**Learning objectives:**

1. Develop a systematic process for the evaluation and classification for a patient with chronic heart failure (HF).
2. Describe evidence-based therapies for heart failure with reduced ejection fraction (HFrEF) and their impact on patient outcomes.
3. Initiate and titrate GDMT to HFrEF based on patient characteristics and medication side effects.
4. Determine guideline directed therapies for HF with preserved EF, HF with moderately reduced EF, and HF with improved EF.

**Introduction / Outline:**

Plan to spend at least 30 minutes preparing for this talk by using the interactive board for learning/preparing, clicking through the graphic, and becoming familiar with the order the content appears on the graphic. The teaching script below details how to walk through the talk. Every interactive or “clickable” element is denoted with a mouse icon.

**Anticipated time to deliver the talk is 30 min without cases and 40 min with cases.**

**Objective 1: Develop a systematic process for the evaluation and classification for a patient with chronic heart failure (*One-Liner*)**

Patients with HF are classified according to their symptom burden, left ventricular ejection fraction (EF), and etiology of HF. Accurate classification allows clinicians to quickly assess a patient with heart failure and determines therapy recommendations.

*Ask learners to discuss how to classify a patient’s HF. Consider the clinical scenario of medical record review before a clinic visit with a patient. Click on each of the buttons below to reveal each component of the “HF One-liner.”*

**NYHA Class** *– Ask the learners to describe the categories of NYHA classification and click to reveal the table.* New York Heart Association (NYHA) classification describes a patient’s symptom burden and functional capacity. It has been used to assess eligibility for therapy as well as clinical trial enrollment, but it is also a predictor of mortality and most clinicians do not use this as a strict cut-off for treatment (e.g., most would not withhold GDMT in an asymptomatic patient with persistent LV dysfunction).

* Class I: asymptomatic, ordinary physical activity does not cause limitations.
* Class II: mild symptoms with normal activity (e.g., can climb a flight of stairs, walk on level ground, garden, or do heavy housework without symptoms but could not jog, walk briskly, or do higher levels of exertion).
* Class III: No rest symptoms but less than normal activity leads to symptoms (e.g., cannot do the activities class II patients can do).
* Class IV: Rest symptoms or symptoms with even minimal exertion (e.g., symptoms at rest, dressing, bathing, making the bed, or other activities of daily living).

**Ejection fraction** – *Ask the learners to describe the categories of left ventricular ejection fraction and click each to reveal the EF ranges*. Classification of heart failure by left ventricular ejection fraction (LVEF) is the most important classification for determining treatment strategies.

* HF with reduced ejection fraction (**HFrEF**): LVEF≤40%. 2022 guidelines consolidated the indications for pharmacologic HFrEF therapies to LVEF≤40 (previously variable definitions from 35-40%).
* HF with mild reduced ejection fraction (**HFmrEF**): LVEF 41-49%. This is a new category of heart failure in the 2022 guidelines. Patients in this range likely exist on a spectrum between HFrEF and HFpEF and may have different prognosis and treatment recommendations.
* HF with preserved ejection fraction (**HFpEF**): LVEF≥50%.
* HF with improved ejection fraction (**HFimpEF**): History of LVEF≤40% but who have demonstrated recovery of ejection fraction at least 10% and now ≥40%. It is important to distinguish these patients from those with HFpEF or HFmrEF only.

**Etiology** – *Ask the learners to name common causes of heart failure and click to reveal the list.*

* Ischemic cardiomyopathy is the most common form of heart failure, and thus heart failure is commonly broken down into ischemic and non-ischemic cardiomyopathy. This distinction guides therapy, particularly evaluation for revascularization.
* Non-ischemic cardiomyopathy is a heterogenous group with many different causes including drugs, alcohol, hypertension, tachycardia-induced, infectious, and infiltrative etiologies.

The evaluation of new onset heart failure and specific management of ischemic cardiomyopathy are outside the scope of this talk. With a few exceptions, guideline recommended treatments remain the same regardless of the cause of heart failure.

