The Role of Positive Inotropic Drugs in the Treatment of Older Adults with Heart Failure and Reduced Ejection Fraction

Daniel J. Dooley, MD[a,b,1], Phillip H. Lam, MD[a,b,1], Ali Ahmed, MD, MPH[a,c,d], Wilbert S. Aronow, MD[e,*]

KEYWORDS

• Heart failure • Inotropic drugs • Older adults • Mortality • Hospitalization

KEY POINTS

- Except for digoxin, the use of positive inotropes has been shown to be associated with higher risk of death and should not be used on a long-term basis.
- Therapy with short-term intravenous positive inotropes may be considered to maintain systemic perfusion until acute precipitating causes are resolved or a more definitive therapy may be considered, such as coronary revascularization, mechanical circulatory support, or heart transplantation.
- Therapy with short-term intravenous positive inotropes may be considered in patients with low blood pressure and hypoperfusion.
- Therapy with short-term intravenous positive inotropes may be considered as bridge therapy when patients are refractory to other evidence-based therapy and are waiting for mechanical circulatory support or heart transplantation.
- Therapy with long-term intravenous positive inotropes may be considered for patients with endstage heart failure enrolled into palliative and hospice care who are symptomatic despite other evidence-based therapy and are not candidates for mechanical circulatory support or heart transplantation.

INTRODUCTION

Heart failure (HF) is the most common cause for hospital admission in the United States among individuals 65 years of age and older, and is a significant burden on the health care system. It has been projected that by 2030, the total cost of HF will be $69.7 billion, an increase from the $30.7 billion spent in 2012.[1] About half of HF admissions derive from patients with HF and reduced

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[a] Center for Health and Aging, Veterans Affairs Medical Center, 50 Irving Street NW, Washington, DC 20422, USA; [b] MedStar Heart and Vascular Institute, Georgetown University/MedStar Washington Hospital Center, 110 Irving Street NW, Washington, DC 20010, USA; [c] Department of Medicine, George Washington University, 2150 Pennsylvania Avenue, NW Suite 8-416, Washington, DC 20037, USA; [d] Department of Medicine, University of Alabama at Birmingham, 933 19th Street South, CH19 201, Birmingham, AL 35294, USA; [e] Cardiology Division, Westchester Medical Center, New York Medical College, Macy Pavilion, Room 141, Valhalla, NY 10595, USA
[1] Equal contribution.
* Corresponding author.
E-mail address: wsaronow@aol.com

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ejection fraction (HFrEF), defined as left ventricular ejection fraction less than 40%.[1] One of the most common modes of death in patients with HFrEF is pump failure, an outcome preceded by deteriorating hemodynamics.[2] Several positive inotropic drugs have been studied in the treatment of HFrEF patients with low cardiac output who are unable to tolerate the standard guideline-directed medical therapies used in the treatment of HFrEF. The purpose of this article is to review these agents in the treatment of patients who have HFrEF, with a focus on older adults.

POSITIVE INOTROPIC DRUGS

Positive inotropic drugs have been shown to improve hemodynamics in patients with HFrEF in the acute decompensation setting in whom they are efficacious in improving symptoms. However, long-term use of these drugs has been associated with higher mortality. Except for digoxin, none of the positive inotropes are recommended for routine use in chronic HFrEF.[3] Many randomized clinical trials have been conducted to measure the clinical impact of these drugs on HFrEF (**Table 1**).[4–12] Evidence for increased mortality risk in studies of most positive inotropic drugs in patients with HFrEF suggests that the decision to initiate these drugs should be individualized.

ADRENERGIC AGONISTS

The adrenergic agonists stimulate the heart through the autonomic nervous system pathway. Most adrenergic agonists (dopamine, epinephrine, isoproterenol, norepinephrine, and phenylephrine) are not commonly used in the treatment of HF because of their vasoconstrictive and proarrhythmic properties, and their association with a higher risk of death. Although dobutamine is a more commonly used adrenergic agonist in HFrEF, its use is also associated with a higher risk of death.[13] However, when carefully used, dobutamine and dopamine may play a role in the management HFrEF patients who are refractory to other HF therapy.[3]

Dobutamine

Dobutamine stimulates beta-1 and beta-2 adrenergic receptor subtypes, thus increasing contractility through its beta-1 effect and vasodilation because of its beta-2 effect. At higher doses, dobutamine stimulates alpha-1 receptors and causes vasoconstriction.

Dobutamine has been evaluated in several clinical trials.[10,11,13–19] The Dobutamine Infusion in Severe Heart Failure (DICE) trial was designed to evaluate intermittent low-dose dobutamine.[11] In the trial, 38 subjects with an average age of 65 years were randomized to receive optimized oral therapy and intermittent ambulatory low-dose dobutamine versus optimized oral therapy alone. Although it did not achieve statistical significance, there was a trend toward a reduction in the primary outcome of reduced HF hospitalizations.[11] Although no significant impact on mortality in subjects who received dobutamine was observed,[11] an earlier study investigating the effects of intermittent dobutamine infusion in HF subjects was stopped early due to increased rates of death in the dobutamine group.[20] Subsequently, the effect of continuous dobutamine use was studied in a post hoc analysis of the Flolan International Randomized Survival Trial (FIRST), which analyzed 80 subjects receiving continuous dobutamine at the time of randomization compared with 391 who were not receiving this drug.[13] In that study, the use of continuous dobutamine was associated with an increase in 6-month all-cause mortality rate ($P = .001$). Some studies have shown association of dobutamine use with improved 6-minute walk tests and cardiac function[17,19] but large-scale randomized trials displaying these benefits are lacking.

Although specific investigations of the impact of dobutamine in older subjects with HF are limited to case series,[19] subjects in the relatively small (sample size 38) randomized controlled DICE trial had a mean age of approximately 65 years.[11] In that study, although there were no significant between-group differences in all-cause and HF hospitalizations, likely due to small sample size, these events were numerically lower in the dobutamine group.[11] Similarly, there were no significant between-group differences in all-cause mortality but these events were numerically higher in the dobutamine group.[11] Taken together with findings from other studies,[11,13,15,16,20] this suggests that dobutamine use does not prolong life and may be associated with a higher risk of mortality in patients with advanced HFrEF.

Dopamine

Dopamine stimulates not only alpha-adrenergic and beta-adrenergic receptors, which allows for vascular, inotropic, and chronotropic support, but also dopaminergic receptors. Stimulation of dopaminergic receptors results in proportionately greater increases in splanchnic and renal perfusion relative to other vasoactive drugs.[21]

Dopamine's use in the treatment of shock has been well studied.[22–24] Several studies have also examined the role dopamine in HF.[25–30] In older subjects (mean age, 75.7 years) hospitalized for acute decompensated HF, a low dose of IV