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Ambulatory Inotrope Infusions in Advanced Heart Failure: A Systematic Review and Meta-Analysis

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Abstract

Background—Ambulatory inotrope infusions are sometimes offered to patients with advanced stage D heart failure (HF); however, an understanding of the relative risks and benefits is lacking.

Objective—To systematically review the available evidence on the risks and benefits of ambulatory intravenous inotropes in advanced HF.

Methods—On August 7, 2016, we searched SCOPUS, Web of Science, Ovid EMBASE, and Ovid MEDLINE for studies of long-term use of intravenous inotropes in outpatients with advanced HF. Meta-analysis was performed using random effects models.

Results—A total of 66 studies (13 randomized controlled trials [RCTs] and 53 observational studies) met inclusion criteria. Most studies were small and at high risk for bias. The pooled rates of death (41 studies), all-cause hospitalization (15 studies), central line infection (13 studies), and implantable cardioverter defibrillator shocks (3 studies) on inotropes were 4.2, 22.2, 3.6, and 2.4 per 100 person-months follow-up, respectively. Improvement in New York Heart Association (NYHA) functional class was greater in patients on inotropes compared to controls (mean difference 0.6 NYHA classes, 95% CI 0.2–1.0, $P=.001$; 5 trials). There was no significant difference in mortality on inotropes compared with controls (pooled RR 0.68 CI 0.40–1.17, $P=.16$; 9 trials). Data were too limited to pool for other outcomes or to stratify by indication (bridge to transplant, palliative).

Conclusions—High-quality evidence about the risks and benefits of ambulatory inotrope infusions in advanced HF is limited, particularly when used for palliation. Available data suggest that inotropes improve NYHA functional class and do not impact survival.

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Disclosures: None

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Keywords

transplant; palliative; death; hospitalization; risk

INTRODUCTION

An estimated 6.5 million adult Americans are living with heart failure (HF), and the prevalence is expected to increase. A fraction of those have advanced (stage D) HF characterized by symptoms that limit daily life and are refractory to usual recommended therapies.(1) Patients with advanced HF are sometimes offered ambulatory intravenous inotropic support either while awaiting cardiac transplantation (a class IIa recommendation(1)), or as an advanced palliative therapy (a class IIb recommendation(1)). Use of ambulatory inotropes increased markedly from 2010–2014 in Medicare beneficiaries. (2) However, in the 2013 American College of Cardiology Foundation/ American Heart Association HF guidelines, both recommendations were acknowledged to be based upon limited evidence (level of evidence B).(1)

An understanding of the risks and benefits associated with use of outpatient inotropes is vital to the patient's ability to make an informed decision, the clinician's confidence in making a recommendation, and the payer's willingness to cover the costs of their use. While initially touted as an exciting therapy that would restore normal cardiac hemodynamics and alleviate symptoms,(3) concerns were raised when studies demonstrated a higher incidence of ventricular arrhythmias and sudden death with inotropes.(4,5) Contemporary comprehensive reviews of relative risks and benefits of chronic ambulatory inotrope infusions are lacking. Within this setting, intravenous inotrope use is variable across clinicians, centers, and regions.(6)

To address these gaps in knowledge, we sought to systematically review the available evidence on the risks and benefits of ambulatory intravenous inotropes in patients with advanced HF.

METHODS

This systematic review was conducted using PRISMA guidelines.

Search strategy

On August 7, 2016, we searched SCOPUS, Web of Science, Ovid EMBASE and Ovid MEDLINE for articles containing the terms “inotrope”, “heart failure”, synonyms of “advanced” (end stage, stage D, refractory, class IV, terminal), “palliative” (home, end of life, hospice), and “heart transplantation”. The full search strategy is in the Supplementary Methods. We also manually scanned reference lists to identify additional articles.

