Current Heart Failure Reports (2020) 17:314–323
https://doi.org/10.1007/s11897-020-00482-y

ETHICS/PALLIATIVE CARE (S FEDSON, SECTION EDITOR)

Home Therapies in Advanced Heart Failure: Inotropes and Diuretics

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Published online: 24 August 2020

Abstract

Purpose of Review Heart failure (HF) is a significant cause of morbidity, mortality, and decreased quality of life (QOL). Symptoms, including reduced activity tolerance, fatigue, palpitations, and dyspnea, result from volume overload or low output states. Herein, we review the best available literature supporting diuretic and inotropic therapies in advanced HF and how these improve QOL.

Recent Findings While diuretics and inotropes reduce symptoms and hospitalizations in advanced HF, there is an increased risk of harms with both modalities. While diuretic complications include electrolyte and renal function abnormalities, adverse event data with inotropes is more complex and includes possible arrhythmias and death. Further, inotrope utilization is complicated by required intravenous access, infusion costs, and limited outpatient support.

Summary Ambulatory use of diuretics and inotropes may improve patients' QOL through symptom management and reduced hospitalizations. However, risks and limitations of both modalities must be considered as treatment decisions are made.

Keywords Palliative care, inotropes · Diuretics · Dyspnea · Advanced heart failure

Introduction

Heart failure (HF) affects over 6 million American adults, with 8 million projected by 2030, and many more diagnosed worldwide [1]. Patients with advanced heart failure (AHF), classified as American College of Cardiology and American Heart Association (ACC/AHA) Stage D, have persistent severe symptoms despite aggressive and goal directed medical therapy [2]. Though these patients may be candidates for advanced therapies such as heart transplantation, resynchronization therapy, or mechanical circulatory support (namely, left ventricular assist devices [LVAD]), many patients do not qualify for, nor desire, such interventions. In these instances, optimizing quality of life (QOL) by avoiding invasive interventions and recurrent hospitalization is often the goal of therapy. As such, managing symptoms when the underlying problem cannot be durably remedied becomes essential.

HF is a complex pathophysiologic state that results from the heart's inability to pump blood effectively to perfuse the rest of the body. To compensate, the body uses mechanisms to expand intravascular volume to increase mean arterial pressure. However, these compensatory mechanisms inevitably lead to long-term complications. Through a combination of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), mechanisms employed to increase blood pressure ultimately lead to excess volume accumulation. Specifically, the sympathetic nervous system senses hypotension through the juxtaglomerular apparatus, triggering catecholamine release, and, in turn, stimulating the release of renin. Simultaneously, the decrease in serum sodium concentration is sensed by the kidney's macula densa which also promotes renin release. Renin initiates breakdown of angiotensinogen, leading to angiotensin I, angiotensin II, and aldosterone up regulation [3]. As a result, vasoconstriction occurs and water and sodium are retained. Though this temporarily increases blood pressure, fluid retention leads to volume overload, vascular congestion, and adverse cardiac remodeling [4]. The mainstays of HF management usually involve addressing this fluid and salt imbalance, managing pathologic neurohormonal activation, and improving cardiac output [3].

This article is part of the Topical Collection on *Ethics/Palliative Care*

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Accordingly, diuretics and inotropes play a pivotal role in managing HF symptoms; however, both are associated with adverse effects which limit their use. With diuretics, patients may experience increasing resistance, decreased absorption of oral medications, or electrolyte and renal function abnormalities. The use of inotropes continues to be limited by need for intravenous access (other than a few drugs not yet available in the USA), which places patients at greater risk of infection and requires more careful monitoring. Maintenance of inotrope therapy is often cumbersome and costly and requires access to resources including caregivers, follow-up, and supplies. Finally, while inotropes can make patients feel better and have improved effort tolerance, they are also associated with an increased risk of arrhythmia and death [2]. This review provides an overview of the role of diuretics and inotropes in AHF, including their mechanisms of action, potential adverse effects, and evidence that supports their use in outpatient settings.

