CONNECTICUT MEDICAL ASSISTANCE PROGRAM
DEPARTMENT OF SOCIAL SERVICES
&
KEPRO
QUARTERLY NEWSLETTER

Getting to the Heart of the Matter of Guideline Directed Medical Therapy (GDMT)[1]

Heart disease is a leading cause of chronic illness and morbidity in the United States.[1] During 2018, heart disease was listed as the leading cause of death in the U.S. with approximately 58% of those deaths attributable to Heart Failure (HF).[2,3] Similar to other chronic diseases, non-Hispanic black patients have the highest death rate per capita compared with other ethnic groups. According to the American Heart Association (AHA), approximately 6.2 million Americans (1.9%) were living with HF during 2020, a number that continues to grow annually.[2] During the previous one year of claims history, just over 2% of the Connecticut Medical Assistance Program population received a new or recurring diagnosis of HF, in line with national statistics.

HF is defined by structural changes to the heart which cause impaired functional ventricular filling and ejection of blood resulting in clinical disease presentation. While coronary artery disease (CAD) is the leading cause of HF, other causes include ischemic heart disease, myocardial infarction (MI), valvular heart disease, hypertension, atherosclerotic cardiovascular disease (CVD), diabetes, metabolic syndrome, obesity, exposure to cardiotoxic agents, genetics, family history, amyloidosis, autoimmune disorders, sarcoidosis, hemochromatosis, and thyroid disease. Risk factors for HF include smoking, substance abuse, poor diet, and physical inactivity. Signs and symptoms of HF can include edema, dyspnea, chronic coughing or wheezing, fatigue, increased heart rate, and exercise intolerance. HF can further present as episodic worsening of symptoms resulting in hospitalization and continued decline in health. To complicate matters, more than 85% of HF patients have two or more chronic comorbid disease states. It is important to recognize and manage these other chronic illnesses in addition to HF because they can directly influence one another.

The American College of Cardiology (ACC) and AHA have published guidance and recommendations for cardiovascular diseases since 1980, and in May of this year, the ACC/AHA and the Heart Failure Society of America (HFSA) published the 2022 Guideline for the Management of Heart Failure, updating the previously published 2013 and 2017 guidance.[1] There are three systems used to classify HF: Stages A-D (Figure 1), the New York Heart Association (NYHA) system, and measurement of left ventricular ejection fraction (LVEF).

In addition to the 4 stages of HF, the NYHA classification system is used to further categorize stages C and D of HF. NYHA characterizes symptoms and is used to predict patient mortality.

- NYHA functional class I – describes HF patients without limitation to their physical activity
- NYHA functional class II – describes patients who are comfortable at rest but have mild symptoms such as dyspnea, fatigue, and feeling lightheaded during regular activity.
- NYHA functional class III – describes patients who are comfortable at rest but have HF symptoms with less than typical activity.
- NYHA functional class IV – describes patients who are unable to carry out any physical activity without symptoms and also have symptoms at rest.

Stages A-D of heart failure and the NYHA classification system are universally accepted by the medical community and commonly referenced in guidelines, trials, and clinical practice; however, these classification systems are subjective, and interpretation of symptoms can vary case to case. Measurement of the left ventricular ejection fraction (LVEF) provides an objective tool that is used to further categorize, diagnose, and steer selection of pharmacologic treatment in HF patients (Table 1).

50% of HF patients have HF with preserved ejection fraction (HFpEF) which by definition is LVEF ≥ 50%. The remaining 50% of HF patients will either have

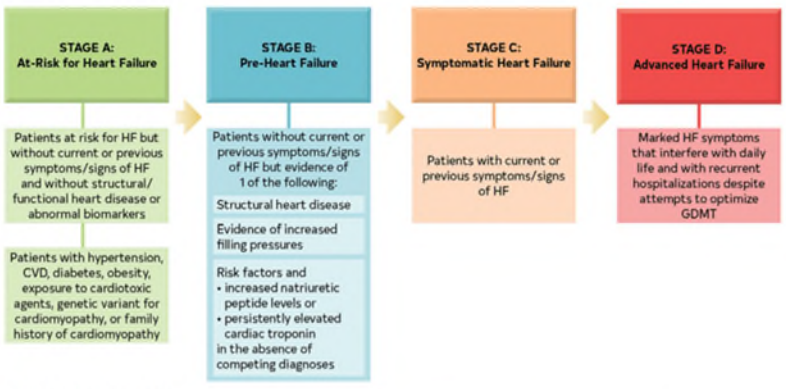

Figure 1. ACC/AHA Stages of HF
The ACC/AHA stages of HF are shown. ACC indicates American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; and HF, heart failure.