Eligibility Criteria and Study Selection

We included randomized controlled trials (RCTs), observational studies, and case series on adult human subjects with advanced HF. We included studies published in all years. We

required studies to have at least one arm that included patients treated with long-term intravenous inotrope infusions (milrinone, dobutamine, dopamine, or levosimendan) as outpatients. Long-term use was defined as either indefinite (palliative) therapy or as bridge to heart transplantation (BTT). If inotrope administration was part of a study protocol, the intended treatment duration had to be at least 4 weeks. Inotrope infusions could be administered either continuously or intermittently. We included studies in which intermittent inotropes were administered in a monitored setting (such as a clinic) if patients were outpatient between infusions. We excluded studies of inotropes in patients hospitalized with acute decompensated HF. We restricted to studies that reported primary data for at least one of our outcomes of interest. We excluded single case reports, non-English language articles, reviews, editorials, meeting abstracts, and studies of oral inotropes. Two study team members (TN, SMD) independently reviewed all titles and abstracts identified by the search strategy. Abstracts that potentially met study criteria were identified and the full-text articles were reviewed in duplicate to determine the final included studies.

Study Outcomes

Outcomes included death, location of death, hospitalization (all-cause and HF-related), health-related quality of life (HRQOL), functional status (New York Heart Association [NYHA] functional class, 6 minute walk test [6MWT] distance), ventricular arrhythmias (sudden death, sustained ventricular arrhythmias, non-sustained ventricular tachycardia [NSVT], implantable cardioverter defibrillator [ICD] shocks), central line complications (infection, deep venous thrombosis), cost and hospice enrollment. We were intentionally broad in inclusion of outcomes to capture all studies that provide relevant insight to stakeholders. Study data were abstracted by TN and manually verified by SMD. In ancillary analyses, we examined reported changes in cardiac structure/ function and hemodynamics on inotropes among included studies.

Risk of Bias Assessment

The risk of bias was assessed for studies with a non-inotrope control group. We used the Cochrane risk of bias tool for randomized trials (Online ref. 1) and the ROBINS-I tool in non-randomized studies of interventions.(Online ref. 2) These domain-based assessments consider different types of bias in studies that are important in interpreting results (See Supplementary Methods for additional details).

Statistical Analysis

For binary outcomes, event rates are reported as the number of events per 100 person-months follow-up with 95% confidence intervals (CI) derived from the Poisson distribution. Meta-analysis of event rates was performed using the random effects model as described by DerSimonian and Laird.(7) The risk of death in patients treated with inotropes vs. controls in RCTs was pooled using a random effects model, with results presented as risk ratio (RR) with 95% CI. For continuous outcomes, random effects models were used to compare 1) difference in NYHA functional class on inotropes compared with baseline, and 2) difference in NYHA functional class in patients treated with inotropes compared with controls in RCTs. Results are presented as mean difference and 95% CI. Mortality and NYHA functional class were the only outcomes with sufficient RCT data to enable pooled

comparisons of patients treated with inotropes and controls. We used the I^2 statistic to assess heterogeneity.(8) Stratified analyses were performed to explore heterogeneity by 1) inotrope indication (palliative vs. BTT), 2) method of inotrope delivery (intermittent vs. continuous), and 3) study design (RCT vs. observational). Analysis was performed using Stata 13.0 (College Station, Texas) and Review Manager 5.1 (RevMan 5.3®, Nordic Cochrane Center and Copenhagen, Denmark).

RESULTS

The search strategy identified 955 abstracts, of which 63 met inclusion criteria. An additional three articles were identified by reviewing reference lists. This resulted in 66 articles including 13 RCTs, four non-randomized controlled trials, and 49 observational studies (Figure 1, Table 1 and Online Tables 1 and 2). Most studies were small (median 34.5, range 2 to 471 patients per study). The most common inotrope used was dobutamine (74.2% of studies). Inotropes were more often administered intermittently than continuously (50.0% vs. 31.8%).

Risk of Bias

Of 13 RCTs, only one was at low risk for bias, three had unclear risk, and nine had high risk for bias (Online Table 3). Of 15 studies that compared patients on inotropes to a control population, most were at critical (seven studies) or serious (six studies) risk of bias (Online Table 4).