Ambulatory Management of Advanced Heart Failure

Effective outpatient management of AHF is crucial to limiting hospital readmissions and providing improved QOL to patients at home. More than 20% of patients hospitalized with a HF exacerbation are readmitted to the hospital within 30 days [5]. Furthermore, some studies have shown mortality rates as high as 7.4% at 30 days and 27.3% at 1 year for patients with recurrent hospitalizations [6]. This evidence highlights the importance of monitoring and managing changes in the patient's volume status to prevent hospitalization. Diuretics and inotropes frequently are utilized together with other guideline-directed medical therapy to optimize volume status and effort tolerance.

Laboratory Considerations

Serum chemistries are monitored to help determine the severity of HF and indicate how well a patient is tolerating treatment. Hyponatremia, for example, is a negative prognostic sign, as studies show that patients with normal sodium levels survive for nearly twice as long as patients with hyponatremia [7]. Similarly, an elevated B-type natriuretic peptide (BNP) level in patients after 3 months of optimized HF treatment is an independent risk factor for mortality even if patients have improvement of symptoms and left ventricular ejection fraction [8]. Serial BNP levels can additionally serve as a useful metric of a patient's volume status [9]. Creatinine monitoring is critical, as renal impairment is common in HF, resulting from low cardiac output, decreased renal perfusion, and is exacerbated by diuretic use. In one meta-analysis of 80,098 patients with HF, 63% of patients had renal impairment (creatinine > 1.0 mg/dL) and of those, 29% had moderate to severe impairment (creatinine > 1.5 mg/dL) [10]. Further, multiple medications (i.e., angiotensin converting enzyme inhibitors, or receptor blockers) used to treat HF chronically may affect renal function, necessitating frequent creatinine and potassium monitoring.

Dietary Considerations and Outpatient Monitoring

Educating patients with HF is paramount in reducing hospital admissions and minimizing symptom burden. Daily weights, restriction of dietary sodium to 2 g/day, and restriction of fluid intake to 1.5–2 l/day can help limit the need for increasing amounts of diuretic or inotropic agents. Additionally, evidence demonstrates that home monitoring with telemedicine or implantable pulmonary artery pressure sensors (e.g., CardioMEMS™) may also aid in symptom management and decrease hospitalizations by identifying changes that precede outward clinical signs of more advanced decompensation [11], improving patient QOL as well as hospitalization and mortality rates.

Pharmacology and Therapeutic Classes of Diuretics

Loop Diuretics

Loop diuretics, which work through inhibition of the Na-K-2Cl cotransporter (NKCC2) in the thick ascending loop of Henle, are highly effective and play an essential role in AHF medication regimens. By inhibition of the NKCC2, they allow for increased sodium and chloride excretion into the urine, resulting in diuresis [12]. Furosemide, torsemide, and bumetanide are the most commonly used oral diuretics in this class. Pharmacodynamics of loop diuretics resemble an S-shaped curve; that is, to effectively induce diuresis, the plasma concentration of the drug must reach a certain threshold to activate nephrons in the kidney [13, 14]. Unless this threshold dose is delivered to its site of action, effective diuresis will not occur [15]. Once the threshold has been reached, diuresis follows, at which point sodium excretion is at its peak rate. Doses that exceed the threshold dose will usually not provide additional diuresis, but may result in adverse effects such as ototoxicity, diuretic resistance, and electrolyte imbalances [16]. Therefore, to minimize side effects, the lowest dose possible that elicits a response should be used. In most patients, a dose of furosemide at 40 mg intravenous or 80 mg oral allows for maximal effect [13]. A higher effective dose may be required when renal perfusion or glomerular filtration are reduced. RAAS activation can also enhance sodium reabsorption in the kidneys, resulting in the need for higher doses of loop diuretics.

