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Medical Management of Heart Failure-Current Treatments and Review of the Latest Evidence

Review Article

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Abstract

Heart failure (HF) is a global concern due to an aging population and lifestyle changes. This abstract stresses the importance of left ventricular ejection fraction (LVEF) in HF and advocates early optimization of treatment with guideline-directed therapies. The 2022 AHA/ACC/HFSA guidelines propose a four-pillar approach supported by the STRONG HF trial. Trials like EMPULSE, DAPA-HF, and EMPEROR-Reduced show the promise of Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors in improving symptoms and overall survival. Combining angiotensin receptor-neprilysin inhibition, especially with sacubitril/valsartan (ARNI), proves superior to ACE inhibition alone, as in the PARADIGM-HF trial.

Beta-blockers (MERIT-HF, COPERNICUS) and aldosterone receptor antagonists (RALES) effectively alleviate symptoms and reduce mortality. Digoxin, while not significantly impacting mortality, slightly reduces hospitalization rates, per the DIG trial and a meta-analysis. Ivabradine, from the SHIFT trial, is beneficial in reducing cardiovascular mortality and HF hospitalization, especially in symptomatic HFrEF patients. Diuretics, class I for symptom improvement, reduce death risk and HF symptoms, supported by a meta-analysis. HF specialist nurses, as in the ETIFIC study, play a crucial role, achieving higher drug doses, reducing adverse events, and lowering hospitalizations. Community care and nurse-led clinics, backed by meta-analyses, cost-effectively reduce hospital stay days.

Abbreviations: HF: Heart Failure; LVEF: Left Ventricular Ejection Fraction; SGLT2: Sodium-Glucose Cotransporter 2; CVDs: Cardiovascular Diseases; HFREF: Heart Failure With Reduced Ejection Fraction; HFPEF: Heart Failure With Preserved Ejection Fraction; GDMTs: Guideline-Directed Medical Therapies; RAAS: Renin-Angiotensin-Aldosterone System; ACEI: Angiotensin-Converting Enzyme Inhibitor; OMT: Optimal Medical Therapy; ARNI: Angiotensin Receptor-Neprilysin Inhibitor; SGLTS2I: Sodium-Glucose Cotransporter 2 Inhibitor

Introduction

Heart failure (HF) is characterized by abnormalities of structure therefore affecting function and the ability of the heart to effectively pump blood leading to characteristic symptoms and clinical signs [1]. Despite significant progress in contemporary cardiology, HF will continue to be a significant global health concern in the coming decades [2]. As the average age of the population increases along with changes in lifestyle there has been a greater occurrence of cardiovascular diseases (CVDs) worldwide with HF being no exception on this trend

[3]. Although there are various definitions of HF, left ventricular ejection fraction (LVEF) has commonly been regarded as the fundamental element in diagnosing, characterizing, predicting outcomes, and selecting treatments for HF [4]. This classification therefore includes heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF) [3]. Early optimization of treatment using guideline-directed medical therapies (GDMTs) in individuals with HF is imperative, avoiding hospital readmission, enhancing quality of life and improving survival. [5].

The 2022 AHA/ACC/HFSA guidelines for HF management have provided a new approach for the treatment of HF [6]. The guidelines stress the importance of prompt initiation of four primary treatment pillars, which include an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor-neprilysin inhibitor, a cardioselective beta blocker, a mineralocorticoid receptor antagonist, and a sodium-glucose cotransporter 2 inhibitor (SGLTS2i) which works by modulating the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. The benefit of the above-mentioned approach has been confirmed by the STRONG HF (safety, tolerability, and efficacy of uptitration of GDMTs for acute HF) which was a randomized, multi-centre, open-label clinical trial which indicates that aggressive treatment approach involving prompt initiation of guideline-recommended medications and frequent monitoring following a hospitalization for acute HF led to symptom alleviation, enhanced quality of life and a decreased risk of all-cause mortality of HF readmission within 180 days [7].