Death

Fifty-eight studies reported on the occurrence of death in patients treated with inotropes; the rate of death per month of follow-up could be calculated for 41 studies (Online Figure 1). The rate of death ranged from 0 to 44.4 with a pooled rate of 4.2 (95% CI 3.2–5.5) deaths per 100 person-months on inotropes. Rates of death were not statistically different in studies of inotropes as palliative therapy (10.5 per 100 person-months, 95% CI 4.8–22.8; 4 studies), compared with BTT (5.0 per 100 person-months, 95% CI 2.7–9.1; 7 studies, P value for interaction=.41). Rates of death were similar in studies administering inotropes as continuous (4.2 per 100 person-months; 95% CI 2.6–6.9; 14 studies) or intermittent (3.3 per 100 person-months; 95% CI 2.0–5.4; 22 studies; P =.75) infusions. Rates of death were similar in trials (2.9 per 100 person-months, 95% CI 1.4–6.1) and observational studies (4.9 per 100 person-months; 95% CI 3.7–6.6, P =.57).

Nine RCTs including 434 patients compared mortality in patients treated with inotropes to a non-inotrope control population (four to placebo infusions,(9–12) two to other infusions, (13,14) and three to usual care(15–17)). Only one RCT reported a significantly lower risk of death in patients randomized to dobutamine plus amiodarone compared with placebo.(11) In pooled analysis, there was no difference in mortality over a median 5.3 months of follow-up (RR inotrope vs. control 0.68, 95% CI 0.40–1.17, P =.16, Figure 2). Results were similar in placebo-controlled studies (RR 0.56, 95% CI 0.25–1.24, P =.15). A funnel plot revealed no asymmetry to suggest publication bias (Online Figure 2).

Location of Death

Five observational studies reported on location of death in patients treated with inotropes: two studies used inotropes as palliative therapy,(18,19) two as BTT,(20,21) and one included patients with both indications.(22) The proportion of deaths at home (vs. hospital) ranged from 7.1%(22) to 64.5%(19), with the highest proportions in the studies of inotropes as palliative therapy.(18,19)

Hospitalization

In 15 studies, the rate of all-cause hospitalization per 100 person-months of follow-up ranged from 9.6 to 55.1, with a pooled rate of 22.2 (95% CI 18.0–27.4, Figure 3). Similarly, in 15 studies the rate of HF hospitalizations ranged from 0 to 41.7, with a pooled rate of 10.1 HF hospitalizations per 100 person-months (95% CI 7.3–13.9, Online Figure 3). There were no differences in rates of all-cause or HF hospitalization by delivery method, indication, or study design (*P* values for interactions >0.10).

There were insufficient data to compare the risk of hospitalization in patients treated with inotropes vs. controls. Eleven studies compared hospitalizations before and after inotrope initiation in the same population.(21–24, online refs. 23, 33–35, 39, 44, 68) While all 11 studies reported a decline in hospitalizations or days hospitalized on inotropes, most did not account for differential follow-up due to death on inotropes. A single study of outpatient inotropes in Medicare beneficiaries accounted for follow-up and observed a decline in average number of days hospitalized per beneficiary from 13.3 in the month prior to milrinone to 4.4, 4.0, and 2.3 days per month in the 30, 60, and 180 days, respectively, after milrinone initiation.(24)

Only three studies of intermittent inotropes including 99 patients compared all-cause hospitalizations on inotropes with a non-inotrope control population.(10,17,25) Repasos reported a higher rate of 6-month hospitalization in patients treated with inotropes vs. renal replacement therapy (mean 1.9 vs. 0.5 per person, respectively, *P*=.001).(25) Elis found no difference in 6-month HF hospitalizations in 19 patients randomized to dobutamine vs. placebo (mean 2.2 vs. 2.1 per person, respectively, *P*=.11).(10) The final study reported 11 total hospitalizations in 6 months in patients on dobutamine compared with 17 in controls. (17)