Clinicians must consider the absorption and bioavailability of common oral diuretics when used in an ambulatory setting. Furosemide, for example, has a variable absorption rate when administered orally, with approximately 50% of the dose reaching the intraluminal site of action compared with intravenous dosing (see Table 1) [17, 18]. Therefore, as a rule, intravenous furosemide is considered twice as potent as the oral formulation. Torsemide and bumetanide, however, have 80–100% oral bioavailability and thus do not require dose conversion between parenteral and enteral administration [19]. Even in the setting of gut edema, which frequently is a consideration in AHF patients, torsemide and bumetanide are well absorbed compared with furosemide [19–21]. It should be noted that torsemide undergoes hepatic metabolism, making it preferred in renal insufficiency [22].

Several trials have evaluated the clinical outcomes of patients receiving loop diuretics. Using data from the ASCEND-HF trial, short-term outcomes of 4177 patients with HF who received torsemide (13%) or furosemide (87%) were reviewed. Although the torsemide group had features of more severe HF (lower ejection fraction, lower blood pressure, and higher creatinine level), 30-day and 180-day mortality were comparable [23]. Similarly, a 2019 retrospective study of 232 patients with decompensated HF randomized to either torsemide or furosemide, demonstrating no clinical difference in HF-related hospitalizations [24].

Two recently published systematic reviews looked at benefit of torsemide versus furosemide. A meta-analysis of 9 randomized controlled trials and 10 observational studies reviewed 19,280 patients. Torsemide demonstrated a statistically significant improvement in functional status in patients with AHF (class III/IV) compared with class I/II patients, and showed a decreased risk of cardiac mortality compared with furosemide. However, no difference in adverse events or all-cause mortality was found [25••]. Another updated meta-analysis included 8127 patients with HF showing torsemide was associated with improvement in functional class, as well as reduction in the intermediate-term hospital readmission for HF and reduction in mortality [26].

Thiazide Diuretics

Thiazide diuretics are often viewed as less "powerful" than loop diuretics; however, they play a critical role in managing volume status in AHF, often in combination with loop diuretics. Chlorothiazide, hydrochlorothiazide, and metolazone are the thiazide diuretics most commonly used in the USA. Although, chlorthalidone and indapamide are also thiazide diuretics, they are more frequently used in management of hypertension than in HF. Much like loop diuretics, thiazide diuretics also promote sodium and chloride excretion in the urine; however, they act in the distal convoluted tubule at the sodium-chloride cotransporter (NCC) [12].

Though thiazide diuretics may induce diuresis when used alone, they are frequently used in conjunction with loop diuretics in patients with AHF. This is due to the development of diuretic resistance in patients who are exposed chronically to loop diuretics requiring increased diuretic doses to maintain the same effects. When loop diuretics are used, NKCC2 activity is inhibited, blocking the resorption of sodium into circulation and promoting excretion of sodium and chloride in the urine. The nephron, in turn, actively tries to reabsorb sodium from other parts of the nephron to maintain homeostasis [27, 28]. This enhanced tubular sodium reabsorption is known as the braking phenomenon. When the nephron is exposed to chronic loop diuretics, the distal tubule hypertrophies to promote increased sodium reabsorption [28, 29]. Thus, thiazide diuretics work in the distal convoluted tubule to counteract this sodium reabsorption, augmenting the loop diuretics's effect.

In the randomized, double-blinded "3T" trial, 60 hospitalized patients with acutely decompensated HF who were already on high dose furosemide infusions were randomized to oral metolazone, intravenous chlorothiazide, or tolvaptan [30•]. Among the three groups, there was no detectable difference in terms of diuresis volume [30•]. Thus, oral metolazone use to potentiate loop diuretic action is a valuable strategy for HF management and can be done in the outpatient setting. Patients are at a higher risk of electrolyte disturbances when

Table 1 Comparison of pharmacological and pharmacokinetic properties of commonly used loop diuretics

