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REVIEW ARTICLE

A Practical Comprehensive Approach to Management of Acute Decompensated Heart Failure

Chukwunweike Nwosu[*,1], Kenechukwu Mezue[2], Kunal Bhagatwala[1] and Nonso Ezema[3]

[1]*Department of Medicine, Abington Memorial Hospital, Abington PA, USA;* [2]*Department of Medicine, Einstein Medical Center, Philadelphia PA, USA;* [3]*Department of Medicine, Mount Sinai Hospital, Chicago IL, USA*

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Abstract: Heart failure (HF) has a high incidence and prevalence in the USA and worldwide. It is a very common cause of significant morbidity and mortality with serious cost implications on the US health sector. The primary focus of this review is to synthesize an effective comprehensive care plan for patients in acute decompensated heart failure (ADHF) based on the most current evidence available. It begins with a brief overview of the pathophysiology, clinical presentation and evaluation of patients in ADHF. It then reviews management goals and treatment guidelines, with emphasis on challenges presented by diuretic resistance and worsening renal function (WRF). It provides information on recognition of advanced HF even during acute presentation, estimation of prognosis and proactive identification of patients that will benefit from mechanical cardiac devices, transplantation and palliative care/hospice. In addition, it presents strategies to address the problem of readmissions, which is an ominous prognostic factor with enormous economic burden.

Keywords: ADHF, diuretic resistance, ultrafiltration, cardiorenal syndrome, re-hospitalization, palliative care.

INTRODUCTION

About 5.8 million adults in the USA have HF [1]. The prevalence increases with age, and is associated with high mortality rate and frequent hospitalization with an annual cost of over $33billion mostly from hospitalization. The prevalence is expected to increase by 25% in 2030. The rate of readmission is 1 in 4 within 30 days of admission, with incidence of mortality and readmission of 20%-50%. ADHF accounts for almost one million hospitalizations per year. Its management transcends the symptomatic treatment to involve a holistic approach that includes identifying patients at increased risk, optimizing chronic therapy, and employment of disease management strategies to prevent frequent hospitalizations. Knowledge of available treatment modalities including appropriate utilization of palliative care and hospice, will significantly affect how physicians approach patients in ADHF, especially those with WRF which is the single most important prognostic factor in outcome of these patients [2].

PATHOPHYSIOLOGY

The neuro-hormonal (NH) system plays a direct role in the development and maintenance of HF. It comprises mainly of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), brain natriuretic peptide (BNP), and antidiuretic hormone (ADH). NH disturbances lead to sodium and water retention, pulmonary congestion, and hyponatremia, observed both in low output and high output HF. This increases preload resulting in cardiac dilation and remodeling. Angiotensin II also activates NADPH/NAD oxidase leading to oxidative injury [3]. Progression of this disorder cycle eventually may lead to functional mitral regurgitation (MR), pulmonary hypertension, increased ventricular wall stress and hypertrophy. Over time, there is diminished ratio of capillaries to cardiac myocytes with myocardial ischemia, even in the absence of coronary artery disease (CAD).

PRESENTATION

The diagnosis of ADHF is made by a constellation of clinical symptoms and signs. It may be the initial presentation or an exacerbation of a chronic disease. Patients commonly present with acute dyspnea from cardiogenic pulmonary edema secondary to fluid overload (pulmonary congestion, peripheral edema, and elevated jugular venous pressure); or less commonly with features of low cardiac output and decreased perfusion (hypotension or cardiogenic shock), characterized by fatigue, marked exercise intolerance, anorexia, and cognitive impairment [4]. Normotensive patients may still suffer from inadequate systemic perfusion in the presence of increased systemic vascular resistance. Other causes of acute respiratory distress such as pulmonary embolism, pneumonia and asthma; should be considered. Non

*Address for correspondence to this author at the Abington Memorial Hospital, 1200 Old York Road, Abington PA. 19001. USA; Tel: 215-481-2056; E-mail: chukwunweikenwosu@yahoo.com

1875-6557/16 $58.00+.00

cardiogenic causes of pulmonary edema include acute respiratory distress syndrome (ARDS), pericardial tamponade or constriction.