Functional Status and Quality of Life

In total, 30 studies presented NYHA functional class before and during use of inotropes, of which 24 included sufficient information to pool data. Of 485 unique patients with NYHA functional class assessed pre-inotropes, 424 (87%) survived to have NYHA functional class reassessed. Prior to inotropes, all patients were NYHA functional class III or IV. Participants experienced a mean improvement in NYHA class of 1.2 (95% CI 1.0–1.4, *P*<.001, Figure 4A) on inotropes. While all studies demonstrated an improvement in NYHA functional class on inotropes, heterogeneity was high (*I*²=89%). NYHA functional class improved in studies(23,26,27) that treated patients with inotropes as palliative therapy (mean –1.1 class, 95% CI 0.8, 1.3, *I*²=0%) and as BTT (mean –1.3 classes, 95% CI 1.2–1.4, *I*²=0%) (21,28,29).

Just five RCTs compared NYHA functional class while on intermittent inotropes to a control population (two studies vs. placebo infusions(11,12), one vs. prostaglandin E1 infusion(13), one vs. furosemide infusion(30), one vs. usual care(15)). Participants treated with intermittent inotrope infusions had lower NYHA functional class (mean difference 0.6 classes, 95% CI 0.2–1.0, $P=.001$, Figure 4B).

Only four studies reported 6MWT distance in patients on inotropes (Online Table 5). Two of three studies(9, online refs. 12, 36) that compared 6MWT distance on inotropes with baseline reported an improvement on inotropes. Two studies measured 6MWT distance in patients treated with inotropes vs. placebo. In one,(9) 6MWT distance improved in patients treated with both levosimendan and placebo and the difference was not significant. The other reported a 23% improvement on inotropes compared to a 1% decline on placebo ($P<.001$). (31)

Six studies reported results of HRQOL assessments in patients treated with inotropes (Online Table 6). All four studies that compared HRQOL before and after inotrope initiation reported improvement on inotropes.(9,32, online refs. 12, 36) However, the only study that compared improvement in HRQOL in patients treated with inotropes vs. placebo found no difference.(9)

Ventricular Arrhythmias

A total of 41 studies reported the frequency of ventricular arrhythmias or sudden death in patients on inotropes (Online Table 7). Many studies were published prior to widespread use of ICDs and capture of ventricular arrhythmias using other methods varied. In four contemporary reports of continuous inotrope infusions,(21,32–34) the incidence of ICD shocks was similar, ranging from 2.2 to 3.0 per 100 person-months of follow-up with a pooled incidence of 2.4 (95% CI 2.1–2.8). While 20 studies reported on sudden death, events were rare (0–6 events per study), and given the variability in ICD use across studies, results were not pooled. Eight studies compared ventricular arrhythmias in patients treated with inotropes vs. controls. Mavrogeni et al(16) found no difference in the mean number of NSVT episodes captured on Holter monitor in individuals treated with intermittent levosimendan vs. controls (12 vs. 13, respectively, $P=.19$). Event rates were otherwise too small to draw meaningful conclusions.

Few studies provided insight as to whether amiodarone abrogates the arrhythmogenicity of inotropes. Nanas et al first compared 11 consecutive patients treated with intermittent dobutamine infusions (as needed) without amiodarone to 11 subsequent patients treated with weekly dobutamine plus amiodarone 400mg/day.(35) One-year survival in those receiving amiodarone was 55% compared with 9% in those not on amiodarone ($p=0.011$). This same group later randomized 30 patients to intermittent dobutamine or placebo infusions; all patients received amiodarone 400–800mg/day.(11) They reported higher 1-year (69% vs. 28%, $p=0.019$) and 2-year (44% vs. 21%, $p=0.041$) survival in patients receiving dobutamine, suggesting that intermittent dobutamine infusions may improve survival when accompanied by amiodarone. Finally, Tsagalou et al assessed ventricular ectopy using 24-hour ECG recordings the day prior to and the day of intermittent dobutamine infusions in 30 patients taking amiodarone 400mg/day.(36) There were no significant differences in mean

ventricular ectopic beats in the total population, though dobutamine was pro-arrhythmic in four patients. These small studies suggest that amiodarone may provide some protection against potential pro-arrhythmic effects of intermittent dobutamine infusions.