	Furosemide	Torsemide	Bumetanide
Relatively potency (IV, in milligrams)	40	20	1
Oral to IV dose conversion (oral:IV)	2:1	1:1	1:1
Bioavailability (%)	10–100 (average 50)	80–100	80–100
Onset (minutes)	30–60 (oral), 5 (IV)	30–60 (oral), 10 (IV)	30–60 (oral), 2–3 (IV)
Drug half-life (hours)	1.5–2	3–4	1
Duration of effect (hours)	6–8	4–6	6–8

IV, intravenous

After Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. J Am Coll Cardiol. 2012;59(24): 2145–53. doi: https://doi.org/10.1016/j.jacc.2011.10.910

loop diuretics are used concurrently with thiazides. Renal function and serum potassium should be monitored given risk of renal failure or hypokalemia with aggressive diuresis.

Aldosterone Antagonists

Aldosterone binds to mineralocorticoid receptors on the distal tubule, leading to increased reabsorption of sodium and water and increased renal excretion of potassium. Mineralocorticoid receptor antagonists block this activity, resulting in increased diuresis and increased potassium reabsorption. As noted earlier, chronic loop diuretic use leads to remodeling in the distal tubule and increased distal sodium reabsorption. Similar to thiazide diuretics, aldosterone antagonists work synergistically with loop diuretics to promote diuresis [31]. Spironolactone and eplerenone, the two most commonly used aldosterone antagonists, have been shown in large clinical trials to provide morbidity and mortality benefits in AHF [32–34], likely due to reducing aldosterone-mediated ventricular remodeling.

Use of aldosterone antagonists requires special considerations to mitigate adverse events. In order to initiate spironolactone, the glomerular filtration rate should be greater than 30 mL/min and serum potassium level should be less than 5 mEq/L. Therapy should be discontinued if potassium levels are persistently greater than 5.5 mEq/L despite dose adjustments. Gynecomastia and gastritis are treatment-limiting adverse events that also require monitoring. Eplerenone is a more selective aldosterone antagonist and may be associated with less gynecomastia, but it has not been shown to be superior to spironolactone and has higher costs. With appropriate monitoring and risk-benefit discussions, aldosterone antagonists can provide a mortality and QOL benefit to some patients with AHF.

Sodium/Glucose Cotransporter-2 Inhibitors

The sodium-glucose cotransporter-2 (SGLT2) is located primarily in the proximal convoluted tubule of the kidney. SGLT2 functions to resorb blood glucose that has been filtered into the urine by the glomerulus, which usually occurs when blood glucose levels exceed 180–200 mg/dL. Inhibition of SGLT2, therefore, decreases blood glucose by inducing glycosuria. Thus, SGLT2 inhibitors were initially developed as anti-hyperglycemic agents and have been demonstrated to improve glycemic control in diabetic patients [35]. More recently, some SGLT2 inhibitors have also demonstrated cardiovascular benefits and improved outcomes in patients with HF, likely in part due to their diuretic effects. At present, empagliflozin, canagliflozin, and dapagliflozin are the SGLT2 inhibitors that have been studied in this capacity.

In a trial to evaluate cardiovascular morbidity and mortality in patients with both cardiovascular disease and diabetes mellitus type 2, patients on empagliflozin (vs. placebo) not only had fewer cardiovascular events, but the HF hospitalization rate was lower in the empagliflozin group [36]. Similarly, in patients with diabetes mellitus type 2 and kidney disease, canagliflozin was associated with reduced cardiovascular event rates, rehospitalizations, and rates of renal dysfunction [37]. Dapagliflozin, evaluated in the DECLARE-TIMI 58 trial, showed decreased rates of HF exacerbations in diabetic patients [38]. In the DAPA-HF trial, patients on dapagliflozin (vs. placebo) demonstrated decreased rates of HF exacerbation, even when patients did not have diabetes as well as an all-cause mortality benefit in patients with HF when compared with placebo [39•].

