Expected vs Actual Outcomes of Elective Initiation of Inotropic Therapy During Heart Failure Hospitalization

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Abstract

Objective: To describe the intent and early outcomes of elective inotrope use during heart failure hospitalization.

Patients and Methods: A prospective multisite design was used to collect data for hemodynamically stable patients started electively on inotrope therapy between January 1 and August 31, 2018. We prospectively recorded data when intravenous inotropic therapy was initiated, including survey of the attending cardiologists regarding expectations for the clinical course. Patients were followed up for events through hospital discharge and an additional survey was administered at the end of hospitalization.

Results: For the 92 patients enrolled, average age was 60 years and ejection fraction was 24%±12%. At the time of inotrope initiation, attending heart failure cardiologists predicted that 50% (n=46) of the patients had a "high or very high" likelihood of becoming dependent on intravenous inotropic therapy and 58% (n=53) had a "high" likelihood of death, transplant, or durable ventricular assist device placement within the next 6 months. Provider predictions regarding death/hospice or need for continued home infusions were accurate only 51% (47 of 92) of the time. Only half the patients (n=47) had goals-of-care conversations before inotrope treatment initiation.

Conclusion: More than half the patients (51 of 92) electively started on inotrope treatment without present or imminent cardiogenic shock ultimately required home inotrope therapy, died during admission, or were discharged with hospice. Heart failure clinicians could not reliably identify those patients at the time of inotrope therapy initiation and goals-of-care discussions were not frequently performed.

npatient heart failure (HF) care has changed tremendously in recent decades. The traditional "HF admission" for volume overload requiring 24 to 48 hours of intravenous diuresis is now less common and has been replaced by the admission for decompensated advanced HF often complicated by chronic kidney disease and diuretic resistance. Patients who are hospitalized with HF are older, sicker, and more frail.[1] These patients are more likely to require high-dose loop diuretics, often with substantial thiazide augmentation or the initiation of inotrope treatment to achieve adequate diuresis.[2]

Several large registry studies have demonstrated increased morbidity and mortality in patients treated with intravenous inotropic therapies (IITs) in the inpatient setting. Such patients experience more arrhythmias, longer lengths of stay, increased in-hospital mortality, higher readmission rates, and increased costs.[3-8] However, none of these registries separate elective initiation as adjunctive therapy (ie, to augment diuresis) from the more common initiation as urgent therapy for progressive hemodynamic decompensation.

Although much is known about the prognosis and outcomes of hemodynamically

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unstable patients started on IIT for cardiogenic shock,[5,9,10] little is known about the prognosis of hemodynamically stable patients with HF started on IIT, typically for inadequate responses to standard decongestion strategies. Given the increasing use of inotropes in the inpatient setting[10] and the increased diuretic resistance among contemporary hospitalized patients with HF, it is imperative that HF specialists and general cardiologists understand the implications and outcomes of starting IIT in hemodynamically stable patients. The aim of this study is to describe the anticipated/predicted and actual outcomes of hemodynamically stable patients with HF electively initiated on IIT in the inpatient setting.

PATIENTS AND METHODS

We used a prospective multicenter design to investigate hemodynamically stable patients with HF electively initiated on IIT from 6 academic medical centers across the United States between January 1 and August 1, 2018. Adult patients admitted to the hospital for a primary diagnosis of acute decompensated HF who were electively initiated on IIT during the admission were eligible for inclusion in the study. Elective initiation of IIT was defined as the initiation of inotrope therapy to assist with diuresis, not to treat hemodynamic instability or critical dysfunction of vital organs. None of the patients had clinical evidence of cardiogenic shock and were rather initiated on inotrope treatment with the intent to assist with diuresis. Patients initiated on IIT for reasons other than HF were excluded and concomitant diagnoses that can affect hemodynamics, including sepsis, acute coronary syndromes, and pulmonary embolism, were used as exclusion criteria. Study patients were identified using institution-specific clinical resources, including continual inpatient provider notifications of study criteria throughout the enrollment period and electronic investigator notifications within the electronic medical record when new orders for inotropes were placed. Patients with preexisting mechanical circulatory support devices or who required treatment with dual inotropes or temporary mechanical circulatory support for worsening cardiogenic shock were excluded.