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HFmrEF with a LVEF of 41-49%, HFrEF with a LVEF ≤ 40%, or HFimpEF with a previous LVEF ≤ 40% and a follow-up measurement of LVEF ≥ 40%. It is important to note that poorer outcomes are predicted in patients who present with a significant reduction in LVEF over the course of their illness.

Patient history and physical exam are foundational and help to guide next steps of treatment. When assessing HF patients, the initial workup should not only include history and exam but also imaging, consideration of differential diagnoses, workup of other cardiac comorbidities, and assessment of congestion. Transthoracic echocardiogram (TTE) is the gold standard imaging technique used to determine cardiac structure and LVEF, guiding pharmacologic treatment. Determining the cause of HF is important, especially when considering differential diagnoses such as amyloidosis, sarcoidosis, hemochromatosis, hypo- or hyperthyroidism, etc. Utilizing traditional HF pharmacotherapy may not be effective or could worsen symptoms in patients with atypical causes and may require other disease specific treatments. Workup of cardiac comorbidities is also recommended as other chronic conditions have a direct effect on HF and vice versa. Additionally, assessment of patient congestion should be performed as this impacts patient quality of life and disease symptomatology.

Evidence-based treatment should be provided to all HF patients by a multidisciplinary team to address initiation of lifestyle modifications, self-care techniques, risk of hospitalization, prognosis, and HF specific education. Treatment of comorbid diseases, screening for mental health issues, addressing isolation and frailty, and ensuring patients are up to date on vaccines are also important aspects of care. Primary prevention is the main treatment approach for patients at risk for HF (stage A) or pre-HF (stage B), and initiation of Guideline Directed Medical Therapy (GDMT) is the cornerstone of treatment for many other HF patients.

Pharmacological Therapy for HF

Diuretics can and should be used to treat HF associated congestion at any stage of HF. The intent of diuretic therapy is to reduce fluid retention using the lowest possible dose. As needed therapy should be used in patients who present with congestion or edema. Maintenance therapy can be considered in patients who have recurrent congestion and fluid retention. Loop diuretics (bumetanide, furosemide, and torsemide) are the gold standard diuretic to be used initially, which work by inhibiting sodium and chloride reabsorption at the loop of Henle within the nephrons of the kidneys. While furosemide is the most used loop diuretic, bumetanide and torsemide have greater bioavailability comparatively.

Thiazide diuretics work by inhibiting the reabsorption of sodium in the distal convoluting tubule within the nephrons of the kidneys. Hydrochlorothiazide (HCTZ), chlorthalidone, and metolazone are commonly used thiazide diuretics used to treat HF associated congestion. It is recommended that either chlorthalidone or hydrochlorothiazide be used to diurese HF associated mild congestion in patients with comorbid hypertension (HTN). Metolazone and chlorothiazide can be used adjunct to loop diuretics in refractory patients, however, add on therapy increases the risk of hypokalemia, hyponatremia, and impaired renal function.

Table 1

Heart Failure Category	Acronym	LVEF measurement
Heart Failure with preserved ejection fraction	HFpEF	LVEF ≥ 50%
Heart Failure with mildly reduced ejection fraction	HFmrEF	LVEF 41-49%
Heart Failure with reduced ejection fraction	HFrEF	LVEF ≤ 40%
Heart failure with improved ejection fraction	HFimpEF	Previous LVEF ≤ 40% with a follow-up measurement of LVEF ≥ 40%

While diuretics are the mainstay of managing congestion, GDMT is the foundation of pharmacologic therapy when treating HF patients. This next section will review GDMT for patients with HFrEF (LVEF ≤ 40%) and classified as NYHA II or III, however, these recommendations can also be considered for patients with HFmrEF, HFimpEF, and HFpEF. Re-evaluation of LVEF should be performed periodically to track disease progression when used in any HF patient. It is important to note that while symptoms may improve during therapy, patients are recommended to continue treatment as HF symptoms will reoccur if therapy is stopped. GDMT is estimated to reduce all-cause mortality by 73% when compared with no treatment and includes 4 therapeutic classes of medications.

- Renin-angiotensin-aldosterone system inhibitors (RAASi)
  - Angiotensin receptor-neprilysin inhibitor (ARNi)
  - Angiotensin-converting enzyme inhibitor (ACEi)
  - Angiotensin receptor blocker (ARB)
- Beta Blockers (β-blocker)
- Mineralocorticoid Receptor Antagonists (MRA)
- Sodium glucose cotransporter-2 inhibitors (SGLT2i)