**Objective 2: Describe evidence-based therapies for heart failure with reduced ejection fraction and their impact on patient outcomes. (*Impact*, *GDMT-Initiation*)**

Guideline Directed Medical Therapy for HFrEF: Why We Care

Before discussing specifics of GDMT for HFrEF, it is worth highlighting the care gaps that currently exist and why it is important for primary care doctors and hospitalists, not just cardiologists, to be familiar with and comfortable initiating and titrating medications.

*Click to reveal the statistics below:*

* Heart failure is highly prevalent, with an estimated **6** million patients in the US.
* Mortality without guideline directed therapy is extremely high. Evidence from the original ACE inhibitor trials showed mortality rates of **25-50%** for patients in placebo arm1.
* GDMT is *very*effective: quadruple therapy at target doses has an estimated combined **73%** mortality reduction.
* However, we are likely not realizing the full benefit of therapy in real world clinical practice. The CHAMP-HF registry2 evaluated medication prescription data for >3000 outpatients with HFrEF and found that only **1%** were on target doses of GDMT (and these data did not include SGLT2 inhibitors). The figure below illustrates the care gaps by individual medication class, highlighting that many patients are not being treated at all, let alone achieving target doses.

GDMT for HFrEF - Initiation

*Ask learners to name the medications classes that make up GDMT for HFrEF and click on “What medication classes comprise GDMT?” to reveal the answer.*

There are four classes of medication that have been shown to improve mortality and hospitalization rates for patients with HFrEF in large clinical trials. These include beta blockers, renin-angiotensin blockers including ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), and angiotensin-neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), and sodium-glucose co-transporter 2 inhibitors (SGLT2i).

*Click on each medication class to reveal the specific medications included in this class, the initial starting dose, and target doses that were achieved in clinical trials demonstrating the benefit of the medication. Click on the number needed to treat (NNT) for mortality over 3 years. We have included the names of the clinical trials that demonstrated these effects for reference.*

* *Beta-blockers*: bisoprolol is less commonly used in the US.
* *ARNI*: when an option, this is preferred over an ACE/ARB.
* *ACEi/ARB*: any medication from this class can be used, but lisinopril and losartan are the most commonly used at our institutions.
* *MRA*: eplerenone is less commonly used as the side effects of spironolactone (e.g., gynecomastia) that typically warrant change to eplerenone are less common at the doses used in HF.

**Objective 3: Initiate and titrate GDMT to HFrEF based on patient characteristics and medication side effects. *(GMDT-Initiation, GDMT-Titration, Other therapies - HFrEF)***

**Initiation:**

Initiation and titration of GDMT does not follow a set order or algorithm and instead is individualized to the patient and is often somewhat stylistic. However, it is important to consider the following factors and contraindications for each class of medication:

*Ask learners to discuss when to initiate each class of medication and click to reveal the answers.*

* Beta blockers: Beta blockers should only be initiated in compensated heart failure (i.e., when approaching euvolemia in the setting of a new diagnosis of heart failure).
  + A common clinical question is when to hold or reduce doses in the setting of a decompensation. A complete discussion of inpatient management of decompensated heart failure is outside the scope of this talk. However, there is data to suggest beta blocker continuation during mild decompensation is safe, and thus during any decompensation managed as an outpatient it is likely okay to continue.
* ARNI: ARNI is recommended over ACEi/ARB and patients do not need to start on ACEi/ARB before transition to ARNI.
  + ARNI can be safely initiated even in inpatients admitted with decompensation. Hypotension is a common limiting barrier, but it is worth trying even with relatively low blood pressure. The PIONEER-HF study3 which evaluated the safety and efficacy of initiating ARNI during an admission for heart failure decompensation only required that patients have a systolic blood pressure great than 100 mm Hg, be on a stable dose of IV diuretics, and not required inotropes within 24 hours.
  + Transitioning from ACEi requires 36-hour washout, but transition from ARB can be immediate (thus it is common to initiate and titrate an ARB rather than ACEi with the goal of eventually switching to ARNI).
  + Lastly, ARNI can be quite expensive depending on insurance coverage, so it is important to evaluate cost and have a discussion with the patient to see if cost is a barrier.
* ACEi/ARB: ACEi/ARBs are typically easy to initiate if renal function and potassium are stable. As noted previously, ARBs are often preferred to facilitate future transition to ARNI.
* MRA: Contraindications to spironolactone include a potassium > 5, GFR is <30, or a serum creatinine >2.5 in men or >2 in women. As a potassium sparing diuretic, spironolactone can be initiated early alongside loop diuretics for decongestion as this may avoid the need for potassium supplementation.
* SGLT2i: Contraindications to SGLT2i include GFR<20 (for empagliflozin, <30 for dapagliflozin), type I diabetes or history of diabetic ketoacidosis. Caution should be used in patients with a history of recurrent urinary tract infections (particularly, for dapagliflozin). Similar to ARNI, cost is a frequent barrier to this medication.

