International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 6 | Nov – Dec 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i6.30

# Chronic Heart Failure Management: A Literature Review of Guideline-Directed Medical Therapy

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**ABSTRACT**

Chronic heart failure (CHF) is a progressive condition with high morbidity and mortality rates worldwide. Guideline-Directed Medical Therapy (GDMT) offers evidence-based guidelines for treating CHF, including pharmacological therapies that have been shown to improve patient outcomes. Despite its benefits, GDMT implementation varies across regions due to factors such as patient non-adherence, healthcare provider gaps, and systemic challenges. This literature review summarizes the current understanding of GDMT, focusing on its components, clinical efficacy, implementation challenges, and strategies to enhance adherence. This literature was conducted using databases such as Google Scholar, PubMed, and ScienceDirect using keywords relevant to chronic heart failure and guideline-directed medical therapy. The review highlights the importance of collaborative efforts to bridge the gap between guideline recommendations and practices, especially in resource-constrained settings, in order to maximize care for CHF patients.

***Keywords:*** chronic heart failure; guideline-directed medical therapy; barriers; strategies.

## INTRODUCTION

Chronic heart failure is a progressive syndrome or an episode of worsening symptoms (such as dyspnea, ankle swelling, and fatigue) and signs (such as elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). These symptoms are brought on by a structural and/or functional cardiac abnormality, which results in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [1]. It is a leading cause of morbidity and mortality worldwide, with prevalence increasing as populations age, and cardiovascular risk factors rise [2]. These occurrences are connected with a worse quality of life, a higher risk of hospitalization and mortality, and a major burden on healthcare resources [3]. According to the Global Burden of Disease 2014-2019 and the Institute for Health Metrics and Evaluation (IHME), heart disease is the leading cause of death in Indonesia. Because individuals with acute heart failure might develop chronic heart failure, the prevalence of heart failure itself is rising. According to data from the World Health Organization (WHO), rising smoking rates, obesity rates, dyslipidemia, and diabetes is all contributing factors to the rise in heart failure cases throughout the globe, including in Asia. Heart failure incidence also rises with age [4]. Dyspnea, exhaustion, and fluid retention are typically the first signs of heart failure in patients. Furthermore, insomnia, restlessness, and disorientation may be present along with further reduced cardiac output. Even with severe chronic heart failure, gradual weight loss can occur [5].

Other than the above, there are also factors contributing namely physical stress. The American Heart Association [6] lists a number of physical stress symptoms, including difficulty sleeping, exhaustion, diarrhea, and strain in the shoulders and neck. Excessive stress is the most prevalent cause contributing to chronic illness. It is crucial to pay attention to stresses and figure out efficient strategies to handle them since the body is always under pressure as it heals. So, it is crucial to identify the stressor's cause and develop strategies for managing it successfully. Therapy for chronic heart failure patients is conducted to make patients feel more comfortable performing various physical activities,

activities, which can enhance quality of life and extend life expectancy [7]. The strategy focuses on three areas: treating illnesses that lead to CHF, removing risk factors that can make CHF worse, and treating chronic heart failure itself [5]. A previous study about patient profiling in heart failure for tailoring medical therapy reported that therapy implementation in HF is low despite guideline recommendations and available data [8].

Initiating guideline-directed medical therapy (GDMT) might have a significant role in treating chronic heart failure. GDMT is the cornerstone of managing CHF, according to international guidelines from the American Heart Association (AHA), the European Society of Cardiology (ESC), and others. Pharmacological therapies such as ACE inhibitors, beta-blockers, and newer medicines like ARNI and SGLT2 inhibitors have been found to reduce disease progression and improve survival in CHF patients [9].

However, its use in clinical practice varies significantly among regions, depending on demographics, healthcare system, and socioeconomic characteristics [10]. This study focuses on the fundamental components of GDMT, its clinical benefits, and its challenges in gaining general adherence.

## METHODS

A comprehensive literature search was conducted to identify relevant studies, reviews, and guidelines on GDMT for CHF. Sources included PubMed, Scopus, Google Scholar, and guideline documents from major cardiovascular organizations to find published articles, journals, and books. The review focused on defining GDMT, its pharmacological components, and barriers to implementation. The search is done by using keywords like “chronic heart failure” and “guideline-directed medical therapy” also “Management of chronic heart failure with Guideline-directed medical therapy” with a total of 33 articles used for this literature review.