Central Line Complications

A total of 26 studies reported the frequency of central line complications in patients treated with inotropes (Online Table 8). Among the 13 studies that provided enough information to pool data and excluding overlapping patient populations, the rate of central line infection varied from 0 to 9.8 per 100 person-months of follow-up, with a cumulative rate of 3.6 per 100 person-months (95% CI 2.4–5.4). Haglund et al observed 9.8 infections per 100 person-months in 129 patients awaiting transplant at a single center.(37) In four studies the incidence of catheter-related thrombosis ranged from 0 to 5.7 per 100 person-months follow-up.(21,37, online refs. 7, 41)

Cost

Nine studies compared the costs of outpatient inotrope infusion to a control population (Online Table 9). Five studies found an outpatient strategy to be cost-saving compared with ongoing hospital-based care in patients awaiting heart transplantation.(28,29,32, online refs 13, 66) The other four studies compared costs on inotropes to a pre-inotrope period in the same patients. The study by Hauptman et al(24) was the only study to account for the costs of outpatient inotrope infusions, and reported cost savings in patients who died within 180 days, attributable primarily to decreased hospitalizations. There were no studies comparing costs associated with outpatient inotropes vs. hospice care in patients who were not candidates for heart transplant.

Hospice Enrollment

Only one study reported on the proportion of patients receiving inotropes who were enrolled in hospice.(38) Of 19 decedents, only seven were said to have “required” hospice or palliative care treatment prior to death, though it is unclear what criteria were used to determine who would benefit from these services.

Ancillary Analyses

A total of 17 studies reported hemodynamics at baseline and on inotropes (Online Table 10). Most studies reported that patients’ cardiac indices were higher and pulmonary capillary wedge pressures lower on inotropes. A total of 17 studies reported echocardiographic findings both pre-inotrope and after initiation of inotropes (Online Table 11). Several studies reported significant improvements in ejection fraction and left ventricular size on inotropes compared with baseline.

DISCUSSION

There were several important findings from this systematic review. First, the quality of data assessing the risks and benefits of ambulatory intravenous inotropes—even among RCTs—is limited, which warrants careful consideration when interpreting results. Second, most studies are small and thus estimates are plagued by wide confidence intervals. Third, data on

inotropes as palliative therapy are particularly lacking which limits our ability to summarize comparative risks and benefits in the majority of patients with advanced HF who are not eligible for mechanical circulatory support or transplant. However, based upon available evidence, inotrope infusions appear to improve NYHA functional class. Limited evidence suggests they do not increase the risk of death. While hospitalizations and ventricular arrhythmias are common, there is insufficient evidence to conclude if inotropes affect the risk of these events. Finally, outpatient inotrope infusions are relatively expensive, and while they appear to be cost-saving compared with ongoing hospitalization in a BTT population, it is unclear whether they are cost-effective as palliative therapy.

Most studies on outpatient inotrope infusions were observational and many reported the experience of patients treated with inotropes without a comparison group. Even among studies with a comparison group, the most common design employed was pre/post. This becomes problematic for outcomes such as HRQOL, which tends to improve following a HF hospitalization regardless of therapy. The influence of death on other outcomes, such as hospitalization, was inadequately accounted for in many studies where the number of survivors on inotropes dwindled over time but was overlooked as a potential reason why fewer hospitalizations occurred. The assessment of non-fatal outcomes such as hospitalizations, NYHA functional class, and HRQOL can be problematic in a population with such a high rate of death. The sickest individuals are not represented in follow-up and can contribute to survivor bias.

