PHARMACIST:

An Update on the Medical Management of Chronic Heart Failure with Reduced Ejection Fraction

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In the United States, the overall cost of heart failure (HF) amounts up to $30.7 billion in healthcare spending and missed work leave every year. This value is projected to increase to up to $69.7 billion annually by the year 2030. One of the biggest sources of these costs is attributed to HF related hospitalization and re-hospitalization.[1,2] For those diagnosed with HF, it is estimated that 25% of patients are re-admitted to the hospital within 30-days of being discharged and the five-year mortality rate for patients carrying the diagnosis is approximately 50%.[2,3]

There is extensive evidence surrounding the medical management of patients diagnosed with HF, especially those classified with "heart failure with reduced ejection fraction" (HFrEF). Guideline-directed medication therapy (GDMT) has been established and outlined by organizations such as the American College of Cardiology (ACC) and the American Heart Association (AHA) and demonstrate positive clinical outcomes for a patient population that continues to contribute to overall healthcare spending.[2,3] This manuscript will focus on the assessment and presentation of HF and the medication management of chronic HF patients specifically related to those with diminished left ventricular ejection fraction (LVEF).

CE FOR **PHARMACISTS**

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Learning Objectives

- Define heart failure and describe clinical features and presentation.
- Discuss the assessment, definition, and functional classification of heart failure.
- Identify medications that are used in the management of heart failure with reduced ejection fraction (HFrEF).
- Outline therapeutic approach of utilizing guideline-directed medical therapy (GDMT) treatment of HFrEF.
- Summarize potential use of newer therapeutic agents and their role(s) in therapy.

TABLE 1. Important Risk Factors for Developing Heart Failure[2]

Family history of heart failure
Hypertension
Diabetes Mellitus
Metabolic Syndrome*
Atherosclerotic Disease
Tobacco use
Alcohol overuse
Cocaine or amphetamine use
Cardiotoxic chemotherapy treatments

**Metabolic Syndrome is defined as having at least 3 of the following: abdominal adiposity, hypertriglyceridemia, low high-density lipoprotein, hypertension, and fasting hyperglycemia.*

Clinical Presentation

HF symptoms may vary depending on the extent of disease or diagnosis of HF "type". Patients with more advanced symptoms tend to experience dyspnea, fatigue, exercise/activity intolerance, unintentional weight loss d/t muscle wasting, volume overload with lower extremity (LE) edema, and hypotension with poor perfusion.[2] The cause of many of these symptoms is a direct result of poor cardiac output (CO) and inefficiency in the heart's normal physiologic capabilities to maintain homeostasis. Risk factors predisposing patients for development of HF can be found in Table 1.

Controlling hypertension, lipid disorders, diabetes mellitus, and a patient's weight have all demonstrated a reduction in risk for disease progression.[2,3] Providers should also recognize that the elimination of harmful agents such as tobacco, amphetamines, cocaine, alcohol, or other cardiotoxic agents should be considered when plausible.[2,4] There is some debate as to whether moderate alcohol intake actually reduces risk of heart disease. Studies have not consistently provided evidence to support the appropriate amount of alcohol nor which specific patient populations show potential benefit versus harm in the setting of HF. Overconsumption of alcohol and alcohol abuse is still considered a risk factor for development of HF and disease progression.[4-6]

Diagnosis and Classification of Heart Failure

HF is commonly diagnosed and classified using a combination of patient reported symptoms, lab monitoring values, and specific cardiac imaging. For patients that report symptoms mentioned in the previous section and HF is suspected, it is

TABLE 2. Cardiac Biomarker Relevant Reference Values[7-10]

Biomarker	Reference Values	Follow
BNP	(pg/mL)	Interpretation
	35	ULN in non-acute setting
	100	ULN in acute setting
	100-500	Utilize clinical judgement to diagnose HF
	>500	HF or cardiac dysfunction plausible, consider HF medication therapy
NT-proBNP	125	ULN in non-acute setting
	300	ULN in acute setting
	>450	Consider HF diagnosis for patients <50 years old
	>900	Consider HF diagnosis for patients 50-75 years old
	>1800	Consider HF diagnosis for patients >75 years old

BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ULN = upper limit of normal.

often confirmed using objective assessment, lab monitoring, and diagnostic imaging.