SGLT2 inhibitors do have risks and possible serious side effects, including hypoglycemia, hypovolemia/hypotension, and urinary/genital tract infections [40]. More recently, a post-market study reported an increased risk of Fournier's gangrene in patients taking SGLT2 inhibitors, although the overall risk remains low [41]. Canagliflozin has been linked to an increased risk of lower limb amputations in patients without existing peripheral vascular disease [42]. Overall, SGLT2 inhibitors are contraindicated in patients with systolic blood pressures < 95 mmHg, glomerular filtration rates of less than 30 mL/min, or in patients experiencing rapidly declining kidney function [40].

Intravenous Diuretics and Novel Administration Options

Most patients with AHF are maintained on outpatient oral diuretic regimens. However, when patients begin to develop symptoms of volume overload despite oral diuretic use, they often require hospital admission for intravenous diuretic administration. To prevent this cycle of repeated hospitalizations and to improve QOL, some hospitals have developed outpatient intravenous diuresis programs. Multiple studies have evaluated the effectiveness of this strategy. In one study of 249 patients, use of an intravenous diuretic clinic resulted in three fewer days of hospitalization per 180-day period [43•]. Hospitals with outpatient intravenous diuretic clinics were also more likely to have lower 30-day risk-standardized mortality rates (although risk-standardized readmission rates were unchanged) [44]. Finally, a retrospective analysis of 107 acutely decompensated HF patients receiving outpatient intravenous diuretics not only had reductions in weight, blood pressure, and BNP levels, 72% of patients improved and did not require hospital admission [45].

Additionally, the argument has been made that patients with acute decompensated HF may need hospitalization for administration of continuous intravenous infusion of loop diuretics as opposed to bolus dosing. However, the DOSE trial, demonstrated that intravenous bolus dosing of high-dose diuretics administered 12 hours apart was noninferior to continuous intravenous diuretic infusions both in terms of overall

symptom burden and in renal function [46••]. Therefore, these studies suggest that outpatient intravenous diuretics are effective alternatives and can be done safely to avoid traditional inpatient hospitalization.

Intravenous administration is often not feasible in the outpatient setting, so alternatives for subcutaneous administration continue to be explored. For instance, in patients with NYHA class II symptoms given either subcutaneous furosemide or intravenous furosemide, urine output was comparable between both groups over 8 hours despite lower peak plasma concentrations in the subcutaneous group [47]. Similarly, a study of 40 patients with HF and NYHA class II–IV symptoms explored this opportunity. Patients were randomized to either intravenous furosemide up to 160 mg or to subcutaneous furosemide of 80 mg total (30 mg in first hour with 12.5 mg for 4 consecutive hours). Hospital readmission rates were comparable, even despite the lower total furosemide dose in the subcutaneous arm [48]. Moreover, in patients with AHF, subcutaneous furosemide has demonstrated decreased hospitalizations, improved breathlessness, less peripheral edema, and less weight gain [49]. A commercially available subcutaneous delivery system for isotonic furosemide called the FUROSCIX Infusor™ uses a micro-piston pump with a 27-gauge needle to deliver a set amount of furosemide over an extended period of time, and its use seems promising in the outpatient setting [50].

Pharmacology and Therapeutic Classes of Positive Inotropic Agents

Inotropic agents are those that augment force of muscle contraction. Inotropes may have positive or negative effects, with positive inotropic agents serving to augment cardiac contractility and improve cardiac output. In AHF, several mechanisms by which positive inotropic agents (hereafter, inotropes) work to improve cardiac contractility: beta-adrenergic agonists, phosphodiesterase-3 (PDE-3) inhibitors, and calcium sensitizers. In conjunction with diuretics, inotropic agents are part of the palliative pharmacologic management of AHF and can lead to symptomatic relief and QOL benefits. Additionally, inotropes can be used as intermediate and long-term therapies to bridge patients to more definitive treatments such as LVAD and heart transplantation [2]. The evaluation for inotropes in stage D AHF must take into account low cardiac output, adequate intravascular volume, and lack of reversible causes.