PRECIPITATING FACTORS

In general, HF may be with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), is commonly determined by echocardiography. HFpEF currently makes up about 50% of cases, commoner in females and more associated with comorbidities. Activation of SNS might play a role in the pathogenesis of HFpEF and renal denervation may become a treatment modality (DIASTOLE trial pending). Major precipitating factors may be cardiac (worsening chronic heart condition, new myocardial infarct, valvular disease, arrhythmias, drugs and toxins), or non-cardiac (adherence and process of care issues such as dietary indiscretion, non-adherence to medications, iatrogenic volume overload, some medications that affect preload/afterload; worsening or new comorbidities).

CLASS AND STAGE

The cardiac status of the patient at presentation determines both the acute and chronic management. The class is an assessment of functional status which although subjective is useful in the determination of severity and disability. The stage assesses disease progression. Both are important in estimation of prognosis and are represented in Table **1**. Stages C and D are the clinical diagnosis of HF. Many of the predisposing conditions to HF are highly prevalent; hence Stage A is very common making up about half of all patients. Stage B is about 3 to 4 times the number of patients in Stages C and D combined. Most of the patients in ADHF will be in Stage C. Stage D makes up about 5% of patients and has a mortality rate of 28-80%.

EVALUATIONS

Following a thorough history and physical examination are laboratory tests and imaging to determine patient's baseline health status, elicit risk factors, identify a cause and determine the class and stage. These include electrocardiography, chest x-ray, laboratory tests (CBC, CMP, BNP, Troponin, ABG), echocardiography, invasive hemodynamic monitoring, and coronary angiogram.

Troponins: Increased levels may result from subendocardial ischemia, myocyte apoptosis, inflammatory mediator activation, and increased myocardial oxygen demand in the setting of fixed coronary disease. It does not necessarily indicate acute coronary syndrome, especially in the absence of typical electrocardiographic findings.

BNP: Initial measurement of BNP supplements clinical judgment. It has been found useful for risk stratification and prognosis, and also monitoring therapy (especially when used with change in weight) [5], but not to be used to guide therapy. There are no defined targets and values may not necessarily alter use of guideline determined medical therapy (GDMT) [6].

Invasive hemodynamic monitoring: Routine use is not recommended. The ESCAPE trial showed no improvement in survival with increase in adverse event with use of pulmonary catheter-guided therapy. Indications include hemodynamic uncertainty, persistent symptoms especially with WRF, requirement of parenteral vasoactive agents, and consideration of advanced device therapy or cardiac transplantation. When used, pulmonary capillary wedge pressure (PCWP) ≥18 mmHg favors cardiogenic pulmonary edema but does not exclude non-cardiogenic causes.

TREATMENT

Table **2** shows the goals of treatment by Heart Failure Society of America 2010 Comprehensive HF Practice Guideline [4].

1) Oxygenation

Thorough patient examination, using pulse oximetry and ABG will help to assess requirement for supplemental oxygen, noninvasive positive pressure ventilation (NPPV), or assisted ventilation.

Table 1. Heart failure class and stage.

Class: New York Heart Association functional classification	
NYHA 1	Cardiac disease without limitations of physical activity
NYHA 2	Cardiac disease resulting in slight limitation of physical activity
NYHA 3	Cardiac disease with marked limitation of physical activity
NYHA 4	Cardiac disease with inability to do physical activity without discomfort.
Stage: American College of Cardiology/American Heart Association stages	
STAGE A	At risk (hypertension, diabetes mellitus, obesity, etc.)
STAGE B	Structural abnormalities, no symptoms
STAGE C	Structural abnormalities with symptoms
STAGE D	Refractory to guideline determined medical therapy

Table 2. Goals of treatment for patients in ADHF by HFSA 2010 guidelines.

Improve symptoms, especially congestion and low-output symptoms
Restore normal oxygenation
Optimize volume status
Identify etiology
Identify and address precipitating factors
Optimize chronic oral therapy
Minimize side effects
Identify patients who might benefit from revascularization
Identify patients who might benefit from device therapy
Identify risk of thromboembolism and need for anticoagulant therapy
Educate patients concerning medications and self-management of heart failure
Consider and, where possible, initiate a disease-management program