Lab Monitoring and Cardiac Biomarkers

Lab monitoring plays an important role in initial diagnosis and assessment of patients with possible new-onset HF. Evidence suggests all patients obtain routine clinical laboratory testing including complete blood count (CBC), urinalysis, serum electrolytes, serum creatinine (SCr), glucose, fasting lipid profile, liver function tests (LFTs), and thyroid-stimulating hormone (TSH).[2]

Obtaining cardiac biomarkers can also contribute to the diagnosis and ongoing assessment of HF.[2,3,7-10] The two commonly referenced cardiac biomarkers include brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Both biomarkers are released from cardiomyocytes in reaction to increased myocardial stretch or other stressors. These specific biomarkers are considered the clinical standard for diagnosing HF and assessing cardiac function by the ACCF/AHA and European Society of Cardiology (ESC) guidelines. General cutoffs are noted in Table 2. Recommendations and interpretation of labs may vary based on institution, but using cardiac biomarkers to help diagnose or rule our HF and other cardiac causes has been demonstrated with current evidence.[9,10] Cardiac biomarkers can be elevated by a wide range of causes and in acute settings can often be more helpful in ruling out HF as a cause for dyspnea if levels are not considered "elevated".

Diagnostic Imaging

Patients who present as symptomatic, with suggestive lab data leading toward new-onset HF will likely undergo non-invasive imaging to determine the extent to which heart function is diminished. Patients in the acute setting are recommended to undergo non-invasive cardiac imaging using a chest x-ray to rule out other potential causes of common symptoms like congestion and dyspnea that could be non-cardiac related.[2] For patients in the outpatient setting, more specific recommendations for cardiac imaging may occur after HF symptom presentation and elevated cardiac biomarkers. Cardiac imaging is recommended after other causes are ruled out, or a provider has reasonable certainty to suggest HF. The goal is to get a complete picture of possible abnormalities in the left ventricle (LV) structurally and functionally. Imaging procedures can help assess a variety of results including the estimated left ventricular ejection fraction (LVEF), which is a primary factor in determining the HF diagnosis and helps drive decisions for GDMT. Table 3 references how HF is diagnosed based on LVEF.

Various non-invasive imaging strategies have been used to evaluate patients with possible HF for LVEF and volume status which include strategies such as transthoracic echocardiography

ACRONYM KEY

ACC(F) = American College of Cardiology (Foundation)

ACEi = angiotensin-converting enzyme inhibitor

AHA = American Heart Association

ARA = aldosterone receptor antagonists

ARNI = angiotensin receptor neprilysin inhibitor

ARB = angiotensin II blocker

BBs = beta-blockers

BNP = brain natriuretic peptide

BPM = beats per minute

CBC = complete blood count

CMR = cardiovascular magnetic resonance

CO = cardiac output

EF = ejection fraction

EKG = electrocardiogram

ESC = European Society of Cardiology

GDMT = guideline-directed medication therapy

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HFpEF = Heart Failure with preserved Ejection Fraction

HYD/ISDN = hydralazine plus isosorbide dinitrate

K+ = serum potassium

LE = lower extremity

LFT = liver function test

LV = left ventricle

LVEF = left ventricular ejection fraction

MUGA = multiple gated acquisition

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

RAAS = renin-angiotensin aldosterone system

RCT = randomized controlled trial

SCr = serum creatinine

SPECT = Single photon emission computed tomography

SGLT2is = Sodium-glucose cotransporter-2 inhibitors

T2DM = type=2 diabetes mellitus

TSH = thyroid-stimulating hormone

TTE = transthoracic echocardiography

TABLE 3. Definition of Heart Failure Based on LVEF*

Definition	Measured LVEF
Heart Failure with preserved Ejection Fraction (HFpEF)	≥50%
Heart Failure with preserved Ejection Fraction, borderline (HFpEF Boderline)	41% to 49%
Heart Failure with reduced Ejection Fraction (HFpEF)	≤40%

**This table has adapted the information as defined in the 2013 ACCF/AHA heart failure guidelines2Post-graduate year 1*

TABLE 4. Components of ACCF/AHA Staging for Heart Failure*

Stage Title	Structural Heart Disease Present	Heart Failure Symptoms Present
A	No	No
B	Yes	No
C	Yes	Yes
D	Yes	Yes

**This table has adapted the information as defined in the 2013 ACCF/AHA heart failure guidelines[2]*
ACCF = American College of Cardiology Foundation; AHA = American Heart Association

(TTE), radionucleotide tomography (eg. Single photon emission computed tomography (SPECT) or multiple gated acquisition (MUGA)), and cardiovascular magnetic resonance (CMR). Evidence suggests that each method of imaging has value in evaluating LVEF and assessing level of dysfunction. When utilizing follow-up imaging for reassessment it is recommended that different imaging methodologies are not compared against one another.[11] TTE's are generally regarded as the most common non-invasive method as they are the least time-intensive and do not require patients to be administered a radionucleotide or to lay in a magnetic resonance imaging (MRI) machine for an extended period of time.

