0.93	-14.18	<.0001	201.13	0.92	0.91	0.93	-14.29	<.0001	204.27	<.0001
Female	1.04	0.98	1.10	1.27	0.2057	1.60	1.04	0.98	1.10	1.26	0.2071	1.59	0.2071
Race: Other	0.82	0.74	0.91	-3.75	0.0002	20.25	0.82	0.74	0.91	-3.66	0.0003	19.08	<.0001
Race: Black	0.88	0.81	0.95	-3.21	0.0013		0.88	0.81	0.95	-3.09	0.0020		
Race: White	1.00		Reference				1.00		Reference				
No Insurance	0.80	0.70	0.92	-3.12	0.0018	13.45	0.80	0.70	0.92	-3.13	0.0017	13.33	0.0040
Medicare	1.01	0.94	1.08	0.19	0.8455		1.00	0.94	1.07	0.12	0.9055		
Medicaid	1.06	0.96	1.16	1.12	0.2652		1.05	0.96	1.16	1.07	0.2843		
Private Insurance	1.00		Reference				1.00		Reference				
MHX: Ischemic Heart Disease	1.03	0.97	1.09	1.06	0.2906	1.12	1.03	0.97	1.09	1.08	0.2801	1.17	0.2801
MHX: Atrial fibrillation or flutter	1.06	1.00	1.12	2.04	0.0416	4.15	1.06	1.00	1.12	2.03	0.0428	4.10	0.0428
MHX: Valve Disease	1.42	1.33	1.52	10.20	<.0001	104.11	1.42	1.33	1.52	10.20	<.0001	104.13	<.0001
MHX Diabetes	0.98	0.93	1.04	-0.68	0.4949	0.47	0.98	0.93	1.04	-0.67	0.5013	0.45	0.5013
MHX Hypertension	0.86	0.81	0.92	-4.86	<.0001	23.58	0.86	0.81	0.92	-4.84	<.0001	23.38	<.0001
MHX Dyslipidemia	1.03	0.98	1.09	1.14	0.2523	1.31	1.03	0.98	1.09	1.15	0.2511	1.32	0.2511
MHX Peripheral vascular disease	1.14	1.05	1.23	3.23	0.0012	10.45	1.14	1.05	1.23	3.23	0.0013	10.41	0.0013
MHX Renal insufficiency, dialysis	0.54	0.44	0.66	-5.99	<.0001	39.70	0.54	0.44	0.66	-5.99	<.0001	39.62	<.0001
MHX Renal insufficiency, no dialysis	1.02	0.95	1.10	0.56	0.5724		1.02	0.95	1.10	0.57	0.5718		
MHX Anemia	0.97	0.90	1.04	-0.81	0.4172	0.66	0.97	0.90	1.04	-0.89	0.3748	0.79	0.3748
MHX COPD	1.00	0.94	1.06	-0.04	0.9663	0.00	1.00	0.94	1.06	-0.05	0.9574	0.00	0.9574
MHX Smoking	0.87	0.81	0.94	-3.60	0.0003	12.97	0.87	0.81	0.94	-3.61	0.0003	13.04	0.0003
MHX Depression	1.03	0.95	1.12	0.67	0.5007	0.45	1.03	0.94	1.12	0.63	0.5262	0.40	0.5262
SBP, per 5 mmHg	0.90	0.90	0.91	-37.47	<.0001	1404.16	0.90	0.90	0.91	-37.49	<.0001	1405.53	<.0001
HR, <=75 bpm	1.00	0.99	1.00	-1.15	0.2482	1.33	1.00	0.99	1.00	-1.16	0.2478	1.34	0.2478
HR, 75-105 bpm	1.01	1.01	1.01	7.11	<.0001	50.58	1.01	1.01	1.01	7.10	<.0001	50.35	<.0001
HR, >=105 bpm	1.00	1.00	1.00	0.53	0.5990	0.28	1.00	1.00	1.00	0.52	0.6013	0.27	0.6013
LVFE, per 5% decrease from 60%	1.18	1.17	1.19	33.70	<.0001	1135.45	1.18	1.17	1.19	33.73	<.0001	1137.75	<.0001
Serum sodium, >140 mmol/L	1.01	0.99	1.03	0.97	0.3311	0.94	1.01	0.99	1.03	0.99	0.3221	0.98	0.3221
Serum sodium, <=140 mmol/L	0.95	0.94	0.95	-15.87	<.0001	251.76	0.95	0.94	0.95	-15.89	<.0001	252.43	<.0001
Blood urea nitrogen, per mg/dL increase	1.01	1.01	1.01	13.99	<.0001	195.66	1.01	1.01	1.01	13.99	<.0001	195.83	<.0001
Serum creatinine, >2.5 mg/dL	0.84	0.80	0.87	-8.72	<.0001	76.06	0.84	0.81	0.87	-8.72	<.0001	75.98	<.0001
Serum creatinine, <=2.5 mg/dL	1.83	1.70	1.97	16.41	<.0001	269.30	1.83	1.70	1.97	16.41	<.0001	269.19	<.0001