2) Decongestion

Diuretics: They remain first line although there is lack of safety and efficacy data from randomized clinical trials (RCTs). Patients with increased BUN but stable or mild increase in serum creatinine should continue diuresis with serial monitoring of their BMP. Modest increase in serum creatinine reflecting intravascular volume depletion may require reduced/temporary discontinuation of diuretics, including ACEI/ARB if the patient was on it prior [4]. Adjunctive inotropic therapy may be required. In patients with WRF, use of ultrafiltration, inotropes, or Nesiritide remains controversial, except if refractory to optimal diuretic treatment. Such patients are frequently discharged without adequate decongestion and hence have high rate of short term re-hospitalization. Aggressive decongestion leading to WRF may be associated with improved survival [7]. Diuretics can improve renal function by decreasing renal venous pressure and improving cardiac output which will subsequently improve renal perfusion. Monitoring of treatment involves re-evaluation of volume status, evidence of congestion, oxygenation, daily weights, fluid intake and output, watching for and guarding against side effects (WRF, electrolyte abnormalities, metabolic alkalosis), arrhythmia risk, hypoxia, and symptomatic hypotension). Telemetry is usually continued for at least 24 to 48 hours.

When a patient fails to achieve the therapeutic target of decongestion and fluid removal despite large doses of diuretics, usually 0.5-1 kg of weight per day on adequate diuretic therapy in clinical practice, it is referred to as diuretic resistance [8]. Causes include use of sub-therapeutic doses, poor absorption from edematous gut, poor diuretic delivery to its site of action, WRF, high dietary salt intake, braking phenomenon and auto regulation by nephrons to maintain sodium homeostasis, and post diuretic sodium retention (rebound) which occurs when diuretic concentrations in the tubule decline. Strategies to overcome this are shown in Table **3** [9-12].

Ultrafiltration: It works by using hydrostatic pressure gradient. Its use in WRF is controversial. PARID CHF trial suggested it may be used as an adjunct therapy to reduce resistance to diuretics, but not alternate therapy. The UNLOAD trial showed greater control of rate of fluid removal, greater net loss of sodium, less NH activation (isotonic fluid removal), removal of pro-inflammatory cytokines (with potential restoration of responsiveness to diuretics), shortened shorter length of stay (LOS) and readmissions, decreased risk of electrolyte disorder and decreased WRF in diuretic resistant patients [13]. CARRESS-HF trail revealed that stepped diuretic therapy remains superior for preservation of renal function, but non-superior for body weight, although subjects included in the trial were not diuretic resistant. There was also higher rate of adverse events (sepsis, bleeding, WRF) observed in patients that underwent ultrafiltration [14]. In the short term, ultrafiltration has been shown to result in faster and greater weight loss, and LOS for NYHA 3 and 4 patients, with preserved/stable renal function observed [15]. Another trial showed no significant WRF in patients that had only ultrafiltration, compared to diuretics [16]. The AVOID HF trial was designed to investigate the role of ultrafiltration in reduction in hospitalization but was terminated due to patient recruitment challenges [17]. Cost is another concern, but should be balanced with LOS and re-hospitalization results.

Table 3. Strategies to prevent diuretic resistance.

1	Use of more reliably absorbed oral loop diuretic (torsemide or bumetanide), or high doses of oral furosemide. Intravenous use is mostly preferred.
2	Continuous intravenous infusion of a loop diuretic has been thought to prevent post diuretic salt retention but has uncertain benefit. The DOSE trial revealed no difference in symptom relief in the absence of resistance
3	Addition of a thiazide-type diuretic or aldosterone antagonist which are especially useful against braking phenomenon.
4	Addition of acetazolamide can be very effective in blocking sodium reabsorption in nephrons, but long-term use can cause metabolic acidosis and this combination is rarely used in clinical practice.
5	Rolofylline (A1 adenosine antagonists which prevents renal vasoconstriction) had the potential to improve renal failure and reverse diuretic resistance in HF patients, but the PROTECT 1 and 2 trials showed no improvement in renal failure and congestion in ADHF patients.
6	In patients with severely low albumin, addition of albumin infusion has been suggested as hypoalbuminaemia reduces the delivery of diuretic to its action site and may contribute to diuretic unresponsiveness.

Aquaretics (ADH receptor antagonists – conivaptan, tolvaptan): These were originally used to correct hyponatremia in SIADH and cirrhosis, but have been shown by the EVEREST-Outcomes trial to potentially ameliorate fluid overload via excretion of free water in the short term (in addition to diuretics), and also correct hyponatremia [18]. They however did not show any long term benefit on mortality and morbidity.