Diagnosis of Heart Failure with Reduced EF (HFrEF)

LVEF is important in determining a patient's HF status and can also be used to assess response to GDMT. In most cases a patient may be reassessed for improvement in their cardiac function (based on LVEF) after being established on GDMT. Reimaging may also be performed in the setting of increased symptoms or reduced functional status. Diminished status may necessitate the need for mechanical intervention such as a left ventricular assist device (LVAD). Patients generally obtain follow-up imaging after 3-6 months of optimized GDMT to determine if objective improvement can be seen.[12]

Patient's with HFrEF can present with the common symptoms discussed earlier such as dyspnea and volume overload due to the heart's inability to eject blood efficiently. A diagnosis of HFrEF carries with it a number of recommendations for adequate self-care practices and initiation of appropriate medical therapy to maintain (and possibly improve) cardiovascular function over time. HFrEF has often been referred to as "systolic heart failure" because, generally speaking, inefficiencies in ejection fraction (EF) are a result of damage to the myocardium affecting the systole period. More recently guidelines have noted that patients with HFrEF may also have some level of diastolic dysfunction, thus it is considered more accurate to refer to patients based on their EF versus the type of dysfunction they present with.[2,3]

Staging and Classifying Heart Failure

After diagnosing HF based on EF, patients are also staged and classified into two distinct groups based on their structural ("staging") and functional ("classification") statuses. The ACCF/AHA staging criteria focus on cardiac structural damage and presence of HF symptoms. Stages are labeled alphabetically from A through D (Table 4). Stage A HF is defined as high risk for HF development without structural damage or symptoms, while Stage D is defined as refractory HF that requires specialized intervention despite optimal GDMT. When considering a patient's ACCF/AHA stage, note that they are unable to regress back to a previous stage. This is demonstrated most noticeably within the difference between Stage B and Stage C HF. Patients with Stage B HF have structural damage and no history of symptoms, while Stage C patients have structural abnormalities and have demonstrated symptoms of HF currently (or at any point in the past). Those who become diagnosed with Stage B HF are often categorized following cardiac imaging being used to evaluate for other disorders as they are not symptomatic for HF.[2]

Table 5 outlines The New York Heart Association (NYHA) Functional Classification system which is considered a more subjective measure and has greater variability.[2,13-15] The NYHA criteria focus on patient reported physical activity limitations and occurrence of HF symptoms. In patients with low health literacy this may be difficult to assess. Providers need to utilize clinical abilities to effectively gather information, compare previous patient reports, and use the opportunity to educate patients on proper self-assessment for HF management. Despite a number of limitations in relation to the variability on how to collect functional class information, and the possibility of underestimating true functional class, evidence still supports use of this method as it also helps to determine what GDMT is recommended in patients with chronic HFrEF.[13-15]

Review of Available Medication Classes Used for HFrEF

Angiotensin Converting Enzyme Inhibitors and Angiotensin II Blockers

Angiotensin converting enzyme inhibitors (ACEi) have displayed benefits and are indicated in all patients with HFrEF unless contraindications are present.[2] Results of the CONSENSUS Trial Study Group (1987) and SOLVD Investigators (1992) demonstrated the efficacy of enalapril across varying levels of HF and concluded that ACEis resulted in decreased mortality and hospitalization and improvement in HF symptoms.[15,16]

Selection of a specific ACEi agent can be determined based on availability, cost and ease of administration. Although captopril, ramipril, enalapril, and

trandolapril have been studied in specific randomized controlled trials (RCT's) and demonstrated benefit for use in HF, there has not been any identified difference among agents in terms of effects on symptoms or survival.[18,19]

ACEi should be initiated at a low dose and titrated slowly based on tolerability. Renal function should be assessed 1-2 weeks after beginning therapy and monitored as clinically indicated or after dose increases.[12] A common adverse effect includes ACEi-induced cough. For individuals that experience an ACEi-induced dry cough it is recommended to switch to an alternative agent like an Angiotensin II blockers (ARBs). ARBs are less likely to cause this effect as they demonstrate their effect at a later point in the renin-angiotensin aldosterone system (RAAS) that does not interfere with the breakdown of bradykinins thought to induce the cough. There are currently three ARB medications which are recommended based on available evidence for use in HFrEF including losartan, candesartan, and valsartan.[2,12] Similar to ACEis, these medications have demonstrated a decrease in mortality and hospitalizations and improvement in HF symptoms.[10-22]

Initiation with ARBs follows a similar method as ACEis: doses should be started at a low dose and titrated slowly based on tolerability and monitoring parameters. The most severe side-effects associated with ARBs are hypotension, renal dysfunction, and hyperkalemia.[2] These risks are exponentially increased when combined with ACE inhibitors and patients should never use both agents concomitantly. Although there exists some evidence that suggests ACEis and ARBs used concomitantly increases their efficacy in the setting of HFrEF, the risk of synergistic side effects related to electrolyte abnormalities and kidney dysfunction outweighs the potential benefit.[23,24] Patients should also be counseled regarding the rick of angioedema for both of these classes of medication.

