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Geographic variation in the use of continuous outpatient inotrope infusion therapy and beta blockers

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ABSTRACT

Background: Continuous outpatient inotrope infusion therapy (COIIT) can be used as palliative or interim treatment in patients with advanced heart failure (AHF). Despite widespread use, there is a relative lack of data informing best practices. This study aimed to examine whether patterns of COIIT use differed by region and to explore whether observed differences influenced clinical outcomes.

Methods: Retrospective study of AHF patients receiving COIIT from May 2009 through June 2016. The primary outcome was regional difference, the secondary outcome was persistence (duration) on therapy. Cox proportional hazards model was used to calculate hazard ratios for treatment regimens.

Results: There were 3,286 patients, mean (SD) age 61.9 (14.4) years and 74.0% (2,433) male. Inotrope selection and beta blocker use varied by region by chi square ($\chi 2$ (21) = 166.9, $p < 0.001$). Persistence was greater on milrinone compared to dobutamine (HR (for discontinuation) 0.54, CI 0.41–0.70, $p < 0.001$). Concurrent beta-blocker was associated with greater persistence for patients receiving milrinone (HR 0.13, CI 0.08–0.20, $p < 0.001$) and dobutamine (HR 0.36, CI 0.18–0.71, $p < 0.001$).

Conclusions: Patterns of COIIT use varied by region, and variations in use were associated with differences in clinical outcomes.

1. Introduction

Continuous outpatient inotrope infusion therapy (COIIT) can serve as palliation in select patients with advanced heart failure (AHF) ineligible for definitive intervention and as interim therapy for patients destined for such interventions. Despite increasing use, limited data inform optimal management of patients on COIIT. The majority of clinical trials of inotrope agents are from an earlier treatment era and typically involved formulations and dosages that are markedly dissimilar from contemporary medical practice [1–4]. Contemporary studies of COIIT are primarily limited to single-center cohorts of modest sample sizes [5–7] or involve agents not currently approved for use in the US [8]. The continued use of guideline directed therapy, beta-blockers in particular and especially in combination with dobutamine is controversial for patients on COIIT in the US [9]. While some studies suggest advantages of one agent relative to another, none are definitive and none examine the potential impact of adjunct beta-blockers in mitigating the known risks of inotropes. Standards of care may vary in

Abbreviations: AHF, Advanced Heart Failure; COIIT, Continuous Outpatient Inotrope Infusion Therapy; MCS, Mechanical Circulatory Support.

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the absence of evidence sufficient to guide clinical practice [10]. There is a need for assessment and characterization of these commonly used drugs in the current treatment milieu.

The objectives of this retrospective study were to examine patterns of COIIT use in a national (US) cohort of AHF patients and explore whether inotrope selection and continuation of beta-blocker influenced persistence. These results are intended to provide hypothesis-generating insights into the current management of patients on COIIT.

2. Methods

2.1. Study subjects

We performed a retrospective analysis of data from adult AHF patients (age $\geq$ 18 years) who received ambulatory inotrope therapy from 05/01/2009 until 06/30/2016 through Option Care™, the largest national provider of home infusion services in the United States. Patients were treated in accordance with contemporaneous Centers for Medicare and Medicaid Service criteria which necessitated: (1) diagnosis of heart failure, (2) dyspnea at rest or mild exertion, (3) Fick cardiac index $\leq$ 2.2 L/min/m^2 or pulmonary capillary wedge pressure $\geq$ 20 mmHg and $\geq$ 20% improvement in either parameter with inotrope infusion, (4) treatment with guideline-directed medical therapy or rational explanation for no treatment, and (5) in-hospital failure to wean. (Chartwell Diversified Services IN. Medicare Coverage Criteria for Infusion Therapy.2008, https://www.uwhealth.org/files/uwhealth/docs/pdf/Chartwell_Medicare_Coverage.pdf).

De-identified administrative data were obtained at the request of the authors. Available variables included age, gender, region of service, inotrope type, duration of infusion, physician-reported goal of therapy, beta-blocker, and patient status at the time of COIIT discontinuation or end of study (deceased, discharged alive, or actively receiving infusion). Access to the data, methods used in the analysis, and materials used to conduct this study are available upon reasonable request and at the discretion of the authors and OptionCare.