GDMT - Titration & Common Roadblocks

A common clinical question is which medication to initiate or titrate at a given visit, given the complexity of using 4 different medications. Guidelines do not clearly specify specific recommend titration strategies. Many cardiologists attempt to initiate low doses of all 4 medications and then titrate up over time. The exact medication adjustment made at each visit will depend on patient characteristics, expected side effects, and patient preference. However, the main teaching point here is to titrate or add something at each available opportunity.

GDMT titration requires frequent re-evaluation to achieve optimal doses. Typical outpatient titration can occur as frequently as every 1-2 weeks, with close monitoring of heart rate, blood pressure, renal function, potassium, and volume status. Even faster titration strategies have been shown to be safe and effective. For example, the STRONG-HF trial4 showed safety and efficacy of an intensive intervention to titrate patients to maximal doses of all medications within just 2 weeks after discharge!

To play an active role in the initiation and titration of GDMT, it is important to be familiar with strategies to overcome common barriers that arise.

* AKI: AKI is common in the heart failure population. First, it is important to note that when initiating SGLT2i and ACEi/ARB/ARNI a mild reduction in GFR is possible and expected, and a decrease <30% does not necessarily warrant dose reduction.
  + In the event of true AKI, assessment of volume status and adjustment of diuretics is the first step.
  + Temporarily holding or reducing the dose of ACEi/ARB/ARNI can be helpful, but re-trialing these medications after resolution of AKI is also important.
  + Lastly, hydralazine + isosorbide combination can be a useful tool for afterload reduction that does not affect renal function.
* Hypotension: Most components of GDMT have an anti-hypertensive effect, and hypotension is a frequently encountered barrier to GDMT titration. When confronting hypotension, it is important to consider a patient’s symptoms, not just their blood pressure number. An asymptomatic systolic blood pressure of 90-100 is an appropriate target. Several strategies can help mitigate hypotension when it arises:
  + Avoid non-GDMT anti-hypertensives such as calcium channel blockers or thiazide diuretics
  + Stagger medication dosing (e.g. AM vs PM)
  + Switch carvedilol (which has more alpha blockade) to metoprolol succinate
* Hyperkalemia: Spironolactone and ACEi/ARB/ARNI can all increase potassium and hyperkalemia may develop, particularly in patients with renal dysfunction.
  + Addition of SGLT2 and ARNI: evidence from ARNI and SGLT2 trials show mitigating effects of these drugs on hyperkalemia
  + Counsel patients on a low potassium diet
  + Consider hydralazine and isosorbide as a last resort if unable to tolerate ACEi/ARB/ARNI

Other Therapies - HFrEF

After titration to maximally tolerated doses of GDMT, repeat evaluation of LV function is recommended after ~3-6 months. If patients have persistent severe LV dysfunction (EF<35%), additional therapy may be warranted:

* Wide-QRS - When patients have a wide QRS it indicates conduction system disease that leads to asynchronous activation of the ventricles. Lack of synchrony between the right and left ventricles as well slow, myocyte-to-myocyte conduction leads to inefficient cardiac function. Cardiac resynchronization therapy (CRT) involves implanting a pacemaker with both RV and LV leads, simultaneously pacing both ventricles to allow more synchronous contraction.
  + This procedure has been shown to improve patient outcomes, particularly in patients with very wide QRS (>150 ms) in a left bundle branch pattern.
  + It is important that patients receive an adequate trial of GDMT before considering invasive therapies for those with persistent LV dysfunction.
* >1 year life expectancy - Patients with HFrEF and EF<35% are at high risk of sudden cardiac death from ventricular arrhythmias, and multiple trials have demonstrated mortality improvement with implantable cardiac defibrillators (ICD).
  + The decision around ICD implantation is complex and requires a risk/benefit discussion with an electrophysiologist, but patients should have at least a 1-year life expectancy to consider ICD therapy.
  + Similar to CRT, patients need a trial of GDMT before ICD implantation. ICDs can be implanted with CRT (i.e., CRT-D) or without (single chamber ICD).
* Hydralazine + Isosorbide - The combination of the vasodilators hydralazine and isosorbide dinitrate has been shown to improve mortality in a trial of self-identified African-Americans with HFrEF, most of whom were on background therapy with beta blockers and ACE inhibitors. Given this evidence, this combination is given a 1a recommendation in recent guidelines.
  + There are obviously inherent issues with race-based guidelines, and in other fields (e.g. race-adjusted GFR and PFT calculations) this has led directly to health inequities.
  + Hydralazine and isosorbide are dosed three times daily which leads to a high pill burden and difficulties with compliance.
  + Given these issues, most providers focus on quadruple therapy for all patients and reserve hydralazine and isosorbide for cases when ACEi/ARB/ARNI cannot be used.

**Objective 4: Determine guideline directed therapies for HF with preserved EF, HF with moderately reduced EF, and HF with improved EF. (*Other therapies – EF Spectrum*)**

*Click to reveal recommendations for medical therapy for heart failure across the spectrum of LV function.*

* HFimpEF: With implementation of GDMT, it is possible that some patients with HFrEF recover cardiac function and LVEF can improve to >40% or even normalize with therapy. However, these patients should continue their current GDMT indefinitely even with recovery.
  + The TRED-HF trial5 was a small study of only 50 patients randomized patients with recovered EF to withdrawal or continuation of GDMT – over 40% of the withdrawal developed evidence of recurrent cardiomyopathy compared to none who continued treatment.
  + Most cardiologists extrapolate this data to all forms of cardiomyopathy (even more reversible causes), but will stop titrating/adding medications when EF has recovered and are quicker to pull back for side effects.
* HFmrEF: Heart failure with mildly reduced ejection fraction is a new category in recent guidelines and reflects that heart failure is a spectrum across a range of ejection fractions and trajectory over time is important to consider.
  + A patient with a declining LVEF of 41% is likely going to respond well to typical GDMT for HFrEF, whereas a patient with a stable EF of 49% may not.
  + Based on studies of SGLT2i in HFpEF (inclusion criteria was an LVEF>40%), they are recommended in this population.
* HFpEF: Heart failure with preserved ejection fraction, unlike HFrEF, has few therapies that have been shown to reduce patient centered outcomes.
  + SGLT2 inhibitors were shown in the EMPEROR-Preserved and DELIVER trials to reduce heart failure hospitalizations (but not mortality) and should be strongly considered in this population.
  + MRA and ARNI have been studied in HFpEF (TOPCAT, PARAGON-HF) and these trials had negative results for the primary outcome. However, there was signal towards benefit for reducing hospitalizations, so some cardiologists use these medications in HFpEF and they have a 2b recommendation in 2022 guidelines.

**Take Home Points:**

1. Heart failure (HF) is classified by functional status (NYHA class), ejection fraction, and etiology. Using a "one-liner" containing these elements allows clinicians to quickly assess a patient with heart failure and determine therapy recommendations.
2. Guideline-directed medical therapy (GDMT) for HFrEF includes 4 medications: beta blocker, ACEi/ARB/ARNI, MRA, and SGLT2i. GDMT at target doses dramatically decreases HF mortality.
3. Guideline recommended therapy for HFmrEF and HFpEF includes SGLT2i.
4. GDMT for heart failure is underutilized and often underdosed. Each clinic visit and hospitalization represents an opportunity to optimize HF regimens.

References

Unless otherwise specified, material is drawn from the 2022 AHA/ACC/HFSA Guidelines for the Management of Heart Failure6 and the 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment7. Images from Biorender.com.

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