Beta-Adrenergic Antagonists or Beta-Blockers

Beta-Blockers (BBs) are often used in long-term treatment plans due to evidence for improved patient clinical status, and reduced risk of death and hospitalization.

TABLE 5. NYHA Functional Classification of Heart Failure*

Classification Title	Definition
I	• No limitation of physical activity • Ordinary physical activity does not cause symptoms of HF
II	• Slight limitation of physical activity • Comfortable at rest • Ordinary physical activity results in symptoms of HF
III	• Marked limitation of physical activity • Comfortable at rest • Less than ordinary activity causes symptoms of HF
IV	• Symptoms present at rest **OR** • Unable to carry on any physical activity without symptoms of HF

**This table has adapted the information as defined in the 2013 ACCF/AHA heart failure guidelines[2]*
HF = heart failure; NYHA = New York Heart Association

BBs should be initiated in all HFrEF patients unless contraindications are present. BB combination therapy with ACEi is preferred in patients with HFrEF as opposed to ACEis alone. The combination of the two classes has shown greater improvement in symptoms and decreased mortality versus ACEi monotherapy or ACEi dose optimization.[25,26]

When considering BBs for use in chronic HFrEF, choices are limited to bisoprolol, metoprolol succinate, or carvedilol. These three BBs have demonstrated clinical evidence for benefit in decreased mortality and hospitalizations, as well as symptom improvement. This is not considered a class-wide effect.[2]

Patients should be initiated at low doses and should have slow and gradual titration based on tolerability. Vitals and HF symptoms should be monitored before and after dose increases.[12] Most commonly BBs are titrated upward based on their heart rate remaining in an acceptable range. Although there is no official recommendation for a lower limit of heart rate with use of BBs, commonly it is suggested that dose adjustments occur when the heart rate (HR) drops below 55 bpm.

Possible adverse effects related to BBs include fluid retention and worsening HF, bradycardia or heart block, fatigue, or hypotension. Historically, BBs were avoided and thought to cause adverse outcomes in patients with HF, but over time evidence from RCTs like MERIT-HF (1999), CIBIS II (1999), and COPERNICUS (2002) demonstrated the value of use in patients. This was considered a breakthrough in common practice as patients with HFrEF had often developed the condition following structural damage after an MI in which beta-blockers were indicated.[27-29]

Lowering doses can decrease chance of side-effects related to BBs. Occurrences of hypotension can be minimized with separated administration of BB doses. If therapy were to be withdrawn for any reason, discontinuation should be tapered slowly as abrupt discontinuation can put the patient at risk of clinical deterioration.

Diuretics

Current guidelines discuss the use of two classes of diuretics for use in patients with symptomatic HFrEF as an adjunct to therapy with ACEi/ARB, BB, and an angiotensin receptor antagonist (ARA) unless otherwise contraindicated. Although considered an important part of a medication regimen, diuretics only benefit the patient through improvement of HF-related symptoms associated with fluid retention. No benefit on mortality or hospitalizations have been demonstrated.[30,31]

Loop diuretics are the preferred diuretic when patients present with symptomatic HFrEF, as they are able to quickly remove excess fluid buildup.[2,12] Guidelines also discuss thiazide diuretics as an alternative for mild fluid retention and heavily elevated blood pressure levels due to more consistent antihypertensive effects.[2] Currently available loop diuretics for HF include furosemide, bumetanide, and torsemide all of which may be utilized for

TABLE 6. Evidence-Based Medications for HFrEF Target Dosing*

Drug Class/Name	Target Doses
ACEis: • Captopril • Enalapril • Lisinopril • Ramipril • Trandolapril	 50 mg three times daily 10 to 20 mg twice daily 20 to 40 mg once daily 10 mg once daily 4 mg once daily
ARBs: • Candesartan • Losartan • Valsartan	 32 mg once daily 150 mg once daily (above maximum daily recommended dose for HTN) 160 mg twice daily
Beta-Blockers: • Bisoprolol • Carvedilol • Metoprolol succinate	 10 mg once daily 25 mg twice daily (or 50 mg twice daily if weight > 85 kg) 200 mg once daily (may administer in divided doses)
ARNI: • Sacubitril/Valsartan	 97/103 mg twice daily
ARAs: • Eplerenone • Spironolactone	 50 mg daily 25 to 50 mg daily
HYD/ISDN	40/75 mg three times daily (TDD = 140/225 mg per day)
Digoxin	Based on serum concentrations between 0.5-0.9 ng/mL
Ivabradine	Based on goal HR of 50-60 bpm
SGLT2isa: • Dapagliflozin	 10 mg daily