Sodium -Glucose Cotransporter 2 (SGLT2) Inhibitors

Sodium- Glucose cotransporter 2 (SGLT2) inhibitors are emerging as a primary therapy for individuals dealing with cardio-renal conditions [8]. Several studies have shown the benefits of starting patients on SGLT2 inhibitors. The EMPULSE trial [9] indicates that starting empagliflozin in patients admitted for acute HF provides clinical benefits, irrespective of their initial symptom severity. It improved symptoms, reduced physical limitations, and improved the quality of life, with positive effects noticeable as early as 15 days and sustained for up to 90 days. The DAPA-HF trial studied the prolonged impact of dapagliflozin, an SGLT2 inhibitor, in comparison to a placebo when added to optimal medical therapy (OMT), in terms of morbidity and mortality in ambulatory HFrEF patients [10]. Dapagliflozin not only lowered the risk of cardiovascular death and HF exacerbation, but also enhanced symptoms, physical capabilities, and quality of life in individuals with HFrEF. Additionally, it increased the number of patients who saw noticeable improvements in their health status, ranging from small to large improvements, and these effects were clinically significant. Moreover, in the EMPEROR-Reduced trial for individuals with HFrEF, empagliflozin decreased the risk and overall occurrences of both inpatient and outpatient worsening HF events [11]. These advantages were noticeable shortly after treatment initiation and remained consistent throughout the double-blind therapy period.

Angiotensin-Converting Enzyme Inhibitor (ACEI) or an Angiotensin Receptor-Neprilysin Inhibitor (ARNI)

Recent studies have demonstrated that combining angiotensin receptor-neprilysin inhibition is more effective than using ACE inhibition alone in reducing the likelihood of death and hospitalization due to HF [12]. In the PARADIGM-HF trial, sacubitril/valsartan, an ARNI, demonstrated its superiority over enalapril in reducing hospitalizations from worsening HF, cardiovascular mortality, and all-cause mortality in patients with HFrEF with a LVEF of less than 35% [6]. As the initial class of medications proven to decrease both mortality and morbidity in patients with HF, ACEi were recommended in all patients unless contraindicated or not tolerated [13]. To assess the impact of the angiotensin-converting enzyme inhibitor, enalapril (2.5 to 40mg/day), on the prognosis of severe congestive heart failure, characterized by New York Heart Association (NYHA) functional class IV, the CONSENSUS investigators conducted a double-blind study [14]. In this study, 253 patients were randomly assigned to either receive placebo (n=126) or enalapril (n=127), in addition to conventional treatment, including vasodilators [14]. The enalapril group demonstrated a notable improvement in New York Heart Association classification, coupled with a decrease in heart size and a decrease need for additional heart failure medication [14]. This leads to the conclusion that incorporating enalapril into the standard treatment for individuals with severe congestive heart failure can result in the reduction in mortality and an improvement in patient symptoms [14].

A prospective systematic literature review, conducted by Flather MD, et al. in 2000, examined the effectiveness of ACEi in patients with left ventricular dysfunction or HF, obtaining the data from individual patients participating in 5 long-term randomized trials [15].This study indicates that the use of ACEi led to reduction in the rates of mortality, myocardial infarction, and hospitalization for HF in patients with left-ventricular dysfunction or HF, regardless of whether they had experienced a recent myocardial infarction.

The SOLVE researchers investigated the impact of an angiotensin-converting enzyme inhibitor, enalapril, on mortality and hospitalization in individuals with chronic heart failure and left ventricular ejection fraction of less than or equal 35%. It was a randomized, double-blind, and placebo-controlled trial, with participants being followed up for an average of 41.4 months [16]. This research illustrated a notable decrease in mortality and hospitalizations related to congestive heart failure among patients who received treatment with an angiotensin-converting-enzyme inhibitor, specifically enalapril, in conjunction with conventional heart failure therapy [16].