2.2. Statistical analysis

We used descriptive statistics to characterize the cohort. Persistence (relative duration of therapy) was expressed as mean days on therapy. The relative likelihood of persistence with therapy and the secondary outcome of relative likelihood of death on therapy were estimated through a Cox proportional hazards model. Coefficient and confidence interval (CI) estimations for both models were obtained via bootstrapping [11,12]. Post-estimation validation of the Cox model included testing for proportional hazards (PH) violations, outlier observations, and non-linear associations between continuous variables and survival. Patients on dopamine or combined dual inotrope were excluded from the Cox models due to their relatively low numbers. A natural log transformation was applied to the time-interaction terms based on Martingale residual-versus-survival plots. The fit of the final models was assessed through Cox-Snell residual plots. Due to the high rate of censoring a sensitivity analysis, assuming all patients exiting the study met the failure endpoint (death), was performed to address the potential for unknown confounders that might introduce bias.

In an additional exploratory analysis, we used Cox proportional hazards modes to measure the relative likelihood of death while on therapy. The coefficient and confidence intervals of each covariate were compared across models. We also examined E-values, a statistic used in observational studies to estimate the strength required of any unmeasured confounder to negate the treatment effects demonstrated by the model [13]. STATA 14.2 was used for statistical analysis. The University of Southern California Institutional Review Board authorized the study.

3. Results

The 3,286 subject cohort was 74% male and the mean age was 61.9 $\pm$ 14.4 years (Table 1). Milrinone was prescribed in 2,294 patients (68.8%), mean dose 0.35 $\pm$ 0.19 μg/kg/min. Dobutamine was prescribed for 816 patients (24.8%) at a mean dose of 4.22 $\pm$ 2.94 μg/kg/min. Beta-blockers were continued for 797 patients (24.2%), with 18.0% (n = 592) receiving carvedilol, 3.6 % (n = 111) receiving metoprolol succinate and 0.2% (n = 5) on bisoprolol. The remaining 89 patients were continued on non-guideline directed medical therapy recommended beta blockers (nebivolol, propranolol, metoprolol tartrate, etc.). Adjunct beta-blocker was prescribed twice as often in combination with milrinone (28.1%) than dobutamine (14.6%).

There were 562,566 observed patient days, and the mean duration of therapy (persistence) was 171 days (standard deviation 231). The minimum duration was 1 day, and maximum duration was 2,204 days. Information on the goal of therapy was available for < 5% of the sample. By the end of the observation period 2,457 patients had been discontinued from inotropic infusion and discharged alive from Option Care™ home health services. There were 664 deaths while on therapy, and 166 patients remained active on therapy at the end of the observation period.

3.1. Regional variation in inotrope and Beta-Blocker use

The largest proportion of patients in the study cohort were in the Southeast (35.8%, 1,177), the U.S. region with the highest prevalence of heart disease. (Table 2.). Although milrinone was overall the most frequently used inotrope, there was significant variation in inotrope selection across regions. The Northeast had the highest milrinone use (84.3%), whereas dobutamine use was highest in the Mountain States region at 48.0%. The difference in inotrope selection between regions was statistically significant (chi-squared (21, N = 3286) = 166.9, $p < 0.001$. Beta-blocker use also varied across regions of service ($p < 0.001$). (Fig. 1B) The Southeast had the highest incidence of simultaneous inotrope-beta-blocker use at 35.4%, and the lowest was in the Appalachian Region at 7% (Fig. 2).

3.2. Persistence on COIIT with and without Beta-Blocker

The Cox proportional hazards model indicated longer persistence with milrinone than with dobutamine (HR, 0.54; $p < 0.001$; 95% CI, 0.41–0.70). Beta-blocker use in conjunction with either milrinone or dobutamine was associated with longer persistence with therapy (HR, 0.13; $p < 0.001$; 95% CI, 0.08–0.20 and HR, 0.36; $p = 0.003$; 95% CI, 0.18–0.71, respectively). (Table 2)

Persistence also differed by region. Regions with greater dobutamine use were associated with earlier discontinuation of COIIT (HR: Great Lakes-1.17, Pacific Northwest-1.51, and Mountain States-1.57) (Table 2).

3.3. Exploratory analysis

The pattern of death on COIIT was similar to persistence. Compared to dobutamine, milrinone was associated with a reduced risk of death on COIIT (HR, 0.45; $p = 0.002$; 95% CI, 0.27–0.75). Adjunct beta-blocker, with either milrinone or dobutamine, was also associated with reduced risk of death (HR, 0.07; $p < 0.001$; 95% CI, 0.03–0.14 and HR, 0.27; $p = 0.018$; 95% CI, 0.09–0.79, respectively).