**Chart based on guidance from the 2013 ACCF/AHA Guidelines2, the 2017 Updated ACC/AHA/HFSA guidelines3, the 2017 ACC Expert Consensus pathway47, and other relevant clinical trial data*
aDoses for canagliflozin and empagliflozin for use in HF not established d/t pooled analysis or composite outcome in RCTs
ACEi = angiotensin-converting enzyme inhibitor; ARA = aldosterone receptor antagonists; ARB = angiotensin II blocker; ARNI = angiotensin receptor neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; HYD/ISDN = hydralazine plus isosorbide dinitrate; RCT = randomized controlled trial; SGLT2is = Sodium-glucose cotransporter-2 inhibitors

chronic management based on their oral bioavailability.[32]

For patients with chronic HFrEF on long-term loop diuretic therapy, it is recommended to monitor weight daily in the morning after using the bathroom and before eating/drinking to record an accurate "dry weight".[2,3] Significant fluctuations in weight should be reported immediately to a provider so they can adjust dosing as needed. Many institutions have their own protocols for when patients should outreach for dose adjustment consideration, but a common rule of thumb is that if a patient gains 2-3 pounds over 1 day or ≥5 pounds over 7 days they should be contacting their clinic for dose adjustment or additional assessment.

The most common adverse effects with diuretics include electrolyte imbalances (most commonly potassium and magnesium), fluid depletion, and a chance of developing hypotension.[32]

Aldosterone Receptor Antagonists

ARAs are another GDMT option that have also demonstrated a reduction in mortality and hospitalizations as well as improved HF symptoms.[33] Eplerenone specifically has shown these reductions in a wider range of patients with HFrEF compared to spironolactone.[34,35]

Current recommendations suggest that patients with HFrEF and NYHA classes II through IV should add ARA therapy to their existing regimen for additional benefit if they continue to be symptomatic while on ACEi/ARB and a BB. The RALES (1999) and EMPHASIS-HF (2011) RCTs demonstrated the clinical benefits of using this class of medications. Spironolactone demonstrated a 30% reduction in all-cause mortality.[33] It is commonly cited that these RCTs included only patients with lower LVEFs as a part of their studies (<35% for RALES and ≤30% for EMPHASIS-HF); however, current guidelines support use for any patient with symptomatic HFrEF meeting initiation criteria.[2]

ARAs should be initiated at a low dose and slowly titrated based on tolerability. When starting ARAs patients should have their renal function and serum potassium (K+) levels checked before therapy begins, within two to three days of use, and after seven days of use. Individuals using these agents carry a higher risk of developing life-threatening hyperkalemia. This increased risk is mitigated by recommendations that SCr should be <2.5 mg/dL and K+ should be <5.0 mEq/L, with no history of severe hyperkalemia.

Potassium supplementation should also be discontinued, and patients should be educated on avoiding foods high in potassium as well as NSAIDs. Although spironolactone is more commonly used as initial ARA therapy, individuals may experience gynecomastia or breast pain. For patients who demonstrate this side effect, switching to eplerenone is advisable as incidence with spironolactone is listed as 10% compared to <1% with eplerenone.[33-35]

Hydralazine plus Isosorbide Dinitrate

In adjunct to ACEi and BBs, the use of a combination Hydralazine plus Isosorbide Dinitrate (HYD/ISDN) is GDMT recommended especially in black or self-described African American individuals with NYHA class III or IV HF that remain symptomatic despite appropriate therapy. The combination is also indicated in who can't tolerate or have a contraindication to ACEi or ARB therapy.[36,37]

Current evidence demonstrates this combination's ability to decrease mortality and hospitalizations and improve HF symptoms specifically in black patients as demonstrated by the V-HeFT (1986) and A-HeFT (2004) studies.[38,39] For non-black patients, this combination of medications did not show mortality benefit. It did improve some HF symptoms but there was no difference in hospitalization rates as HYD/ISDN does for black patients.[36] This suggests there may still be room for use of HYD/ISDN in non-black patients who cannot tolerate ACEis or ARBs.