## RESULTS AND DISCUSSION

### Chronic Heart Failure

Heart failure is a clinical syndrome caused by structural and functional myocardial defects that impair ventricular filling or blood ejection. Myocardial dysfunction, whether systolic, diastolic, or both, is the most frequent cause of HF. However, problems in heart rhythm and conduction as well as disease of the valves, pericardium, and endocardium can also cause or contribute to HF. Due to the lack of a definite boundary for ventricular dysfunction, a straightforward objective definition to establish the limits of chronic heart failure is difficult to achieve. For practical purposes, chronic heart failure is defined as a complicated clinical illness characterized by symptoms of heart failure in the form of rigidity, fatigue at rest or during activity, edema, and objective signs of cardiac dysfunction at rest [11] [12].

Chronic heart failure differs from acute heart failure in that CHF refers to heart failure that is comparatively more stable but has a symptomatic state, which is sometimes referred to as compensated heart failure. The specific conditions that lead to a person with heart failure progressing from a compensated to a decompensated situation vary, are not completely understood, and can take days to weeks. Due to reduced cardiac output and neurological impulses from injured and under-perfused cardiac muscle, chronic heart failure may cause fatigue. Fluid buildup may ensue, resulting in pulmonary congestion and peripheral edema, which will progress to congestive heart failure [13].

- *Epidemiology*

According to a report from the WHO (World Health Organization), cardiovascular disorders killed 17.5 million people worldwide, and more than 75% of individuals suffer from the disease. Nations with middle and low incomes are most impacted by cardiovascular disease. As per the 2021 American Heart Association Statistical Update, 6 million people, or 1.8% of the US population, are estimated to have HF. In accordance with other estimates, HF affects 1.5% to 1.9% of people in the United States and Canada, also 1% to 2% of people in Europe. The prevalence of HF is much higher in older age groups, reaching 4.3% among people 65 to 70 years old. Black people with heart failure, particularly women, have a disproportionately high excess prevalence of disability [14].

- *Etiology*

CHF can be brought on by a variety of systemic disorders, genetic abnormalities, and cardiac problems. CHF patients may have several etiologies. The Global Burden of Disease Study revealed that there are 17 major etiologies for HF. Four underlying diseases, including ischemic heart disease, chronic obstructive pulmonary disease, hypertensive heart disease, and rheumatic heart disease, represent more than two-thirds of all cases of HF. Other structural causes of CHF include myocardial infarction, valvular heart disease, uncontrolled arrhythmia, myocarditis, and congenital heart disease. Diastolic heart failure with impaired ventricular filling can be caused by restrictive cardiomyopathies and constrictive pericarditis, in addition to the etiologies identified above [2] [15].

- *Clinical Manifestation*

The most common complaint in the distribution based on the patient's primary complaint was shortness of breath. This is in line with a study that explains why shortness of breath symptoms are present in 93% of HF patients [16]. In another study that conducted a retrospective study of elderly patients with HF due to mitral valve stenosis, it was discovered that all of these patients complained of shortness of breath as the main symptom [17]. The findings of this study are also supported by another research, which explains that shortness of breath and chest pain, with or without

trigger factors are common symptoms in the population of cardiovascular disease (ischemic heart disease and HF) patients that have been studied [18]. To further categorize shortness of breath, it must be determined if it is acute or chronic, whether it is caused by exertion, postural changes (orthopnea), or both. Chest pain, palpitations, anorexia, and fatigue are a few more HF symptoms that are frequently noticed. Some individuals could show up with a recumbent cough that could be caused by orthopnea [2].