In patients with HFrEF, inhibition of the RAAS with either an ARNi, or ACEi, or ARB has been proven to reduce mortality and decrease hospitalization. ARNi therapy is preferred over ACEi and ARB medications due to increased benefits on morbidity and mortality. Sacubitril/valsartan is the only ARNi medication available in the US, made up of a neprilysin inhibitor which works to breakdown vasoactive peptides, and an ARB. Any patient presenting with HFrEF, acute or chronic, should be started on ARNi therapy. ACEi therapy is considered second line in patients who cannot tolerate ARNi therapy. All ACEi's are comparable in the treatment of HF and have been shown to slow or stop maladaptive modeling post MI in patients with reduced EF. ARBs are considered third line in patients who cannot tolerate ARNi or ACEi therapy due to cough or angioedema. Regardless of RAASi selection, it is recommended to use caution in

patients with low blood pressure, renal disorders, and high serum potassium levels. Use of ARNi's or ACEi's in patients with a history of angioedema is contraindicated and concurrent therapy with ARNi's and ACEi's (or within 36 hours of one another) is contraindicated due to risk of angioedema. Any patient receiving an ACEi or ARB who can be safely switched to an ARNi should do so due to the increased benefit on mortality and hospitalization.

In patients with HFrEF, with current or previous symptoms, β-blocker therapy has been proven to reduce mortality and decrease hospitalization. This is not a class wide effect and benefits are seen with 3 β-blockers: bisoprolol, carvedilol, and sustained release metoprolol. When used in HF, these medications improve LVEF, decrease symptoms, and improve clinical status. β-blockers slow or stop maladaptive modeling post MI in patients with reduced EF and are recommended to be used in all patients presenting with symptomatic HF with reduced LVEF.

In patients with HFrEF and NYHA class II-IV symptoms, MRA therapy is recommended to reduce mortality and decrease hospitalization. MRAs or potassium sparing diuretics, spironolactone and eplerenone, have proven benefits on mortality and hospitalization in HF patients. Both medications carry an absolute contraindication in patients with an eGFR ≤ 30 mL/min/1.73 m^2 or serum potassium levels > 5 mEq/L. Recommended monitoring includes serum potassium and renal function at week 1, week 4, then every 6 months. Spironolactone has a greater affinity for the aldosterone receptor when compared to eplerenone and is associated with higher rates of gynecomastia and vaginal bleeding. Patients with uncontrolled hypertension should receive spironolactone versus eplerenone due to improved antihypertensive effects. There is a risk of hyperkalemia in patients receiving concurrent therapy with either ACEi's or ARBs therefore, MRA therapy should be held in patients with dehydration, loop diuretic therapy holds, hyperkalemia, or worsening of renal function.

In patients with symptomatic HFrEF, SGLT2i therapy is recommended to reduce mortality and decrease hospitalization. SGLT2i therapy improves cardiovascular outcomes in HF patients regardless of the glucose lowering effect and do not require a diagnosis of Type 2 diabetes for use in HF. These medications may have a positive effect on renal function but should not be used in patients with severe renal impairment. Risks associated with use include genital infections and ketoacidosis. In patients who have diabetes, and either are at risk for, or have established CVD, multiple clinical trials have proven that the addition of an SGLT2i prevents HF associated hospitalization and improves overall survival.

In African American patients with HFrEF and NYHA class II-IV symptoms, combination of hydralazine and isosorbide dinitrate is recommended to reduce symptoms, morbidity, and mortality. The addition of these agents to GDMT has significant benefit, however, they have not been studied directly with ARNi therapy.

It is recommended that dosing, sequencing, and uptitration of GDMT be performed at low doses and slowly until target amounts are reached. Clinical trials specified doses that have proven safety and efficacy (Table 2). If patients cannot tolerate these doses, it is recommended to use the highest dose tolerated, closest to what was used during clinical trials. Literature acknowledges that it may take a few attempts to reach target doses and encourages providers to be persistent with repeat uptitration efforts in patients who previously could not tolerate them. Recommended monitoring during titration of GDMT includes heart rate, blood pressure, electrolytes, and kidney function.

While GDMT is the gold standard treatment of HF, other therapies to consider include anticoagulants, statins, omega-3s, potassium binders, and other rate control medications. HF patients with Atrial Fibrillation (Afib) should receive anticoagulation therapy and statins should be used in patients with history of MI or ACS (Acute Coronary Syndrome) to prevent symptomatic HF and adverse cardiovascular events. In patients with NYHA class II-IV it may be reasonable to add adjunct omega-3 therapy. Hyperkalemia can increase the risk of arrythmias. Potassium binders such as patiromer or sodium zirconium cyclosilicate can be considered for use in patients with hyperkalemia (≥ 5.5 mEq/L) who are receiving RAASi therapy, however, benefit to clinical outcomes has yet to be proven. Heart rate can predict cardiovascular outcomes, therefore ivabradine therapy should be added to patients with NYHA class II – III with chronic, stable HFrEF ≤ 35% who are also receiving GDMT. Low dose digoxin can be considered in patients with symptomatic HFrEF despite GDMT to reduce the risk of hospitalization but has no risk reduction on mortality. Digoxin used at higher doses can negatively affect HF symptoms. Oral soluble guanylyl cyclase stimulator (vericiguat) can be considered in high risk HFrEF patients who are receiving GDMT and have experienced recent worsening of HF. Addition of this agent may reduce the risk of hospitalization and cardiovascular death by increasing vasodilation, improving endothelial function, and decreasing fibrosis during cardiac remodeling. Nitrate and phosphodiesterase 5 inhibitor therapy have no proven benefit and should be avoided, but may still be used to treat CAD symptoms in HF patients.