TABLE 7. Summary of GDMT Approaches to HFrEF Medical Management

Medication Class	HFrEF Indication	Place in Therapy	Clinical Benefit(s)
ACEi or ARB	Stage B or Stage C HFrEF	First Line Agent	• Reduce mortality • Reduce morbidity • Improved HF symptoms • Reduced hospitalizations
BB	Stage B or Stage C HFrEF (especially with history of MI or ACS)	First Line Agent	• Reduce mortality • Reduce morbidity • Improved HF symptoms • Reduced hospitalizations
ARNI	Stage C HFrEF	• Alternative Agent • NYHA Class II or III • Replaces ACEi or ARB therapy (36 hr washout required after ACEi discontinued)	• Superior to ACEi therapy • Reduce mortality • Reduce morbidity • Improved HF symptoms • Reduced hospitalizations
Diuretics (loop preferred)	Stage C HFrEF	• Add-on Therapy • NYHA Class II to IV • For fluid overload symptom management	Improved symptoms related to fluid retention
ARA	Stage C HFrEF	• Add-on Therapy • NYHA Class II to IV • Stable kidney function, and controlled serum K+	• Reduce mortality • Reduce morbidity • Improved HF symptoms • Reduced hospitalizations
HYD/ISDN	Stage C HFrEF	• Add-on Therapy • NYHA Class III or IV • Black/African American patients or unable to tolerate ACEi/ARB/ARNI	**In black patients only:** • Reduce mortality • Reduce morbidity • Improved HF symptoms • Reduced hospitalizations
Digoxin	Stage C HFrEF	• Add-on Therapy • NYHA II to IV • Persistent symptoms treated to range of 0.5 to 0.9 ng/mL	• Improved HF symptoms • Improved HRQOL • Improved exercise tolerance • Reduced hospitalizations
Ivabradine	Stage C HFrEF	• Add-on Therapy • NYHA Class II or III • Resting HR ≥70 bpm, normal sinus rhythm, and on maximally tolerated beta-blocker therapy	Reduced hospitalizations

ACEi = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARA = aldosterone receptor antagonists; ARB = angiotensin II blocker; ARNI = angiotensin receptor neprilysin inhibitor; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HRQOL = Health-Related Quality of Life; HYD/ISDN = hydralazine plus isosorbide dinitrate; MI = myocardial infarction; NYHA = New York Heart Association

Common adverse effects of HYD/ISDN include headache and dizziness. This combination can be given as either a single-combination tablet or separate tablets, but evidence-based recommendations specifically note fixed dose combination regardless of the method that is used as shown in Table 6. The isosorbide mononitrate formulation does not currently demonstrate any evidence suggesting benefit for use in HF patients without other compelling indications.

Digoxin

Digoxin may be used as an adjunct for patients with HFrEF without contraindications to use. Digoxin has been shown to reduce hospitalizations, improve HF-related symptoms, improve exercise tolerance, and improve health-related quality of life. Despite these benefits it has not shown an effect on mortality. These benefits have been observed in individuals regardless of their underlying rhythm, cause of HF, or concomitant therapy.[40]

Digoxin is considered an option for symptomatic patients not responding to GDMT. It is typically reserved as a last line option due to its need for therapeutic drug monitoring, the risk of adverse effects, and long list of drug-drug interactions.[2]

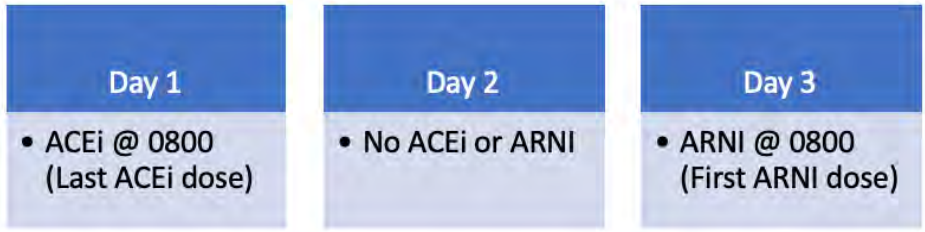
Digoxin must be limited to patients without specified contraindications, and providers must weigh the risk benefit based on major adverse effects such as cardiac arrhythmias, gastrointestinal symptoms, and mental disturbances related to toxicity. Unlike with the treatment of atrial fibrillation, digoxin concentrations when used in HF are recommended to stay between 0.5 to 0.9 ng/mL. Levels exceeding 2 ng/mL carry a much higher chance of toxicity related adverse effects.[2]

Newer Medications in the Management of HFrEF

Angiotensin Receptor Neprilysin Inhibitor

As of 2017, ACC/AHA/HFSA published an update to the 2013 Management of Heart Failure guidelines which now recommends the novel class of medication, Angiotensin Receptor Neprilysin Inhibitor (ARNIs), for individuals with NYHA class II and III as a replacement for ACEi/ARB therapy if

FIGURE 1. Example Schedule for Switch from ACEi to ARNI



patients have tolerated either in the past.[3]

This recommendation is based on the PARADIGM-HF (2014) RCT that demonstrated the superiority of sacubitril in combination with valsartan (an ARNI) compared to enalapril in the reduction of cardiovascular death (13.3% vs. 16.5%, HR 0.80; 95% CI 0.71-0.89; P<0.001; NNT 31) and HF hospitalization (12.8% vs. 15.6%, HR 0.79; 95% CI 0.71-0.89 P<0.001; NNT 36). The only available ARNI medication which contains a combination of valsartan and sacubitril reduced cardiovascular death or HF hospitalization by 20%.[41] Sacubitril is not available as a single agent. The sacubitril/valsartan combination tablet is currently marketed under the brand name Entresto® by drug manufacturer Novartis.