To address the high rate of censoring as patients exited active treatment (patients' data were collected by OptionCare only while they received active inotropic therapy, therefore survival post discontinuation is unknown), we performed sensitivity analyses, in which the failure outcome, death, was assigned to all subjects exiting the study. The results revealed no changes in the statistical significance or direction of the estimates, demonstrating the robustness of the core model against non-

Table 1
Persistence on Continuous Outpatient Inotrope Infusion Therapy. Persistence, expressed as mean days on therapy, by treatment combination. Categorical data is presented as number (%) percentage, of the study population and continuous date is presented as mean (SD) standard deviation. BB = beta-blocker, SD = standard deviation.

Therapy	N	Person- Days Observed	Gender No. (%) Male	Female	Age (years) mean (SD)	Observed Deaths No. (%)	Days on Therapy, mean (SD)
All	3,286	562.566	2,433 (74.0)	854 (26.0)	61.9 (14.4)	664 (20.2)	171(231)
Milrinone	2,294	432,403	1,716 (74.8)	578 (25.2)	61.4 (14.4)	430 (18.7)	188 (246)
No BB	1.650	269,131	1,218 (73.8)	432 (26.2)	61.6 (14.4)	325 (19.7)	163 (224)
With BB	644	163,272	498 (77.3)	146 (22.7)	60.9 (14.2)	105 (16.3)	254 (285)
Dobutamine	816	95,697	585 (71.7)	231 (28.3)	63.6 (14.1)	192 (23.5)	117 (169)
No BB	697	75,335	506 (72.6)	191 (27.4)	63.6 (14.2)	176 (25.3)	108 (156)
With BB	119	20,362	79 (66.4)	40 (33.6)	63.8 (13.9)	16 (13.5)	171 (225)
Dual	133	29,351	101 (75.9)	32 (24.1)	59.8 (13.9)	30 (22.6)	221 (264)
Dopamine	44	5,115	31 (70.4)	13 (29.6)	59.5 (17.6)	12 (27.3)	116 (143)

Table 2
Regional Variation in Inotrope and Beta-Blocker Use and Persistence on Therapy (expressed as mean days on therapy). HR: hazard ratio; CI: confidence interval; BB: beta blocker. *hazard ratio point estimates and 95%-confidence intervals obtained from full model, with Southeast region serving as the reference group. Categorical data is presented as number (%) percentage, of the regional population. The "n" column includes the total count of patients receiving inotrope therapy in each region, including those patients on dopamine or dual inotropes. Subjects on dopamine or dual inotropes were excluded from the point estimates due to low representation.

Region	Total	Dobutamine		Dobutamine + BB		Milrinone		Milrinone + BB		HR Point Estimate	95% CI Estimation	
Appalachian State	267	59 (22.9)	(22.9)	4	(1.6)	179	(69.4)	14	(5.4)	1.05	0.95	1.17
Central	443	110(26.0)	(26.0)	14	(3.3)	226	(53.4)	58	(13.7)	0.96	0.87	1.06
Great Lakes	385	106	(29.0)	12	(3.3)	199	(54.5)	46	(12.6)	1.17	1.05	1.31
Mountain States	137	52	(40.9)	9	(7.1)	44	(34.7)	21	(16.5)	1.57	1.29	1.92
Northeast	532	65	(12.6)	6	(1.2)	316	(61.2)	119	(23.1)	1.03	0.92	1.16
Pacific Northwest	193	59	(31.4)	4	(2.1)	91	(48.4)	25	(13.3	1.51	1.30	1.5
Southeast	1,177	198	(17.5)	59	(5.2)	530	(46.9)	341	(30.2)	-*	-*	
West	153	48	(32.7)	11	(7.5)	65	(44.2)	20	(13.6)	1.15	0.96	1.39

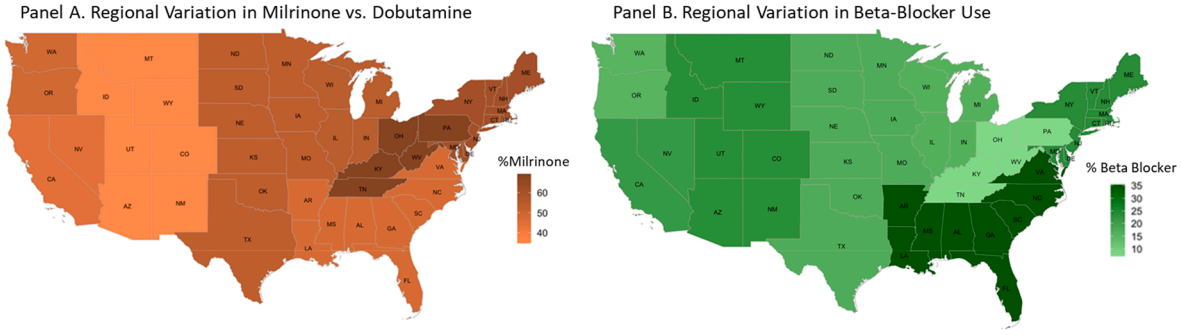

Fig. 1. Choropleths of Regional Variation in Inotrope (Milrinone vs. Dobutamine) and Beta-Blocker Use. Panel A. Regional use of milrinone vs dobutamine with increased percentage of milrinone represented by darker shading. Panel B. Percentage of beta-blocker by region with higher percentage represented by darker shading.