While many medications are beneficial to HF patients, there are many drugs that are harmful and should be avoided. Non-Steroidal Anti Inflammatory Drugs (NSAIDs) cause sodium and water retention and block the effectiveness of diuretic agents. Thiazolidinediones, saxagliptin and alogliptin, increase the risk of HF and associated hospitalization in patients with LVEF < 50%. The increased risk is thought to be associated with fluid retention and, it has not been determined if this is a class wide effect. There is no survival benefit observed with the use of dihydropyridine calcium channel blockers, amlodipine and felodipine, however, they may be used in patients with uncontrolled hypertension who are optimized on GDMT. Nondihydropyridine calcium channel blockers with negative inotropic effects, diltiazem and verapamil, are myocardial depressants and are harmful to patients with LVEF <

Getting to the Heart of the Matter of Guideline Directed Medical Therapy (GDMT)[1]

50%. There is an increased risk of mortality with the use of class IC antiarrhythmic agents, encainide or flecainide, and class III antiarrhythmics, dronedarone or sotalol. Amiodarone and Dofetilide are the only antiarrhythmic agents with neutral effects on HFrEF patients.

While it should be noted that GDMT must be optimized and exhausted prior to consideration of device or implantable electrical interventions, recommendations for these therapies, as well as treatment of Stage D (advanced HF) during inpatient care is beyond the scope of this newsletter. It should be noted that advanced HF can occur in patients of all EF measurements. Patients with advanced disease should have care provided by a team specializing in HF that can assist with prolonged survival goals, advanced care planning, palliative care and hospice options, and end of life care.

Summary

Heart disease and HF are leading causes of chronic illness, morbidity, and mortality in the United States. GDMT is the essence of HF pharmacologic treatment consisting of four classes of medications: RAASi, β-blockers, MRAs, and SGLT2i, that drastically reduce mortality and risk of hospitalization in patients with HF. The focus of GDMT falls on patients with HFrEF, however, these recommendations can be extrapolated to patients with HFmrEF, HFimpEF, and HFpEF. Making healthy lifestyle choices, eating right, and staying physically active can help prevent the development and progression of HF, and are also tools patients with existing HF can use as self-care techniques. Treatment should be provided to all HF patients by a multidisciplinary team to address lifestyle modifications, risk of hospitalization, prognosis, and HF specific education. Treatment of the whole patient including addressing comorbid illnesses, mental health issues, and isolation are important aspects of care.

Drugs Commonly Used for HFrEF[1]		
Drug	**Initial Daily Dose**	**Target Dose**
ACEi		
Captopril	6.25 mg TID	50 mg TID
Enalapril	2.5 mg BID	10-20 mg BID
Fosinopril	5-10 mg QD	40 mg QD
Lisinopril	2.5-5 mg QD	20-40 mg QD
Perindopril	2 mg QD	8-16 mg QD
Quinapril	5 mg BID	20 mg BID
Ramipril		
Trandolapril		
ARB		
Candesartan	4-8 mg QD	32 mg QD
Losartan	25-50 mg QD	50-150 mg QD
Valsartan	20-40 mg QD	160 mg BID
ARNi		
Sacubitril-valsartan	49 mg sacubitril and 51 mg valsartan BID but may be initiated at 24 mg sacubitril and 26 mg valsartan BID	97 mg sacubitril and 103 mg valsartan BID
B-Blockers		
Bisoprolol	1.25 mg QD	10 mg QD
Carvedilol	3.125 mg BID	25-50 mg BID
Carvedilol CR	10 mg QD	80 mg QD
Metoprolol succinate extended release (CR/XL)	12.5-25 mg QD	200 mg QD
MRAs		
Spironolactone	12.5-25 mg QD	25-50 mg QD
Eplerenone	25 mg QD	50 mg QD
SGLT2i		
Dapagliflozin	10 mg QD	10 mg QD
Empagliflozin	10 mg QD	10 mg QD
Isosorbide dinitrate and hydralazine		
Fixed dose combination	20 mg isosorbide and 37.5 mg hydralazine TID	40 mg isosorbide and 75 mg hydralazine TID
Isosorbide dinitrate and hydralazine	20-30 mg isosorbide and 25-50 mg hydralazine TID-QID	120 mg isosorbide total daily in divided doses and 300 mg hydralazine total daily in divided doses

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