Variable	Model Fixed Effects Patient + Hospital Characteristics C Index=0.828										Model Fixed Effects ONLY Patient Characteristics C Index=0.8427				
	Adjusted OR	Lower 95% CI	Upper 95% CI	T-Value	P-value	Global Test Chi-Sq	P-Value Chi-Sq	Adjusted OR	Lower 95% CI	Upper 95% CI	T-Value	P-value	Global Test Hi-Sq	P-Value Chi-Sq	
HgB, per g/dL, increase up to 11	1.04	1.00	1.07	2.05	0.0400	4.22	0.0400	1.04	1.00	1.07	2.01	0.0445	4.04	0.0445	
Time: per 1 yr	0.97	0.96	0.99	-2.73	0.0064	7.44	0.0064	0.97	0.96	0.99	-2.67	0.0075	7.15	0.0075	
Teaching hospital	0.84	0.63	1.14	-1.10	0.2727	1.20	0.2727								
Hospital beds, per 200	1.22	1.06	1.42	2.72	0.0066	7.39	0.0066								
Heart transplants performed	1.25	0.68	2.27	0.72	0.4706	0.52	0.4706								
Rural-(ref. urban)	0.74	0.51	1.09	-1.50	0.1335	2.25	0.1335								
Region West	1.57	1.00	2.48	1.95	0.0510	11.11	0.0112								
Region South	1.80	1.27	2.55	3.30	0.0010										
Region Midwest	1.57	1.06	2.32	2.25	0.0247										
Region Northeast	1.00	Reference													

OR=odds ratio; LVEF=left ventricular ejection fraction; HgB=hemoglobin; HR=heart rate; bpm=beats per minute; MHX=medical history; COPD=chronic obstructive pulmonary disease; SBP=systolic blood pressure; LVEF=left ventricular ejection fraction; BUN=blood urea nitrogen.

**Table 5**

Outcomes, stratified by quartiles of risk-standardized hospital rates of inotrope use.

Variable	Overall	Q1 Low Use Hospitals N=52	Q2 N=52	Q3 N=53	Q4 High Use Hospitals N=52	P value
In-hospital mortality, % patients by hospital, median (IQR)						
Observed	3.1 (1.6–4.3)	2.4 (0.8–3.7)	3.3 (1.7–4.2)	3.3 (1.9–5.3)	3.0 (1.7–4.3)	0.12
Adjusted	3.1 (2.5–3.8)	2.9 (2.3–3.5)	3.2 (2.6–3.7)	3.2 (2.6–4.1)	3.5 (2.6–4.1)	0.13
Length of stay, > 4 days, % patients by hospital, median (IQR)						
Observed	43.3 (35.3–50.7)	39.5 (33.9–48.7)	41.8 (34.0–48.1)	43.6 (33.7–48.3)	46.5 (40.8–56.5)	0.0040
Adjusted	45.4 (39.6–51.4)	42.7 (38.1–47.6)	42.4 (39.0–48.4)	43.6 (39.9–51.8)	49.9 (47.1–55.2)	<.0001
Performance Measures, % of eligible						
Discharged home, among patients eligible, % by hospital, median (IQR)	89.6 (75.4–95.5)	87.0 (67.0–95.4)	90.0 (77.9–96.6)	88.5 (73.0–95.3)	91.0 (81.4–95.5)	0.51
Documentation of LVEF, % by hospital, median (IQR)	97.7 (93.9–99.7)	97.5 (93.2–99.6)	97.6 (94.3–99.8)	97.5 (92.7–99.5)	98.6 (95.7–99.8)	0.50
Discharged on ACEI/ARB, among patients with LVSD and no contraindication, % by hospital, median (IQR)	90.0 (77.7–95.0)	89.3 (78.2–96.1)	89.4 (76.9–94.3)	89.4 (76.0–94.5)	91.2 (80.9–95.3)	0.86
Discharged on beta-blocker, among patients with LVSD and no contraindication, % by hospital, median (IQR)	94.5 (87.0–97.8)	93.4 (85.6–97.9)	94.7 (89.4–96.9)	95.2 (88.0–98.0)	94.0 (89.3–97.2)	0.92
Smoking cessation counseling, among patients with smoking history, % by hospital, median (IQR)	97.3 (85.7–100)	95.3 (80.3–100)	96.6 (85.5–100)	97.1 (83.3–100)	99.0 (88.8–100)	0.30
Composite for 100% compliance, % by hospital, median (IQR)	82.7 (64.9–90.8)	78.5 (56.5–90.0)	84.2 (64.1–89.8)	79.6 (64.5–91.0)	84.8 (67.6–91.5)	0.59

Q=quartile; IQR=interquartile range; LVEF=left ventricular ejection fraction; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; LVSD=left ventricular systolic dysfunction.

All tests treat the column variable as ordinal.

Adding insurance status and race to the adjustment process made no significant change on any of the adjusted results.