Despite evidence that inotropic agents improve symptoms and QOL in HF patients, there are side effects which could increase mortality [51•]. When compared with more definitive therapies such as LVAD and transplantation, continuous inotropes have not been shown to have a mortality benefit in multiple studies [52–54]. Comparing the three modalities, the mean survival of patients with stage D AHF who receive heart transplantation is 11 years [55], those receiving destination LVAD have a mean survival of greater than 7 years [56], but those receiving continuous inotropic support survive on average 9 months [57•]. This decreased survival is in part related to advanced disease state, but also to the proarrhythmic activity of inotropes [57•]. Outpatient support with continuous inotrope therapy may be a reasonable option for patients in whom inotropes cannot be discontinued due to hypotension, hypoperfusion, worsening dyspnea, and renal dysfunction [58, 59].

Beta-Adrenergic Agonist Therapies

Dobutamine is the most common beta-agonist inotrope used in decompensated HF. It is a catecholamine which acts on beta-1 and beta-2 receptors to increase myocardial contractility and cardiac output and decrease total peripheral resistance [60]. Doses less than 5 mcg/kg/min promote vasodilation and inotropic support, whereas doses greater than 10 mcg/kg/min cause inotropic, chronotropic, and vasoconstrictive effects. Common side effects associated with dobutamine include hypotension, angina, and palpitations—with dobutamine having proarrhythmic effects in an estimated 21% of cases [61, 62]. Dobutamine is administered through central venous access, typically a peripherally inserted central catheter (PICC). PICC lines are also associated with harms independent of inotrope use including pneumothorax, venous clot formation, and line infection. Despite these risks, there is evidence to suggest that dobutamine infusion in the outpatient setting can be beneficial to patients with AHF. In a small retrospective analysis of 21 patients with AHF and low cardiac output, dobutamine was associated with improved symptoms, reduced hospitalizations, and reduced health care costs [63•]. Dopamine and norepinephrine are also beta-1 agonists which can have inotropic activity; however, these drugs are less selective and have more vasoconstrictive effects, limiting their long-term use.

Phosphodiesterase-3 Inhibitors

Phosphodiesterase-3 inhibitors (PDE3i) indirectly increase intracellular calcium from the sarcoplasmic reticulum to increase myocardial contractility, resulting in positive inotropic effects [64]. PDE3i can also decrease pulmonary and systemic vascular resistance by acting on vascular smooth muscle to promote vasodilation [64].

Milrinone is the most commonly utilized intravenous PDE3i in the USA, both continuously and intermittently. Intermittent milrinone infusions have been shown to improve QOL outside of the hospital. One small study of 10 AHF patients receiving home intravenous milrinone therapy showed a 4-fold decrease in hospitalizations [65]. Further, intermittent home infusions (i.e., 4 cycles of 3 days per week) were shown to improve hemodynamics even up to 4 months after discontinuation [66]. Compared with nitroglycerin, milrinone provided more rapid improvement of

hemodynamics, decreased systemic vascular resistance, and increased stroke volume in 125 patients with decompensated HF in a randomized, open-label trial [67].

Similar to dobutamine, milrinone also has been associated with increased side effects and mortality, and requires intravenous administration in the USA [51•]. A group of 951 patients with decompensated HF were randomized to receive 48 hours of intravenous milrinone or saline infusion (placebo). Arrhythmias and hypotension were more common with milrinone, although in-hospital mortality and 60-day mortality were similar [52]. In the USA, milrinone is only available for intravenous administration, although oral milrinone has been shown to improve hemodynamics, but carries an increased morbidity and mortality risk [68, 69]. A recent pilot study of 23 patients who received extended-release oral milrinone tolerated it well and reported improved QOL, but this population has preserved ejection fraction and no further data is available regarding adverse events [70].