• *Pathophysiology*

Vessel remodeling (LV remodeling) is a process where the heart undergoes molecular, cellular, and structural changes due to damage. This process is part of the body's compensatory mechanism to maintain arterial pressure and vital organ perfusion. In the early stages of heart failure, the body uses various mechanisms to maintain cardiac output and meet systemic demands. These include the Frank-Starling mechanism, which increases end-diastolic pressure, causing cardiac muscle fibers to stretch and increasing the volume of cardiac chambers. However, as dilatation progresses, ventricular wall tension rises, increasing the need for oxygen in the myocardium. Over time, the weakening myocardium can no longer pump enough blood to fulfill the body's demands, leading to decompensated heart failure. Additionally, the neurohumoral system, including the release of norepinephrine, renin-angiotensin-aldosterone, and atrial natriuretic peptide, is activated [13]

• *Comorbidities*

According to a study, the most prevalent co-morbidities in studies that provided data included hypertension (63%) ischemic heart disease (44%), hyperlipidemia (48%), diabetes (33%), chronic renal disease (25%), and atrial fibrillation (25%). Comorbidities like hypertension, atrial fibrillation, and chronic renal disease became increasingly prevalent with time, whereas smoking became less prevalent in HFrEF studies [19]. Comorbidities in chronic HF are significant for numerous reasons. First, comorbidities may interfere with optimum HF therapy (e.g., poor RAAS inhibitor dose in patients with renal impairment and/or hyperkalemia, or beta-blockers in patients with severe asthma). Second, the pharmaceutical therapy of chronic HF and comorbidities may interact (e.g., beta-adrenergic agonists for chronic obstructive pulmonary disease and beta-blockers for chronic HF) [20].

**Guideline-directed Medical Therapy**

Guideline-directed medical therapy (GDMT), as demonstrated by a number of major randomized clinical studies carried out in stable outpatients, reduced mortality and morbidity in heart failure patients. We concentrate on beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs)/ Angiotensin Receptor-Neprilysin Inhibitors (ARNI), mineralocorticoid receptor antagonists (MRAs), and Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i) as these drugs serve as the basis of the majority of GDMT regimens and are appropriate for a large number of patients with HF. In the Kaplan-Meier survival analysis, patients in the GDMT group had the lowest mortality, whereas those in the no GDMT group had the worst outcomes [21] [22]. Additionally, a study shows that GDMT was associated with decreased all-cause mortality in elderly patients with HFrEF, prescribing beta-blockers or RAAS inhibitors only was also associated with decreased all-cause mortality when compared to no GDMT, and the effect of GDMT also appeared to be effective for decreasing all-cause mortality in very elderly patients (age 80 years) [22].

• *Angiotensin-converting Enzyme Inhibitor (ACE-I)*

ACE-I or inhibition of renin-angiotensin-aldosterone system (RAAS) that regulates blood pressure, plasma volume, and electrolyte balance in response to renal perfusion should be administered to all patients with symptomatic heart failure and left ventricular ejection fraction unless contraindicated [23]. Patients with heart failure receive ACE-I as their first-line therapy [5]. ACE enhances ventricular function and quality of life, minimizes hospitalizations for increasing heart failure, and boosts survival rates with an indication that is good for patients with LVEF < 40% (use with beta blocker). ACE-I can infrequently induce renal dysfunction, hyperkalemia, symptomatic hypotension, cough, and (rarely) angioedema. As a result, only individuals with sufficient renal function and appropriate potassium levels are given ACE-I [4].

• *Angiotensin Receptor Blockers (ARB)*

ARB was created on the premise that angiotensin II synthesis continues in the midst of ACE inhibition, although via other enzyme routes. ARBs suppress the renin-angiotensin-aldosterone system (RAAS) by preventing angiotensin II type I from binding to its receptor, causing vasoconstriction and preventing the production of aldosterone. Similar to ACE inhibitors, ARBs should be used with caution to patients who have low systemic blood pressure, renal failure, or excessive serum potassium (>5.0 mEq/L). However, ARBs do not block kininase and are linked with a significantly lower incidence of cough and angioedema than ACE inhibitors. ARBs have been proven in RCTs to reduce morbidity and mortality, particularly in ACE inhibitor-intolerant patients, and to trigger hemodynamic, neurohormonal, and clinical effects similar to that expected following interference with the renin-angiotensin system [4].