At the time of IIT initiation, the clinical team managing each patient was asked to complete a questionnaire assessing various parameters including perceived likelihood of inotrope dependence and need for advanced therapies evaluation within the first 24 hours of inotrope treatment initiation. A second questionnaire was provided at time of discharge or death assessing patient outcomes and discharge disposition. Using electronic medical records, we collected clinical information at the time of admission and discharge for all patients.

For ease of comparison, β-blocker dosing was converted to daily metoprolol succinate equivalents. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and angiotensin receptor neprilysin inhibitor therapies were converted to daily lisinopril equivalents. Mineralocorticoid receptor antagonist therapies were converted to daily spironolactone equivalents. Loop diuretic regimens were converted to daily furosemide equivalents. All conversions were based on previously published algorithms.[1,11] Advanced therapies were defined as cardiac transplantation, inpatient transplant listing, or durable mechanical circulatory support device placement.

Three groups were compared: (1) patients discharged without inotropes, (2) patients discharged with inotropes, and (3) patients who died or were discharged on hospice. Normality was determined using the Shapiro-Wilk test. For normally distributed continuous variables, we present mean ± SD values. For non-normally distributed continuous variables, we present values as median and interquartile range. For categorical variables, we present values as frequency. To compare variable frequency between patients discharged alive and off IIT with those discharged with home IIT, discharged to hospice, or who died before discharge, analysis of variance was used for continuous variables and χ^2 test was used for proportional data.

We created 2 multivariable logistic regression models to determine the association between the attending cardiologists' prediction regarding short-term outcomes and patients' actual short-term outcomes. The 2 outcomes analyzed in these models were: (1) the frequency of inotrope dependence, and (2) a combined outcome of death, ventricular assist device (VAD) implantation, or transplantation in the subsequent 6 months. A coefficient of

determination (Cox and Snell R^2) was measured to compare the explanatory power of a model with clinical variables but without provider prediction with a model with both clinical variables and provider predications.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc). Institutional review board approval at all sites was obtained before study initiation. The study was designed and performed within the Heart Failure Apprentice Network, which is supported by the National Heart, Lung, and Blood Institute. These patients were not enrolled in the formal Heart Failure Network studies.

RESULTS

A total of 92 patients admitted to 6 academic medical centers (institution 1, n=31; institution 2, n=10; institution 3, n=18; institution 4, n=6; institution 5, n=6; and institution 6, n=21) for acutely decompensated HF were prospectively identified and enrolled in the study. The average age was 60±12 years, most patients (n=62; 67%) were men and had a nonischemic cause of their HF (n=62; 67%; Table 1). The average ejection fraction was 24±12%. The 3 compared groups (patients discharged without IIT, patients discharged with IIT, and patients who died in the hospital or were discharged with hospice care) were similar in their admission laboratory results, baseline neurohormonal therapy, and prevalence of comorbid conditions. Systolic blood pressure was lower among those discharged with home inotrope therapy on hospice or who died before admission (100 mm Hg) compared with those who were discharged alive and off IIT (110 mm Hg; P=.001).

Data regarding IIT initiation and treatment are displayed in Table 2. Milrinone (46%; n=42) and dobutamine (43%; n=40) were used in approximately equal proportions, with only 11% (n=10) of patients initiated on dopamine treatment. New arrhythmias occurred in 33% (n=30) of all patients while on IIT, 63% (n=58) ultimately were treated in an intensive care unit, and the average ± SD duration of inpatient inotrope therapy was 11±12 days. There were no statistical differences detected in any of these parameters based on the patient's ultimate outcome.

