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Ambulatory Inotrope Infusions in Advanced Heart Failure

A Systematic Review and Meta-Analysis

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ABSTRACT

OBJECTIVES This study sought to systematically review the available evidence of risks and benefits of ambulatory intravenous inotrope therapy in advanced heart failure (HF).

BACKGROUND Ambulatory inotrope infusions are sometimes offered to patients with advanced Stage D HF; however, an understanding of the relative risks and benefits is lacking.

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 and 53 observational studies) met inclusion criteria. Most studies were small and at high risk for bias. Pooled rates of death (41 studies), all-cause hospitalization (15 studies), central line infection (13 studies), and implantable cardioverter-defibrillator shocks (3 studies) of 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 taking inotropes than in controls (mean difference of 0.60 NYHA functional classes; 95% confidence interval [CI]: 0.22 to 0.98; $p = 0.001$; 5 trials). There was no significant difference in mortality risk in those taking inotropes compared with controls (pooled risk ratio: 0.68; 95% CI: 0.40 to 1.17; $p = 0.16$; 9 trials). Data were too limited to pool for other outcomes or to stratify by indication (i.e., bridge-to-transplant or palliative).

CONCLUSIONS High-quality evidence for the risks and benefits of ambulatory inotrope infusions in advanced HF is limited, particularly when used for palliation. Available data suggest that inotrope therapy improves NYHA functional class and does not impact survival. (J Am Coll Cardiol HF 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

An estimated 6.5 million adult Americans are living with heart failure (HF), and the prevalence is expected to increase. A fraction of those patients 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

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ABBREVIATIONS AND ACRONYMS

6MWT = 6-min walk test

BTT = bridge to transplant

HF = heart failure

HRQOL = health-related quality of life

ICD = implantable cardioverter-defibrillator

NSVT = nonsustained ventricular tachycardia

NYHA = New York Heart Association

2010 to 2014 among Medicare beneficiaries (2). However, in 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 inotropes on an outpatient basis 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. Although inotrope therapy was initially touted as an exciting alternative that would restore normal cardiac hemodynamics and alleviate symptoms (3), concerns were raised when studies demonstrated a higher incidence of ventricular arrhythmia 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, use of intravenous inotropes is variable across clinicians, centers, and regions (6).

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

METHODS

This systematic review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-analyses (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 described in Online Appendix. 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 of adult human subjects with advanced HF. We included studies published in all years. We required studies to have at least 1 arm that included participants 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 studies that reported primary data for at least 1 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 (T.N., S.M.D.) 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, where death occurred, hospitalization (all-cause and HF-related), health-related quality of life (HRQOL), functional status (New York Heart Association [NYHA] functional class, 6-min walk test [6MWT] distance), ventricular arrhythmias (sudden death, sustained ventricular arrhythmias, nonsustained 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 (T.N.) and manually verified (S.M.D.). 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 Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool in nonrandomized studies of interventions (Online Ref. 2). These domain-based assessments consider different types of bias in studies that are important in interpreting results (see the Online Appendix 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 (CIs) derived from the Poisson distribution. Meta-analysis of event rates was performed by using the random effects model as described by DerSimonian and Laird (7). The risk of death in patients treated with inotropes compared with that in controls in RCTs was pooled using a random effects model,