• *Angiotensin Receptor-Neprilysin Inhibitor (ARNI)*

ARNI, which is a molecular combination of valsartan and sacubitril, is an innovative drug that may also be used as a replacement for ACE-I/ARB in individuals who are still symptomatic at dosages of ACE-I/ARB, beta blocker, and MRA. Sacubitril is a neprilysin enzyme inhibitor that improves myocardial remodeling, diuresis, and natriuresis while also decreasing vasoconstriction, fluid, and salt retention. Sacubitril/valsartan is a combination of the neprilysin inhibitor sacubitril and the ARB valsartan.

However, angiotensin II is also a neprilysin substrate. Thus, the addition of an ARB to the neprilysin inhibitor is necessary to prevent activation of the RAAS [4] [24].

• *Beta Blocker*

Adrenergic neurohormones, which are part of the autonomic sympathetic nervous system's 'fight or flight' response, stimulate the heart. Adrenoreceptor blockade provides therapeutic advantages such as lowering afterload, decreasing heart rate, boosting myocardial perfusion, suppressing arrhythmias, and vasodilation, lowering renin excretion, and promoting cardiac remodeling [23]. Patients with HFrEF have been proven to benefit from the use of three beta-blockers: bisoprolol, sustained-release metoprolol (succinate), and carvedilol. These three agents all follow the same pathway: They all inhibit the β1-adrenergic receptor. In an attempt to make up for the decreased EF, HfrEF activates the RAAS and sympathetic system. This activation, though, could accelerate ventricular remodeling. These beta blockers stop the ventricular remodeling caused by activated RAAS and the sympathetic system by inhibiting β1 receptors. While metoprolol and bisoprolol are selective for the β1 receptor, carvedilol also inhibits the β2 and β1 receptors, resulting in vasodilation [24].

• *Mineralocorticoid Receptor Antagonist (MRA)*

MRA is advised for NYHA class II-IV HF patients with an EF of 35% or less, a glomerular filtration rate of at least 30 mL/min/1.73 m2, and a potassium level of 5.0 mEq/dL or below. Aldosterone is an endogenous steroid hormone that enhances sodium retention and accelerates magnesium/potassium loss. Aldosterone antagonists block collagen and matrix deposits which trigger myocardial fibrosis, vascular injury, and baroreceptor dysfunction. MRAs may decrease HF progression and prevent or reverse cardiac remodeling and arrhythmia development. Moreover, although ACEI and MRA are frequently administered together to individuals with HFrEF, doing so might result in hyperkalemia, which can be fatal [24].

• *Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i)*

SGLT2 inhibitors are a new class of medications recommended for the treatment of patients with HFrEF, whether they have diabetes or not. These drugs inhibit the renal glomerulus's proximal tubules from reabsorbing water and glucose. Although initially utilized as a diabetes medication, RCTs involving HF patients have progressively supported their use as a primary therapy for HFrEF, regardless of diabetes status, along with renin-angiotensin inhibitors, beta-blockers, and MRA [25]. The DAPA-HF and EMPEROR-Reduced trials demonstrated that SGLT2i (dapagliflozin and empagliflozin, respectively) improved outcomes over placebo. Patients included had symptomatic chronic HFrEF and were already taking GDMT. According to the trials, SGLT2i decreased the risk of cardiovascular death or heart failure hospitalization by about 25%, with a greater impact on HF hospitalization (30%). Dapagliflozin significantly reduced the risk of all-cause mortality by 17% and cardiovascular death by 18%. In a meta-analysis of both studies, empagliflozin did not significantly lower cardiovascular mortality [9].

**Barriers to GDMT Implementation**

Clinical and organizational barriers limit the effective implementation of GDMT in chronic heart failure therapy. One important issue is therapeutic inertia, which is defined as a delay or inability to initiate or optimize suggested therapies. Clinicians frequently see patients as clinically stable or at their maximum suitable therapeutic levels, even when additional titration or treatments could result in significant advantages. This hesitancy gets worse because of concerns about potential side effects or the difficulty of controlling comorbid conditions [26] [27]. In addition, general practitioners have less expert knowledge than cardiologists, which adds to inadequate management. General practitioners, who frequently work as primary care physicians, may lack a deep understanding of current recommendations of GDMT optimization, resulting in missed opportunities for intervention [28]. These issues get worse by limitations in the healthcare system, especially in countries with low or middle incomes with limited resources. Insufficient healthcare financing, restricted public reimbursement for newer medicines, limited access to crucial medications, and the lack of integrated care systems make it difficult to guarantee consistent GDMT implementation. These systemic challenges frequently result in differences in care, limiting many patients access to the entire range of recommended therapies. Addressing these challenges requires an integrated strategy that includes improved medical staff training, optimized healthcare regulations to promote equal access to treatment, and effective care coordination systems to guarantee that evidence-based therapies reach all eligible patients [29].