The only outcome in which there was consistent evidence favoring inotropes was improvement in NYHA functional class. However, while five RCTs compared NYHA functional class on inotropes to a control population,(11–13,15,30) all of them administered inotropes as intermittent infusions. Similarly, nine RCTs compared risks of death on inotropes to a control population but only one administered inotropes as continuous infusions and it only included BTT patients.(14) The overall paucity of data in patients on continuous infusions and in those using inotropes as palliative therapy, leave us to extrapolate observed results to these populations commonly encountered in contemporary practice. Furthermore, response to inotropes may differ by various patient factors, such as etiology of HF and ejection fraction. Studies are needed to identify patient phenotypes that may respond best to inotrope infusions.

Additionally, the indication for inotropes (palliation or BTT) is important in decision-making. Mechanical circulatory support with a left ventricular assist device (LVAD) is used in over half of patients awaiting transplant, but for those who are not candidates for LVAD, inotropes may be the only strategy offered to maintain clinical stability and increase the likelihood of receiving a transplant. As such, BTT patients may weigh benefits and risks of alternative strategies differently than other patient populations.

Advanced HF clinicians that offer inotropes as palliation often explain their goal is to “improve symptoms but not survival.” Overall, our findings do not refute this notion, as NYHA functional class improved and there was no significant impact on mortality. As most studies were performed at a time when ICD use was rare; it is unclear if association of inotropes with risk of death would be more favorable with ICD use. However, the estimates

lacked precision as studies were small. Most studies were not limited to patients receiving inotropes as palliation, which impairs our ability to apply these data to that population. Furthermore, patients considering inotropes as palliation have important options to consider including ongoing medical therapy with or without enrollment in hospice. There are no data comparing the risks and benefits of palliative inotropes with hospice. While some hospice agencies will consider enrolling patients on palliative inotropes,(39) the cost of inotropes is often prohibitive due to the capitated, per diem reimbursement model of hospice.(24,40) As such, inotropes can serve as a direct barrier to hospice enrollment. Furthermore, patient and clinician perceptions of inotropes may be clouded by infusion therapy company advertisements, which sometimes overstate the benefits of inotropes while rarely mentioning potential harms. The results of this review highlight the need for studies comparing the risks and benefits of palliative inotropes with alternative strategies in patients with advanced HF ineligible for LVAD or transplant.

We did not include studies of inotropes administered in patients hospitalized with acute decompensated HF. However, a recent trial of hospitalized patients found that levosimendan provided symptomatic relief but also increased the risk of hypotension and cardiac arrhythmias.(41) Finally, while we excluded studies of oral inotropes as their use is not recommended,(1) a large RCT found an increased risk of death and hospitalization in patients treated with outpatient oral milrinone.(5)

We are forced to practice and make decisions using the data that we have. There are no large RCTs that delineate the risks and benefits of outpatient intravenous inotropes compared with alternative options. As such, a detailed review such as this provides information that can be tremendously helpful to clinicians, patients, and payers faced with making challenging decisions. Overall, available data suggest that patients treated with inotropes, on average, experience an improvement of one NYHA functional class regardless of indication (BTT or palliative). In addition, infection is a known complication of the need for a central line for inotrope delivery and available studies provide estimates of that risk. Finally, knowledge of the average observed rate of outcomes on inotropes may be beneficial in counseling patients considering inotropes on what to expect (Figure 5, Table 2). It is important to acknowledge that heterogeneity of pooled estimates was high for most outcomes, and users should view these rates as average across diverse settings.