Serelaxin: This is a recombinant human relaxin-2, a vasoactive peptide hormone that causes vasodilation, increases cardiac output and renal blood flow. The RELAX-AHF trial reported relief in dyspnea and other clinical outcomes in patients in ADHF treated with serelaxin, but had no effect on readmission to hospital [19]. Treatment was well tolerated and safe, supported by the reduced 180-day mortality. It is yet to be approved in the USA due to efficacy concerns. There are many other ongoing trials to address this.

3) Vasodilator therapy

This is for patients with adequate end-organ perfusion (e.g. normal or elevated blood pressure) and signs of ADHF. Nitroglycerin or nitroprusside are commonly used, in addition to diuretics. The use of diuretics and venodilators in preload-dependent patients should be done with caution to prevent hypotension. Nitrates are contraindicated after use of PDE-5 inhibitors (e.g. sildenafil). Coronary steal may occur (diversion of blood away from already compromised areas leading to more ischemia).

4) Intravenous inotrope

According to ACC/AHA HF guidelines, patients with severe or refractory symptoms may require intravenous positive inotropic agents (dobutamine and/or milrinone). Their use is reserved for HFrEF with severe ADHF and hypotension (HF with low blood pressure (HF-LBP) or cardiogenic shock. Routine use is not recommended (OPTIME-CHF). Inotropes may cause decrease in blood pressure and increase in heart rate requiring more myocardial oxygen consumption with risk of arrhythmias. Milrinone effect is bidirectional with increase in cardiac contractility, decrease in pulmonary vascular resistance, and vasodilation reducing afterload thus improving pumping [20]. Levosimendan is an inotrope which improves cardiac contractility without concomitantly increasing myocyte oxygen consumption. It has been shown by REVIVE II study to confer early additional benefit in addition to standard therapy in ADHF patients, but it is yet to be approved in the USA due to a possible trend towards increased mortality [2].

5) Vasopressors/*B*-Blockers/ACEIs

Use of vasopressors is mostly for HFpEF patients with severe ADHF and hypotension or signs of shock. Levophed and dopamine are commonly used. HF-LBP makes up about 15-25% of HF patients and management is challenging as medications that improve symptoms and mortality also reduce blood pressure. It is associated with higher in hospital and post discharge mortality [21]. Consider possibility of acute mitral regurgitation (MR) or aortic regurgitation (AR), or aortic dissection in this patient group. They may need emergent surgical intervention. Obtaining immediate echocardiography and invasive monitoring can be helpful. *B*-blockers should be continued only for chronic users in minimal decompensation and stable vitals (OPTIMIZE-HF). The same goes for ACEIs, in the absence of contraindications like hypotension, acute kidney injury and hyperkalemia. Some increases in creatinine should be tolerated in patients on ACEIs as their role in delaying progression and death in HF is undeniable [3]. Continued use should be balanced with need for diuresis and patient's hemodynamic status. Both *B*-blockers and ACEIs should not be initiated for the first time in the acute phase of management.

6) Circulatory assist devices

These devices are reserved for patients who are refractory to optimal medical management. They include counterpulsation devices (intra-aortic balloon pump and non invasive devices), cardio-pulmonary assist devices (veno-arterial extracorporeal membrane oxygenation - ECMO), and left ventricular assist devices - LVADs (heart mates, impellas) [22]. LVADs have been shown to both prevent further maladaptive remodeling and to induce reverse cardiac remodeling [23]. They are used mainly for transition to cardiac transplant although recently have been used as destination therapy for people who do not qualify for transplant.

7) Natriuretic peptides

BNP is secreted by the heart. Its serum level increases with age, is higher in women, and lower in obese. Not all symptomatic HF patients have high levels, and not all asymptomatic patients have low levels. It induces vasodilation, increase sodium excretion in urine, and suppresses RAAS and SNS [17]. These effects are however attenuated in advanced HF with down-regulation of BNP receptors. Nesiritide (a natriuretic peptide) was shown to be useful in VMAC study as it reduces PCWP, but there are concerns for WRF with hypotension and activation of RAAS/SNS. The ASCEND-HF trial did not show any clear benefit, but reported no WRF. Its use is still controversial. TRUE-AHF trial for evaluation of the efficacy and safety of Ularitide (another natriuretic peptide) on clinical status and mortality outcomes of patients with AHF is currently still recruiting [24].

AT DISCHARGE

Patients should be discharged on appropriate guideline determined medical therapy (GDMT) [25].