The assessments of the attending HF cardiologist survey at inotrope intiation and discharge/death are presented in Table 3. Fifty percent (n=46) of patients were thought to have a "high" or "very high" likelihood of long-term IIT dependence. Fifty-eight percent (n=53) of patients were thought to have a "high" likelihood of death/VAD/cardiac transplant within the next 6 months. Interestingly, neither of these varied significantly by the patient's ultimate outcome. Despite the prediction of poor outcomes, only 51% of patients (n=47) had a "goals-of-care" conversation before IIT initiation, with no significant variance by ultimate outcome. A total of 53% of patients (n=49) underwent formal advanced therapy evaluation during the index admission and 29% (n=27) went on to receive a VAD during the index admission, 10% (n=9) were listed for transplant, and 3% (n=3) underwent cardiac transplant during the index admission. Palliative care was involved in the care of only 61% of patients (56 of 92) initiated on inotrope treatment, but they were involved in the care of 87% (21 of 24) of those who ultimately died or were discharged with hospice care.

The Figure demonstrates physicians' predictions regarding patient outcomes at the time of IIT initiation in comparison to the actual outcomes of patients. To determine whether physicians' predictions regarding outcomes at the time of IIT initiation were associated with patient outcomes, we performed multivariable regression (Table 4). We found that a provider's prediction of a poor prognosis at the time of IIT initiation was not significantly associated with poor outcomes for that patient. To further quantify the "added value" of the attending providers' prediction, a multivariable outcome model with and without the attending providers' prediction was created. The addition of the attending providers' prediction increased the R^2 of the model by only 0.5% (from 32.2% to 32.7%), suggesting that the explanatory power gained by adding the attending providers' clinical prediction to the other clinical variables in the model is minimal.

DISCUSSION

The goal of this multicenter prospective observational study was to describe the relationship

TABLE 1. Patient Characteristics at Admission[a,b]					
	All (N=92)	Alive Off Inotropes (n=49)	Home Inotropes[c] (n=27)	Death or Hospice[c] (n=24)	P
Demographic characteristic					
Age (y), mean ± SD	60±12	59±13	61±11	62±11	
Male sex, %	67	59	70	71	.123
HF cause, %					
Ischemic HF	33	33	30	46	.821
Nonischemic HF	67	67	70	54	
Comorbid condition, %					
Coronary artery disease	34	35	30	46	.984
Hypertension	62	67	56	54	.361
Diabetes	43	51	30	38	.119
Chronic kidney disease	50	53	44	46	.531
Atrial fibrillation/flutter	58	57	59	63	0.747
History of ventricular tachycardia	29	24	33	29	0.391
Implantable cardioverter defibrillator in place	58	59	56	54	0.744
Echocardiography parameter					
Left ventricular ejection fraction (%), median (IQR)	20 (15-28)	20 (15-28)	20 (15-25)	25 (16-33)	.688
Left ventricular end-diastolic diameter (mm)	61 (50-70)	59 (50-66)	63 (48-71)	60 (46-72)	.653
Moderate/severe right ventricle dysfunction, %	62	67	63	63	0.361
Admission medications[d]					
Admission β-blocker, %	75	73	85	70	.766
Average dose (mg/d), median (IQR)	38 (25-100)	44 (25-50)	25 (19-125)	50 (25-00)	.084
Admission ACEi/ARB/ARNI, %	38	35	48	29	.480
Average dose (mg/d), median (IQR)	5 (5-10)	6.5 (2.5-10)	6.5 (5-40)	5 (2.5-10)	.051
Admission mineralocorticoid receptor antagonist, %	52	53	59	38	.686
Average dose (mg/d), median (IQR)	25 (25-25)	25 (25-25)	25 (25-25)	25 (13-25)	.842
Admission loop diuretic use, %	84	78	100	83	.089
Average dose (mg/d), median (IQR)	80 (40-120)	80 (40-120)	80 (40-120)	80 (40-120)	.471
Admission examination data					
Systolic blood pressure (mm Hg), mean ± SD	105±16	110±17	98±14	103±12	.001[e]
Heart rate (beats/min), mean ± SD	89±23	90±25	91±22	88±19	.948
Weight (kg), mean ± SD	87±21	88±22	82±18	87±21	.618
Admission laboratory data					
Sodium (mg/dL), median (IQR)	137 (134-139)	137 (135-140)	137 (134-139)	135 (134-139)	.385
Creatinine (mg/dL), median (IQR)	1.5 (1.2-2.2)	1.5 (1.2-2.1)	1.3 (1.21-2.2)	1.7 (1.3-2.5)	.452
Serum urea nitrogen (mg/dL), median (IQR)	35 (24-54)	34 (23-52)	27 (24-45)	42 (27-57)	.446
NT-proBNP (pg/mL), mean ± SD	9336±8417	8267±8012	10,558±9587	11,125±8330	.200

[a]ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; HF = heart failure; IQR = interquartile range.