independent censoring. In addition, due to the limited nature of the data source, we used E-value analysis a statistic, similar to p-values, but used in observational studies to estimate the strength required of any unmeasured confounder to reverse the risk ratios (apparent treatment effects) revealed by the model [13]. The findings were robust against unmeasured confounding for effect sizes by hazard ratio of up to 2.84, for milrinone alone, 4.36 for dobutamine with beta-blocker, and 10.87 for milrinone with beta-blocker.

4. Discussion

In this national cohort of 3,286 AHF patients on COIIT, there was significant regional variation in the selection of inotropes. In addition, the use of concomitant beta-blocker also varied by region. Overall, those treated with milrinone had longer persistence with therapy than those treated with dobutamine. An exploratory analysis also revealed a lower risk of death on COIIT for those treated with milrinone compared with dobutamine. Furthermore, the presence of concurrent beta-blockers was associated with longer persistence and reduced risk of death on COIIT, regardless of whether patients were treated with milrinone or dobutamine.

According to ACC/AHA HF guidelines [14], continuous outpatient inotrope infusion can be utilized as palliative therapy (class IIb indication) in select ACC/AHA stage D HF patients ineligible for either durable mechanical circulatory support (MCS) or cardiac transplantation [7]. COIIT is also widely used as an interim therapy for many patients eventually destined for cardiac transplantation or mechanical circulatory support (MCS). With the growing number of patients with heart failure, the use of COIIT has also risen. The number of Medicare beneficiaries receiving COIIT more than doubled between the years 2010 and 2014 [15]. Despite evidence of an ongoing role of COIIT in treating patients with AHF, there is very little contemporary data informing clinical decision making and optimal medical management.

The findings of this study are consistent with and expand upon results from earlier studies of chronic inotropes in patients with AHF. A study by Gorodeski et al. of 112 patients treated at Cleveland Clinic

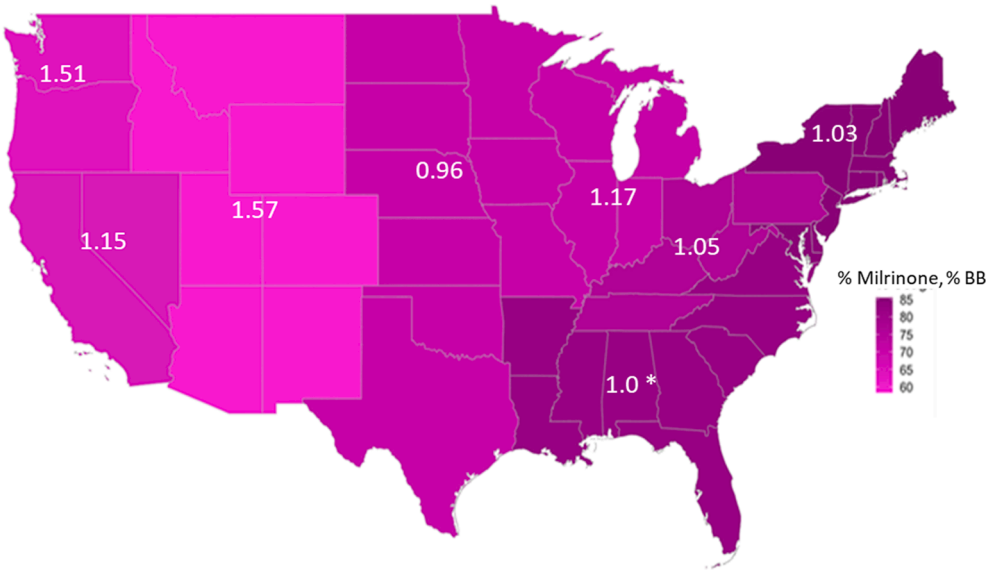

Fig. 2. Milrinone vs Dobutamine and Beta-Blocker Use by Region Fig. 2 Choropleth of Regional Variation in Milrinone vs. Dobutamine and Beta-Blocker use Percentage of milrinone vs. dobutamine overlaying percentage of beta blocker use by region with greater use of either agent represented by deeper shading. Hazard ratios for persistence, as represented by mean days on therapy, superimposed on regions.