CONCLUSIONS

Studies published fail to provide adequate information comparing the risks and benefits of ambulatory intravenous inotropes in populations encountered in contemporary clinical practice. The findings of this review should serve as a call for RCTs or well-designed observational studies of continuous inotrope infusions as palliation compared with other strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATION LIST

BTT	bridge to transplant
CI	confidence interval
HF	heart failure
HRQOL	health-related quality of life
ICD	implantable cardioverter defibrillator
NSVT	non-sustained ventricular tachycardia
NYHA	New York Heart Association
RCT	randomized controlled trial
RR	risk ratio
6MWT	6-minute walk test

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CLINICAL PERSPECTIVES

Competency in Medical Knowledge 1

It is important for clinicians to understand the risks and benefits of outpatient inotropes when offering them to patients with advanced HF. Inotrope infusions improve NYHA functional class, but their impact on HRQOL, and risks of hospitalization and ventricular arrhythmia are unclear.

Competency in Interpersonal and Communication Skills

This review provides a summary of the available evidence on the risks and benefits of outpatient inotropes which can be used to more effectively counsel patients and families considering inotropes as a treatment option.

Translational Outlook

Additional research is needed to understand the risks and benefits of outpatient inotropes as palliation compared with other options.

Figure 1.
Flow Diagram of Identification of Studies for Inclusion

Figure 2. Risk of Death in Patients Treated with Inotropes Compared with Controls

The pooled relative risk of death in patients treated with inotropes compared with controls in RCTs is shown.

Figure 3. Rate of All-Cause Hospitalization in Patients Treated with Inotropes

The rate of all-cause hospitalization per 100 person-months of follow-up in studies of patients treated with ambulatory inotropes is shown.

Figure 4A

Figure 4B.

Figure 4. Changes in New York Heart Association Functional Class on Inotropes

4A. Studies comparing NYHA functional class before and while on inotropes

Change in NYHA functional class in patients before and during use of inotropes in studies is shown. Drakos (Online ref.16), Roffman (27), and Tsagalou 2006 (Online ref.63) excluded as patient populations overlap. WMD= weighted mean difference

4B. Randomized trials comparing NYHA functional class on inotropes compared with controls

The difference in NYHA functional class in patients receiving inotropes compared with controls in RCTs is shown. WMD= weighted mean difference

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Figure 5.
Expected Outcomes in Patients on Ambulatory Inotropes

Table 1

Summary of 66 Included Studies

Characteristic	N (%)
Study Design	
Randomized controlled trial	13 (19.7)
Non-randomized controlled trial	4 (6.1)
Prospective cohort/ case series	23 (34.8)
Retrospective cohort/ case series	24 (36.4)
Historically-controlled study	2 (3.0)
Inotrope Used (can be multiple)	
Dobutamine	49 (74.2)
Milrinone	7 (10.6)
Dopamine	25 (37.8)
Levosimendan	10 (15.2)
Inotrope Administration	
Intermittent	33 (50)
Continuous	21 (31.8)
Combination (intermittent and continuous)	9 (13.6)
Not specified	3 (4.5)
Indication	
BTT	11 (16.7)
Palliative	8 (12.1)
Combination (BTT and palliative)	13 (19.7)
Not specified	34 (51.5)
Number of patients, median (IQR)	34.5 (20.75, 63.25)

BTT=bridge to transplant, IQR= interquartile range

Table 2

Summary of Expected Outcomes in Patients Treated with Outpatient Inotropes

Outcome	Overall	BTT	Palliative
Improvement in NYHA, mean classes (95% CI)	1.2 (1–1.4)	1.3 (1.2–1.4)	1.1 (0.8–1.3)
Death	4.2 (3.2–5.5)	5.0 (2.7–9.1)	10.5 (4.8–22.8)
All-cause hospitalization	22.2 (18.0–27.4)	40.0 (23.3, 68.7)	27.2 (26.4, 28.0)
ICD shock	2.4 (2.1–2.8)*	--	--
Central line infection	3.6 (2.4–5.4)	3.9 (1.4, 10.8)	5.5 (2.3, 13.0)

BTT = bridge to transplant; ICD= implantable cardioverter defibrillator; NYHA= New York Heart Association Rate per 100 person-months of follow-up with 95% confidence intervals are shown unless otherwise noted

* Two of three studies in BTT population and third in mixed BTT and Palliative, so results not stratified by indication