[b]SI conversion factors: To convert sodium values to mmol/L, multiply by 1.0; to convert creatinine values to μmol/L, multiply by 88.4; to convert serum urea nitrogen values to mmol/L, multiply by 0.357; to convert NT-proBNP values to pmol/L, multiply by 0.118;

[c]Eight patients were discharged home with hospice care and palliative inotrope therapy.

[d]Medication dosing equivalents were used, with β-blocker dosing converted to daily metoprolol succinate equivalent; ACEi, ARB, and ARNI converted to daily lisinopril equivalent; mineralocorticoid receptor antagonist converted to daily spironolactone equivalent; and loop diuretic converted to daily furosemide equivalent.

[e]Statistically significant.

between anticipated and actual outcomes of hemodynamically stable patients initiated on IIT to augment diuresis. In this study of 92 patients across 6 academic medical centers, we found that 29% of patients (n=27) ultimately required home IIT and 26% of patients (n=24) either died or were discharged with hospice care. Only 53% of patients (n=49) were discharged alive and without inotropes. Moreover, the attending providers' predicted

TABLE 2. Clinical Characteristics at Inotrope Initiation and During Inotrope Therapy[a]

	All (N=92)	Alive Off Inotropes (n=49)	Home Inotropes[b] (n=27)	Death or Hospice[b] (n=24)	P[c]
Inotrope choice					
Milrinone, %	46	51	30	54	.463
Dobutamine, %	43	41	59	25	
Dopamine, %	11	8	11	21	
Concurrent drug use					
β-Blockers, %	7	6	4	8	.865
ACEi/ARB/ARNI, %	8	10	4	4	.316
Mineralocorticoid receptor antagonist, %	25	31	26	8	.184
Loop diuretic, %	86	88	85	79	.579
Pulmonary artery catheter use					
Right heart catheterization before inotrope start, %	63	67	85	38	.361
Pulmonary artery catheter—guided therapies, %	79	82	81	63	.563
Outcomes					
Arrhythmia (new or worsening), %	33	35	33	42	.802
Intensive care unit admission/transfer, %	63	69	56	46	.178
Days on inotrope (inpatient), mean ± SD	11±12	11±11	12±12	11±11	.906

[a]ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor.
[b]Eight patients were discharged home with hospice care and palliative inotropes.
[c]Comparing those discharged alive off inotrope therapy with the 2 other groups (home inotropes plus death or hospice).

outcomes were not significantly associated with patients' actual outcomes. Despite the high rate of poor outcomes and limited ability of clinical characteristics and attending providers to predict the patients most likely to have poor outcomes, only 51% of patients (n=47) had conversations about their goals of care documented before inotrope treatment initiation. Considering that inotrope use is becoming a more frequent adjunct to medical therapy in patients with decompensated HF, it is important to understand its prognostic significance, particularly in a "healthier" population. Providers should understand the potential downstream effect of such medications and consider the difficulty predicting clinical outcomes at the time of initiation. Although inotropes have benefit in select patients, it is important to realize the uncertainty that may result.

Providers estimated that approximately 50% of patients (n=46) would require home IIT or experience death/VAD/transplant within the next 6 months. Although the clinicians were accurate at predicting the rate of adverse outcomes, they were not able to discriminate which patients were more or less likely to have them. Provider expectations were not associated with actual patient outcomes. However, multivariable modeling explained only 32% of the variability in outcomes between patients. This suggests that there is a tremendous amount of variability in outcomes between hemodynamically stable patients initiated on IIT that is not explained by traditional clinical risk factors or attending providers' expectations. This presents significant challenges for case management and care coordination teams seeking to identify and help the patients most likely to experience poor outcomes and may be one reason that such programs have often not proved successful or financially viable in the past.