Beta-Blockers

One of the fundamental pathophysiological abnormalities in individuals with chronic heart failure is the activation of the sympathetic nervous system [17] and the severity of HF correlates with elevated levels of circulating catecholamines in patients [18].Hence, several clinical trials involving various beta-blockers have demonstrated their ability to alleviate symptoms, improve left ventricular systolic function, and increase functional capacity in patients [17]. The MERIT-HF trial was conducted as a randomized, double-blind, placebo-controlled study, preceded by a single-blind, 2-week placebo run-in period. The objective of the study was to evaluate the impact of β1-blockade on hospitalization frequency, symptoms, and quality of life in patients with heart failure [19].

This study illustrated that metoprolol CR/XL, a once-daily β1-blocker administered in addition to conventional therapy for patients with chronic heart failure, resulted in enhanced survival, decreased hospitalization rates for worsening heart failure, and improvements in symptoms and overall well-being [19]. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial was conducted to assess the impact of the α-, β-adrenergic blocker carvedilol on patients with severe chronic heart failure [20]. The study indicates that in patients with normal fluid balance experiencing symptoms at rest or with minimal exertion, the incorporation of carvedilol into standard therapy mitigates the severity of heart failure and lowers the risk of clinical worsening, hospitalization, and other significant adverse clinical events [20].

Aldosterone plays a significant role in the pathophysiology of HF by promoting sodium retention, causing the loss of magnesium and potassium, activating the sympathetic system, inhibiting the parasympathetic system, inducing myocardial and vascular fibrosis, disrupting

baroreceptor function, and impairing arterial compliance [21]. The researchers in the RALES study examined the hypothesis that blocking the aldosterone production with an aldosterone receptor antagonist would lead to reductions in mortality and morbidity among patients with HF [22]. Their findings indicate that the administration of spironolactone in addition to other ACE inhibitors reduced the risk of death from all causes, death specifically from cardiac causes, hospitalization related to cardiac causes, and the combined endpoint of death from cardiac causes [21]. The study was finished early thanks to the overwhelming benefits of the treatment option in the study group. The EPHESUS double-blind study evaluated the effect of eplerenone on patient with acute myocardial infarction with left ventricular dysfunction and signs of heart failure [23]. The study showed the addition of eplerenone to standard therapy reduced morbidity and mortality versus the placebo group, with a 15% reduction in total mortality.

Digoxin

Digoxin is a cardiac glycoside, that acts as a inhibitor of the inhibits the Na-K ATPase enzyme in order to slow heart rate and is used in HF patients and patients with arrythmias such as Atrial Fibrillation [6]. According to the DIG trial, administration of Digoxin in patients with HfpEF, did not affect mortality rates, however a slight change in reduction of hospitalization rate was noted [24]. The study was conducted on 988 HFpEF patients in sinus rhythm, of which 492 were prescribed placebo and 496 were assigned to placebo. It was noted that hospitalization due to HF or death occurred in 18% of patients in the Digoxin group and 23% of patients in the placebo group at 2 years post-randomization. A meta-analysis was conducted by Ziff et al in 2015, and it looked at administration of Digoxin to HF patients with ejection fraction below 35% [25].The results of the 52 systemic reviews analyzed by Ziff, et al. supported the conclusion from the trial abovementioned, in the sense that Digoxin did not change patient mortality, but a very small reduction in hospital admission was observed. Although it is classed as an agent that can be used for HfrEF by the 2021 Esc guidelines to reduce hospitalization, the meta-analysis showed that Digoxin has neutral effects and did not improve outcomes in HF patients. Furthermore, there have not been enough studies to assess its effect on patients with HF who are concomitantly on beta blockers [6].

Isosorbide Dinitrate and Hydralazine

Some studies have shown there may be differences in metabolism, and hence difference in the efficacy of ACE inhibitors in afro-caribbean people when compared to caucasians. The A-HeFT study compared the addition of isosorbide dinitrate and hydralazine as a single pill, compared to placebo group for black patients with advanced heart failure [26]. This study was terminated early due to significantly higher mortality rates in the placebo group, showing the clear benefits of this medication for this specific group of patients.