Calcium Sensitizers

Levosimendan and Pimobendan

Calcium sensitizers work by sensitizing troponin C to calcium, which increases cardiac contractility without effecting intracellular calcium levels [71]. The most widely used agent is levosimendan, which causes vasodilation by opening ATP-sensitive potassium channels within vascular smooth muscle [71]. Similar to other inotropes, levosimendan has been shown to improve symptoms in patients with acute decompensated HF patients, but also has an increased risk of arrhythmias and hypotension [72]. In the SURVIVE trial, there was no significant difference in mortality at 1 or 6 months when comparing levosimendan with dobutamine [73].

Pimobendan is another calcium sensitizer previously evaluated in the EPOCH trial. Long-term treatment with oral pimobendan showed symptomatic improvement and significantly lower adverse cardiac events compared with placebo [74]. In another trial, pimobendan demonstrated improvement in exercise capacity; however, there was noted to be greater mortality in a stable outpatient HF population [75]. Although levosimendan continues to be used in Europe and is named in European Society of Cardiology treatment protocols [76, 77], both levosimendan and pimobendan are not been approved for in North America.

Digoxin

Digoxin is a cardiac glycoside that has been used as an oral inotrope in HF for over 200 years. Digoxin inhibits myocardial Na-K ATPase pumps indirectly increasing intracellular calcium levels and promoting contractility [78]. In a large randomized control trial of 6800 patients with systolic HF, The Digitalis Investigation Group evaluated patient outcomes by randomization to either digoxin or placebo. Digoxin showed reduction of rehospitalization rate by 6% (although 37-month mortality was unchanged) [79]. Later analysis of this trial demonstrated patients in the digoxin arm with NYHA III/IV symptoms, ejection fraction < 25%, or cardiothoracic ratio of > 55% had improvement in HF mortality and 2-year rehospitalization rate [80]. Despite these outcomes, digoxin use in the USA has decreased from 33.1% in 2005 to 10.7% in 2014 [79], likely in part due to the possibility of drug toxicity. Clinical manifestations of digoxin toxicity include arrhythmias, gastrointestinal symptoms, neurologic changes, electrolyte abnormalities, and visual changes including xanthopsia. In 2014, a large retrospective analysis of 122,465 patients with new diagnosis of atrial fibrillation showed that 23.4% who received digoxin experienced increased risk of death independent of other variables [81].

Inotropic Therapy Considerations in Outpatient Settings

Ambulatory inotropic therapy supports patients with AHF who are unable to be weaned when used acutely in the hospital. However, management of home inotropes involves numerous complexities. First, patients are usually admitted to the hospital to determine a dose needed to improve symptoms and hemodynamics. However, when these patients go home, the medication doses may need to be titrated due to tachyphylaxis, renal impairment, or weight changes [82]. Secondly, the maintenance of central venous catheters for continuous infusion of inotropes places a significant burden on caregivers. Clinicians must determine if patients adequate social support to be placed on outpatient inotrope therapy. Hospice can provide some support in these situations; however, not all hospice agencies are equipped to manage inotropic therapies due to lack of staffing, experience, or cost [83]. Specifically, since hospice agencies receive a per diem rate of payment from Medicare, home inotropes and supplies can be cost prohibitive.

Conclusions

Advanced HF is associated with high symptom burden and impaired QOL that result from volume overload and low output states. Use of diuretics and inotropes has been shown to provide significant QOL benefits to patients who do not qualify for more definitive therapy (i.e., transplantation or LVAD). However, these medications are not without associated risks including renal dysfunction, electrolyte abnormalities, arrhythmias, and death. Use of home inotropes may be cumbersome, costly, and requires additional caregiver support.

Accordingly, there exists a need for continued risk-benefit discussions with patients to understand how each modality of treatment may affect QOL. Opportunities continue to exist in harm reduction as well as in improving access to both diuretics and inotropes in the ambulatory setting.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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