Diuretics: For HF with fluid retention, provides symptomatic benefit.

ACEIs: These became standard of care in HFrEF following survival benefits trials like CONSENSUS and SOLVD. They prevent remodeling. Start at low dose and titrate as tolerated. ACEIs can be safely used in most patients with chronic kidney disease (CKD). According to KDOQI guidelines [26], most common cause of acute WRF in CKD is volume depletion with high doses and concomitant diuretic or NSAID use. ACEIs should not be stopped unless Cr is

>30% above baseline or hyperkalemia >5.6mg/dl. In PARADIGM-HF trial, a novel agent - LCZ696 (a dual inhibitor of angiotensin II receptor and Neprilysin) was found to be superior to Enalapril in reducing the risks of death and of hospitalization for HF [27]. This may prove to be a major advancement in chronic HF regimen in about a decade. Other trials are currently investigating the safety and tolerability of this new agent.

ARBs: For patient intolerant to ACEI. Although the CHARM-added trial showed some increased reduction in HF mortality and hospitalization in combining candesartan with ACEIs, routine combination is not recommended and may be harmful.

B-blockers: Mainly carvedilol, metoprolol and bisoprolol. The COMET trial results favored the use of carvedilol over metoprolol. They became standard of care in HFrEF following results of trials like CIBIC-II, MERIT-HF and COPERNICUS. They were shown to reduce mortality, encourage remodeling, and may provide some symptomatic relief. *B*-blockers should be started for all stable patients at low dose and titrated as tolerated.

Aldosterone receptor antagonists: Recommended for NYHA 2- 4 with EF 35% or less, or following MI with EF 40% or less. They have been shown to lower the incidence of sudden cardiac death (SCD) and to reduce proteinuria. Eplerenone was shown to lower total mortality in early HF in the EMPHASIS-HF trial. The EPHESUS trial revealed that its benefit following acute myocardial infarction (MI) is limited to administration within 3 to 6 days post-MI [28].

Hydralazine and isosorbide dinitrate: For intolerance to ACEI and ARBS, and for African Americans with HFrEF NYHA 3-4 on GDMT. The combination has been shown to improve survival in studies like V-HeFT trail.

Digoxin: This was shown to reduce hospitalization rate by the DIG trial in HFrEF patients. It however did not impact mortality and hence is used mostly for symptomatic treatment.

Anticoagulation: For HF patients with atrial fibrillation and additional risk factor for cardio-embolic stroke.

Long-term use of ACEI/ARBs and B-blockers in HFpEF has not been shown to provide the same benefit as in patients with HFrEF. A recent study in 2014 suggested a possible benefit with *B*-blockers in lowering all-cause mortality but not with combined all-cause mortality or HF hospitalization in patients with HFpEF [29]. The efficacy of aldosterone antagonist therapy in this population is still under investigation. The TOPCAT trial reported small reduction in hospitalization in patient with HFpEF, but no reduction in HF mortality and events.

CHRONIC MANAGMENT

The goal is to prevent remodeling or sustain reverse remodeling, and to prevent death. Reverse remodeling may be spontaneous, but is more commonly achieved by medical, device based or surgical therapies, e.g. B-blockers and ACEIs, revascularization, cardiac resynchronization therapy, valve surgery. Optimizing GDMT is first step. The 2 main causes of death in HF patients are SCD (arrhythmic) and progressive pump failure.

1) Implantable Cardioverter Defibrillation (ICD) has been shown to prevent SCD. This was demonstrated in the MADIT trials and DEFINITE trial in patients with HFrEF. Cardiac Resynchronization Therapy (CRT) reduces symptoms, hospitalizations, and improves survival. A summary of the criteria for their use are shown in Table **4** [1].

2) Wearable Cardioverter-Defibrillator (WCD): This is a device worn externally like a vest with the capability of detection and defibrillation of ventricular tachycardia or fibrillation to prevent SCD. It is mostly employed when an ICD is temporarily required or implantation needs to be deferred. It has been shown to be equally as effective as an ICD when used properly with comparable inappropriate shock rates, but has major limitations such as lack of pacemaker functionality, the requirement for patient interaction and compliance, and potential discomfort due to the size and weight of the device [30].