Adverse effects of ARNIs include hypotension, renal insufficiency, and a rare chance of developing angioedema. ARNIs should not be administered to any individuals with a history of angioedema caused by ACEi/ARB. In order to reduce the risk of side effect occurrence specific transition instructions must be followed when switching from ACEi or ARB to an ARNI. For patients taking an ACEi, an ARNI should only be given to an individual after at least 36 hours from last ACEi dose as a washout. This is demonstrated in a mock schedule seen in Figure 1. Patients switching to an ARB may administer an ARNI after 24 hours since their last dose.

Ivabradine

The 2017 guideline update also highlighted the use of ivabradine in symptomatic individuals with HFrEF, NYHA class II to III who were already receiving GDMT and a maximally tolerated BB dose. Current evidence presented in the SHIFT (2010) trial found that ivabradine reduced the rate of HF hospitalization versus placebo (HR 0.74 [95% CI 0.66-0.83]; p < 0.0001) but did not demonstrate a mortality benefit versus placebo in secondary outcomes.[42]

Ivabradine is a novel agent for the treatment of HF, but is significantly limited by its lack of mortality benefit, adjunct therapy status, long list of contraindications, and initiation criteria. For a patient to be started on therapy and receive benefit in HFrEF they must: 1) have a measured LVEF <35%, 2) be on recommended GDMT including max tolerated BB therapy, 3) demonstrate sinus rhythm by EKG, and 4) have a resting heart rate ≥70 bpm. When initiated the patient is started at a 2.5 or 5 mg twice daily dose and titrated to a maximal dose of 7.5 mg twice daily with a goal to achieve a heart rate between 50-60 bpm. Because of the additional monitoring and extensive criteria, this medication is not as commonly prescribed, but can be beneficial in certain patient populations who qualify for use.[3,12]

Sodium-glucose Cotransporter-2 Inhibitors

A class that primarily is used and approved for type-2 diabetes (T2DM), sodium-glucose cotransporter-2 inhibitors (SGLT2is) are demonstrating efficacy for use in the HFrEF population. SGLT2is work by increasing excretion of glucose in the urine and reducing sodium resorption in the kidneys.

Following evidence from the EMPA-REG OUTCOME (2015) and CANVAS (2017) trials that showed benefits in reduction of HF related deaths and HF hospitalizations, the American Diabetes Association (ADA) recommended SGLT2is therapy as an earlier adjunct therapy choice in patients with comorbid diabetes and HF given potential for favorable outcomes.[43,44] The most recent 2019 ADA Standards of Care guidelines strongly support these previous claims and now recommend that patients with diabetes where HF or chronic kidney disease predominate, should use empagliflozin or canagliflozin.[45]

Following the release of the 2019 ADA Standards of Care, two new studies have emerged suggesting that SGLT2is may have an even larger role in the care of HF patients. In June 2019 the CREDENCE trial was published evaluating usefulness of canagliflozin in reducing risk of end stage renal disease for patients with T2DM and diabetic nephropathy. Among the secondary outcomes this trial demonstrated a significant reduction in a composite of cardiovascular mortality and hospitalization from HF versus placebo (HR 0.69; 95% CI 0.57–0.83; P<0.001).[46] The DECLARE-TIMI 58 trial was also completed evaluating the safety profile of dapagliflozin use in the setting of CV disease. It declared non-inferiority of dapagliflozin therapy when compared to placebo, and demonstrated a reduction in the composite endpoint of CV death and HF hospitalization (HR 0.83; 95% CI, 0.73 to 0.95; P=0.005), and HF hospitalizations alone (HR 0.73; 95% CI, 0.61 to 0.88).[47]

Most recently a landmark clinical trial was published in November 2019, commonly referred to as DAPA-HF (2019). This RCT evaluated the potential benefits of therapy using dapagliflozin in HFrEF patients irrespective of diabetes status versus placebo. The results of this study demonstrated a reduction in its primary composite endpoint consisting of cardiovascular mortality, hospitalization for HF, or urgent HF visit (HR 0.74; 95% CI 0.65-0.85; P<0.001). It also showed that patients in the dapagliflozin group were 15% less likely to die of cardiovascular causes or be hospitalized for HF in this study.[48] In the future, SGLT2is may serve as a new class of medication for FH to assist with symptoms related to fluid retention and have already shown positive HF related outcomes.