between 2002 and 2007 revealed a median survival of 6 months, a modest improvement compared with the "classic studies" of the 90s [7]. The rate of death was significantly higher in the dobutamine group versus the milrinone group (47 patients [84%] versus 35 patients [62%], $p < 0.01$) [7]. A subsequent series by Hashim et al. reviewed outcomes of 197 patients discharged on inotropes from the University of Alabama at Birmingham (UAB) between 2007 and 2013 [6]. Fifty-five patients were bridged to transplant or MCS, 68 died, 24 patients were weaned and 50 remained on COIIT [6]. Those on milrinone had a lower risk of death than those on dobutamine $p = 0.01$ [6]. Most recently, a registry of 1149 patients from an ambulatory infusion service revealed greater 1-year survival associated with milrinone compared with dobutamine (70.7% vs. 46.2%, p, 0.0001) [16]. Subgroup analyses revealed that this relationship was consistent across indications, including bridge to transplant (85.9% vs. 71.3%, p, 0.0001), bridge to MCS (91.4% vs. 71%, p 5 0.001), and palliation (73.6% vs. 63.3%, p, 0.001) [16].

In addition, the continued use of beta-blockers was associated with increased persistence on therapy and reduced risk of death, regardless of whether patients received milrinone or dobutamine. Although this is, to our knowledge, the first description of this association, it is intriguing to review the prior observational studies with this finding in mind. In the early paper from Gorodeski, et al. beta-blockers were present in 19.6 % of patients, and the median survival was six months [4]. In the later study from UAB, 70% of subjects were on beta-blockers, and the median survival for the cohort was 18 months, with those on palliative therapy having a median survival of 9 months [6]. It is also notable that while dobutamine, compared with milrinone, was associated with higher all-cause mortality in the unadjusted analysis of the Cleveland Clinic study (HR, 1.63; 95% CI, 1.06 to 2.52; $P < 0.03$) this difference was nullified after propensity matching, primarily on beta-blocker usage [7].

Although abundant data support the benefit of ß-adrenergic blockade in patients with reduced ejection fraction HF (HFrEF), the use of beta-blockers for patients on COIIT is controversial, especially in combination with dobutamine.[9,17,18] Beta-blockers are viewed as counter-productive and often pre-emptively discontinued in patients on COIIT. [9,19] While beta-blockers may blunt the inotropic effect of dobutamine there is no established evidence of harm [19]. Clinical studies have documented neutral to favorable impacts of the combination [9,19–22]. In sharp contrast, the withdrawal, interruption, and failure to initiate beta-blocker therapy are all associated with substantiated increased morbidity and mortality risk in patients with HFrEF [18,23].

This study also revealed significant regional variation in the selection of inotropes and the concomitant use of beta-blockers. Regions with higher usage of milrinone and beta-blockers tended to have lower hazards for discontinuation or death on COIIT. Although the Southeast and Midwest (Central) regions have the highest mortality rates for HF in the US [24], in this study these regions had the lowest risks of discontinuation/death on COIIT. Of note these regions held the highest prevalence of inotrope with beta blocker and milrinone use respectively. The variation in practice seen in this cohort highlights a lack of treatment consensus.

Despite noteworthy advances in pharmacologic and device therapies, many patients with AHF will arrive at a clinical stage characterized by intractable symptoms, reduced functional capacity and frequent hospitalization. COIIT has been shown to alleviate symptoms, improve functional status and reduce hospitalization in select patients with advanced heart failure. [25,26] Although widely used, the application of these agents has been fraught due to a paucity of contemporary data. This manuscript contributes to a growing body of evidence.

Important strengths of this study include the large sample size and national representation. The primary limitations are the lack of detailed patient-level data and the high rate of censoring upon exiting treatment (in this administrative data set, patient information was collected only while receiving COIIT). Combined, these contribute to appropriate concerns for selection bias and non-random censoring.

In conclusion, in this observational study of a large cohort of patients with advanced heart failure receiving COIIT, the use of milrinone was associated with longer duration of therapy and reduced risk of death on therapy compared with dobutamine, the concurrent use of beta-blockers with either agent was associated with increased duration and reduced risk of death on therapy for either agent. There was also a high degree of geographic variation in treatment strategies and outcomes. Further study is needed to understand whether these strategies can be used to improve clinical outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100948.

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