Despite clinical trials indicating no benefit or even increased risk with inotrope use in patients with HF, inpatient initiation of inotrope therapy remains high. Analysis of Get With the Guidelines—Heart Failure found a stable rate of inotrope use from 2007 to 2011 of approximately 6.1%, with marked variation between centers.[12] A 2007 study by Elkayam et al[13] that reviewed 433 patients from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) found that inpatient inotrope use was the strongest predictor of mortality

TABLE 3. Attending Physician Survey at Inotrope Initiation and Discharge[a]

	All (N=92)	Alive Off Inotropes (n=49)	Home Inotropes[b] (n=27)	Death or Hospice[b] (n=24)	Pc[c]
Inotrope Initiation Survey					
Anticipated outcomes					
High/very high likelihood of inotrope dependence, %	50	49	48	54	.835
Expected duration of inotrope therapy (d), mean ± SD	7±5	6±5	6±2	8±7	.694
Sick enough for advanced therapy evaluation now, %	77	71	85	79	.161
High likelihood of death/VAD/transplant within 6 mo, %	58	57	59	58	.923
Advanced care planning at time of inotrope initiation					
Goals-of-care conversation before inotrope start, %	51	47	59	46	.396
Hospitalization disposition					
Advanced therapy outcomes					
Formal advanced therapy evaluation done during admission, %	53	51	63	48	.722
Received VAD during same admission, %	29	39	15	25	.034
Listed for transplant during same admission, %	10	16	4	0	.024
Underwent transplant during same admission, %	3	2	0	8	.482
Advanced care planning during hospitalization					
Palliative care consultation/involved during hospitalization, %	61	46	78	87	.002

[a]VAD = ventricular assist device.
[b]Eight patients were discharged home with hospice care and palliative inotrope therapy.
[c]Comparing those discharged alive off inotropes with the 2 other groups (home inotropes plus death or hospice).

or rehospitalization, with a hazard ratio of 1.96 (95% CI, 1.37 to 2.82; $P<.001$). Another reanalysis of ESCAPE by Kalogeropoulos et al[6] found that inotrope use was associated with a higher rate of major events regardless of HF cause or systolic blood pressure.
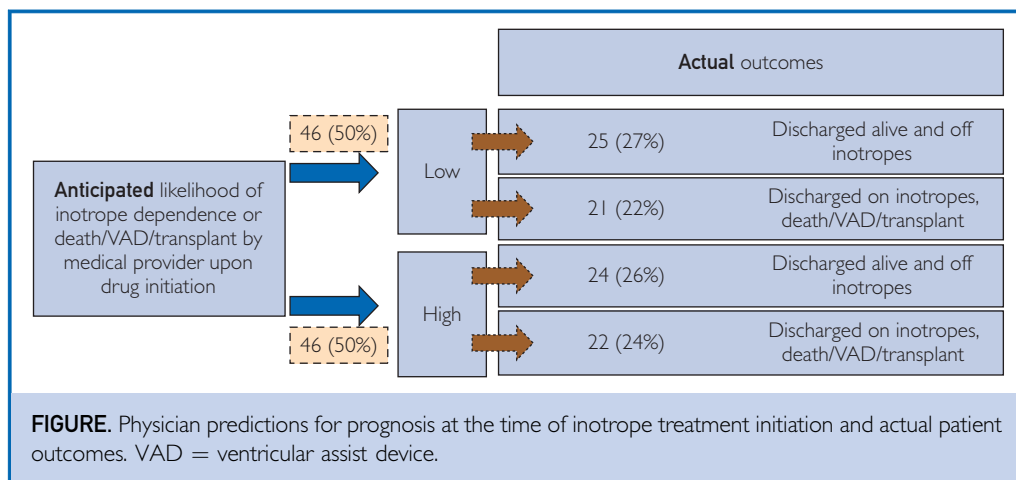
Notably, ESCAPE was not limited to hemodynamically stable patients, as this study is. However, in the almost 15 years since ESCAPE, the hospitalized HF population has evolved and we found that despite limiting our study to hemodynamically stable patients, the rates of adverse events were similarly high. Moreover, as seen in ESCAPE, systolic blood pressure was associated with patient outcomes. When we explored the variable further, we found that a threshold of 100 mm Hg was most predictive of patient outcomes, suggesting that patients with a "normal HF blood pressure" of 80 to 100 mm Hg may be at increased risk for adverse events if started on IIT, even if this occurs in the setting of hemodynamic stability to augment diuresis.