Ivabradine

Ivabradine is a specific and selective If-channel inhibitor whose effects consist of reducing heart rate in order to reduce cardiovascular morbidity. It is recommended for use in patients with HfrEF in sinus rhythm and NYHA II-IV, in order to reduce risk of HF hospitalization and CV death. In the SHIFT trial, a randomised, double-blind, placebo-controlled trial; 6558 patients with HfrEF in sinus rhythm with a heart rate greater than 70bpm were assessed [27]. At the follow-up, it was noted that 5% more patients from placebo group were hospitalized than the study group. The results of the SHIFT trial showed that Ivabradine lowered the combined endpoint of CV mortality and HF hospitalizaion in the study group, proving the importance of heart rate reduction in HF in order to enhance clinical outcomes. Analyzing the patient data from the SHIFT study, Michale Bohm, et al. observed that Ivabradine has the best outcomes in symptomatic patients with HfrEF in sinus rhythm with a heart rate of 75bpm or above [28]. It was showed that Ivabradine offers a survival benefit in this group and succeeds in achieving a heart rate lowering by >10bpm in the study group.

Diuretics

Diuretics are considered a class I drug for symptom improvement in HfrEF patients with signs of congestion, as it enhances exercise capacity and lowers HF hospitalizations [6]. Evidence regarding the use of diuretics and their effects on mortality and morbidity in HF patients is lacking and constitutes a potential starting point for further study. However, it should be noted that the majority of trials conducted to test the effects of the top disease-modifying treatments for HF have been conducted on patients who were on diuretics. A meta-analysis from Faris, et al. conducted in 2002, looked at the use of loop and thiazide diuretics in patients with HfrEF with symptoms of congestion, by analysing 18 trials. The results showed that there was a reduction in the risk of death and worsening of HF symptoms, as well as an improvement in exercise capacity in the study groups compared to the placebo group [29].

HF Specialist Nurses and Community Care Evidence

Importance should also be attributed to the delivery of HF care in addition to the optimization of HF medical therapies. It is widely recognised that HF nurses are a valuable part in the delivery of quality care and improvement on management and monitoring of HF patients [6,30]. In the ETIFIC study, a multicenter noninferiority randomised controlled open label trial, it was demonstrated that compared to cardiologist- delivered drug titration, nurses managed to achieve a 15% higher doses of beta blocker and ACEi regarding target doses. It was also observed that there were fewer drug use related adverse events and hospitalizations in patients who were seen by a HF nurse specialist [31].

A reduction in hospital readmission was noted in services that provide follow-up to HF patients via HF nurses, highlighting that specialist nurse-led clinics and telemonitoring are a cost-effective way of improving HF quality of care. It was also showed that administration of intravenous diuretics to HF patients by nurse specialists led to a 77% cost reduction as it was conducted in a community setting rather than in a hospital setting [32]. A meta analysis conducted by the medical advisory secretariat of Ontario in 2009, showed that HF patients receiving care in the community as well, had a reduction in the number of hospital stay days compared to patients only receiving doctor led care. Thus, it should be widely recognised that community care and HF specialist nurses play a key role in improving the management of HF patients around the world [33].

Conclusion

To summarize, a comprehensive approach involving early initiation of GDMTs, including SGLT2 inhibitors, angiotensin receptor-neprilysin inhibitors, ACEi, beta-blockers, diuretics, ivabradine, digoxin, aldosterone receptor antagonists and isosorbide dinitrate and hydralazine where appropriate is crucial for effectively managing HF, improving patient outcomes, and addressing the ongoing global health concern. Delivery of quality of care is equaly important to improving HF treatments, thus implementation of HF specialist nurses in combincation with MDT approaches should be considered globally, in order to reduce hospitalziation days, inequalities of care and costs.

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