3) Cardiac transplant: This is usually last resort but should be considered early. The ability to estimate prognosis is very important in the selection process. In the absence of contraindications, NYHA 4 patients refractory to maximum

Table 4. A summary of indications for ICD and CRT.

Indications for Implantable Cardioverter Defibrillation (ICD)
Ischemic heart disease, EF ≤30%, NYHA 1, for primary prevention
NYHA 2 or 3, EF <35%, at least 40 days post-MI and >3 months following revascularization
Non-ischemic dilated cardiomyopathy, EF ≤35%, and NYHA 2 or 3, for primary prevention, after 3 months of guideline determined medical therapy
Ambulatory patients with NYHA 4, EF ≤35%, narrow QRS, who are awaiting cardiac transplantation outside the hospital, as a bridge to transplantation
Indications for Cardiac Resynchronization Therapy (CRT)
EF ≤35%, NYHA 3 or 4, and a QRS duration ≥120 ms, combined CRT-D device (biventricular pacing combined with an ICD) rather than an ICD alone. (MADIT-CRT trial suggests a more proactive approach)
Left bundle branch block, QRS duration ≥150 ms, and patients dependent upon ventricular pacing due to atrial-ventricular block have the strongest considerations

medical treatment with EF <20% and maximal oxygen uptake (peak VO2) <10-12 ml/kg/min after cardiac rehab, consistent on repeated measurements are eligible for transplant [31]. There are other indications besides these based on severity of cardiac events and comorbidities. Contraindications may be absolute or relative but generally are advanced age or excessive and life threatening comorbidities.

4) Palliative and hospice care: Palliative care should be an on-going conversation. Advance directives should be encouraged. The highest rate of hospitalizations and cumulative resource utilization in patients with HF occurs at the end of life [32]. Palliative care improves the quality of life and survival [33, 34]. It provides physical and emotional support for patients and their families, as death becomes perceived to be a normal process [33]. In addition, it decreases health care utilization and costs [35]. The decision should be based on patient and family needs, not just on estimated prognosis and cost. Hospice requires the patient to meet certain criteria. Referral guideline by Medicare hospice is NHYA 4 or 3 with other comorbidities, for whom maximal therapy is refractory or refused, with life expectancy of 6 months or less [36]. It may include intravenous inotrope and turning off implantable devices.

PROGNOSIS

Estimation of prognosis is a challenge in HF patients. It is not enough to just predict survival. Proactively Identifying patients at risk before the predicted decline and subsequent intervention will be ideal. In general, survival worsens with age, better in women, varies with cause (worse with ischemic etiology, and restrictive causes like amyloidosis, hemochromatosis, HIV infection, or doxorubicin toxicity). Other predictors of poor survival include NYHA class 3 or 4, peak VO2 <12ml/kg/min, EF<20%, elevated markers of inadequate tissue perfusion (troponin, BUN), hyponatremia, anemia and presence of cormobidities (especially diabetes mellitus, WRF, depression and COPD). Prognostic biomarkers with controversial clinical use and on-going trials include ST2-interleukin family (predictive of mortality), Cystatin C (marker of acute kidney injury during HF hospitalization), NT-proBNP (GUIDE IT-trial on-going), amongst others. Some useful prognostic models of death and readmissions that have been proven to be of benefit include the EFFECT, Seattle HF score and HF Survival Score. These supplement rather than replace clinical judgment [37].

STRATEGY TO REDUCE READMISSION

HF presents a huge economic burden with over 50% of the expenses from hospitalization. The Centers for Medicare and Medicaid Services financially penalize hospitals with higher than expected 30-day readmission rates for pneumonia, acute MI, and HF [38]. Ensuring adequate decongestion on admission prior to discharge is the first step in preventing readmissions. At discharge, proper disease management including discharge planning, patient education, and frequent outpatient assessment should ensure. Most of the patients may benefit from cardiac rehab programs [39]. More recently in 2014, CardioMEMS was approved for HF home monitoring and reduction of related hospitalizations for NYHA 3 as demonstrated by successful trials like the CHAMPION trial [40]. Phase four trials are currently on-going for this product.

CONCLUSION

This review has examined the management of ADHF using a multifaceted yet holistic approach. The different interventions have been discussed and the aim is to improve the patient's quality of life, adding life to years and not just years to lifespan. Health systems should also aim to properly manage HF as this will reduce the 30-day readmission rate after exacerbations which can reduce the cost implications of the condition.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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