The present study also examined various clinical factors at the time of inotrope treatment initiation and found that they were not strongly associated with patient outcomes. Although 33% of patients (30 of 92) experienced a new

or worsening arrhythmia with the initiation of IIT, there was no difference in the frequency of arrhythmias across the various outcomes.

Furthermore, as compared with earlier studies but similar to additional recent work, we found low rates of guideline-directed therapies. Less than half (n=35) the patients were on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor therapy, about half (n=48) were on mineralocorticoid receptor antagonist therapies, and three-fourths (n=69) were on β-blockade at admission, before any inotrope treatment initiation. This is likely reflective of an overall higher-risk population yet confirms recent data from the Heart Failure Apprentice Network research group demonstrating that guideline-directed therapies are unfortunately not often optimized in many patients with HF and emphasizes the need to perhaps push the "guideline-directed medical therapy envelope" a bit farther in this new sicker hospitalized HF population.[1]

Finally, we contend that these findings have significant implications for advanced care planning. The high rate of poor outcomes coupled with the limited ability of clinical variables and attending physicians to predict

FIGURE. Physician predictions for prognosis at the time of inotrope treatment initiation and actual patient outcomes. VAD = ventricular assist device.

patients most at risk underscores the need for goals of care to be defined explicitly before any inotrope therapy, even when initiated in hemodynamically stable patients. In addition to recognition of the potential for in-hospital death or discharge with hospice, consideration needs to be made regarding the difficulty of discontinuation of IIT during transition to hospice. In this study of 6 academic medical centers, despite house staff/resident teams and robust ancillary staff support, only 51% of patients (n=47) had goals of care discussed before inotrope initiation. This highlights an area with tremendous potential for quality and clinical improvement. Considering that goals of care tend to change during critical periods within a hospitalization, continued advanced care planning throughout the entirety of a hospital admission is warranted among this population.[14]

Although this study is limited primarily by its small sample size, it provides important new information about the serious implications of IIT even when started "electively" or to "augment diuresis" in hemodynamically stable patients. It prospectively combines patients from 6 different academic medical centers that are geographically spread across the United States, reflecting many different practice styles and institutional practices. However, the small sample size limits our ability to perform subgroup analyses. In addition, the attending HF cardiologists' expectation may have been limited by inadequate time to consider all data relevant to prognosis. It is also important to note that because the study was performed at 6 centers, some attending HF cardiologists may have contributed to questionnaires for more than 1 patient in the study. However, these constraints reflect real-world practices in which decisions may be even more limited in the absence of the heightened awareness associated with a research study. In the context of relatively frequent use of inotropes in patients with decompensated HF, our study sheds light to the prognostic significance of its use, highlights provider inability to accurately predict outcomes, and ultimately supports the need for a pragmatic clinical trial to better understand these relationships.

TABLE 4. Association Between Provider Prediction of Poor Outcome and Patients' Rates of Poor Outcomes (death/hospice)[a]

	Odds Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	P
Anticipated high likelihood of inotrope dependence	1.80	0.21	15.61	.595
Anticipated high likelihood of death/ventricular assist device/transplant in the next 6 mo	1.21	0.10	14.33	.878

[a]Model is adjusted for age, sex, cause of heart failure, history of ventricular tachycardia, admission systolic blood pressure, admission creatinine level, inotrope choice, arrhythmias on inotrope therapy, and days on inotrope therapy.

CONCLUSION

Hemodynamically stable patients with HF initiated electively on IIT to augment diuresis during hospitalization are at high risk for adverse outcomes. Only 53% of patients (n=49) were discharged alive and without hospice or IIT at home. The high rate of poor outcomes coupled with the limited ability of clinical data and attending providers to identify the highest risk patients underscores the importance of proactive advanced care planning. In this study, only 51% of patients (n=47) had a goals-of-care conversation before the initiation of inotrope treatment, highlighting a significant opportunity for quality and clinical improvement.

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