Patient-related barriers are complex and contribute significantly to the poor application of GDMT for chronic heart failure. The incidence of comorbidities, elderly age, and frailty in individuals with chronic heart failure provide a major problem. These variables make managing GDMT more difficult because multiple drugs are frequently necessary for a variety of medical conditions which raises the possibility of drug interactions and side effects. Drug intolerances and adverse effects including hypotension, renal failure, or hyperkalemia are frequent causes of patients' inability to take their prescribed dosages of essential drugs. The problem gets worse by non-adherence, which can be caused by a lack of awareness of the significance of therapy, fear of adverse effects, or the belief that symptom progress reduces the need for ongoing treatment [29] [30]. Socioeconomic factors remain a major barrier. Due to financial limitations, patients with low socioeconomic levels find it difficult to continue receiving continuous therapy; high prescription expenses are difficult for those without insurance coverage. Furthermore, these patients may have difficulty obtaining healthcare facilities, transportation, or regular follow-up consultations,

which limits efficient management. Poor adherence to medications is frequently a result of these socioeconomic disadvantages, and it is made worse by a lack of health literacy and inadequate patient education. In order to overcome these patient-related obstacles, specific strategies are needed, such as comprehensive patient education to increase awareness of the significance of GDMT, improved patient-provider communication, and modifications to legislation to make pharmaceuticals and medical services more affordable and easily accessible [29].

### Strategies to Overcome Barriers

A comprehensive strategy is needed for dealing with the barriers that prevent GDMT from being utilized successfully in chronic heart failure. Using interdisciplinary care teams, which include doctors, nurses, pharmacists, and other medical specialists, is a crucial way to improve GDMT adherence and results. These groups can be very helpful in helping patients with drug titration, monitoring for side effects, and providing ongoing support. Interdisciplinary teams help make sure that treatment plans are carried out effectively and consistently by assigning specific tasks such as patient education, medication adjustments, and follow-up care [31] [32]. The use of digital health solutions and technology in the treatment of heart failure is another potential approach. Clinicians may track patients' symptoms, medication adherence, and vital signs in real time via online monitoring programs that use mobile devices or telemonitoring platforms. This allows for quick therapy modifications. Additionally, by giving healthcare providers improved access to full patient data and decision-support tools, telemedicine and electronic health records (EHRs) improve patient monitoring and simplify the implementation of guidelines. In addition to improving clinical outcomes, these technological advances assist in reducing care gaps for patients in underserved or remote areas [33]. Furthermore, education and awareness strategies are critical for both healthcare providers and patients. Training programs that bring practitioners up to date on the latest GDMT recommendations and titration techniques can considerably reduce treatment inertia and boost confidence in dealing with complicated cases. Simultaneously, patient education programs focused on the importance of GDMT, minimizing side effects, and understanding long-term advantages can promote adherence to their treatment plans [27] [29].

## CONCLUSION

In conclusion, this review explores about management of heart failure with guideline-directed medical therapy and its challenges, also how to overcome them. GDMT is the cornerstone of chronic heart failure therapy, with significant decreases in morbidity, mortality, and hospitalization. Implementation is still inconsistent despite its demonstrated effectiveness because of organizational, clinical, and patient-related obstacles. In order to narrow the gap between guidelines and practice and eventually improve outcomes for patients with chronic heart failure, it is essential that these issues be addressed through interdisciplinary care teams, advances in technology, and educational programs.

## ACKNOWLEDGMENT

The author would like to thank all supervisors and various parties who have helped carry out this research well.

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