Overview of Guideline Directed Medical Therapy for HFrEF

Treatment recommendations per the 2017 expert consensus management

guidelines are determined based on an individual's classified stage of HF and NYHA functional status (Table 7).[12] For patients with Stage A HF, current guidelines recommend that preventative therapies and management of co-morbidities that contribute to increased risk such as hypertension, hyperlipidemia, obesity, and diabetes mellitus are treated with optimal drug therapies to reduce risk of CV related events or progression of HF.

Patients with Stages B or C HF are recommended to start on evidence based GDMT as is indicated by their presentation, associated symptoms, and patient specific characteristics.[12] The goal for HFrEF patients on GDMT is to optimize a multi-drug regimen to target doses as is tolerated by the patient and indicated based on any comorbid conditions. The rationale for achieved target doses is that those are the doses which were studied and demonstrated positive outcomes for the specific medication. Although target dosing is ideal, safety and tolerability should always outweigh achieving a higher dose. Patients should be appropriately monitored and assessed based on their drug regimen and should regularly follow up with the provider who is managing their medications.

Patients who remain symptomatic on target dosing of GDMT or see worsening of functional status on max tolerated therapy may require additional specialized intervention such as a mechanical device (eg. LVAD) or other assistive strategies to manage their HF.[12] These patients are classified as Stage D HF and can no longer be managed with medications alone.

Conclusion

HF contributes to a significant cost burden on our healthcare system and understanding available medications and how to appropriately utilize GDMT is vital in helping to educate patients. Patients with HF often have a complicated medication regiment with significant pill burden making HF an important opportunity for pharmacist education and impact. As more literature, new medication indications, and entirely new drug classes will emerge in the setting of HF, it is vital that as pharmacists we educate ourselves on current best practices to best assist our patients.

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Assessment Questions

1. Which of the following is a risk factor are associated with the development of heart failure?
   a. Poor hygiene
   b. Moderate alcohol intake
   c. Excess fluid intake
   d. Uncontrolled hypertension

2. According to 2013 ACCF/AHA guidelines, a patient with a measured LVEF of 40% is defined as:
   a. Stage B heart failure
   b. NYHA class III heart failure
   c. HFrEF
   d. HFpEF
   e. NYHA class II heart failure

3. **True or False:** When using cardiac imaging to assess response to GDMT, it is acceptable to compare the results from two different validated imaging techniques.
   a. True
   b. False

4. A patient presents to you complaining that he is able to complete his day-to-day activities without any trouble, but once he starts to exercise, he notices significant shortness of breath and fatigue that resolves with rest. How would you classify this patient based on this information?
   a. Stage B, NYHA II
   b. Stage B, NYHA III
   c. Stage C, NYHA II
   d. Stage C, NYHA III

5. Which of the following is a required criterion for starting ivabradine therapy?
   a. Heart rate > 90 bpm
   b. Electrocardiogram with normal sinus rhythm
   c. Must have beta-blocker therapy discontinued
   d. Serum potassium <5.0 mmol/L
   e. HFrEF with LVEF ≤40%

6. Which of the following medications carries evidence for decreased mortality benefit in patients with HFrEF, Stage C, NYHA III?
   a. Spironolactone
   b. Digoxin
   c. Ivabradine
   d. Furosemide
   e. Canagliflozin

7. AB is a 59-year-old Caucasian male with a history of HTN, CAD, MI, HLD, and diagnosed HFrEF. He presents to the clinic for follow-up on his chronic conditions. Today, he is without complaints and has not seen any change in his symptoms of dyspnea or edema compared to baseline. At baseline, he is considered ACC/AHA Stage C and NYHA Class III. Today, his heart rate is 66 beats per minute and his blood pressure is 138/80 mmHg. His lungs are clear and the most recent laboratory results show a moderate elevation in serum potassium (value is on the upper limit of normal), and an eGFR of 38 ml/min/1.73m2. His in on the following medications: sacubitril/valsartan 97/103 mg BID, metoprolol succinate 150 mg daily, aspirin 81 mg daily, and simvastatin 20 mg daily. Given his history and physical exam, which is the most appropriate modification to make to AB's current drug therapy? infusion.
   a. Increase sacubitril/valsartan dose
   b. Increase metoprolol succinate dose
   c. Add digoxin
   d. Add hydralazine/isosorbide dinitrate
   e. Add spironolactone

8. YZ is a 48-year-old Caucasian female with a history of HTN, CAD, MI, HLD, T2DM, and diagnosed HFrEF. She presents to the clinic for follow-up on her

chronic conditions. Today, she is noticing a little bit of dyspnea or and increased LE edema compared to baseline. She has not noticed any significant weight changes at home. At baseline, she is considered ACC/AHA Stage C and NYHA Class II. Today, her heart rate is 58 beats and her blood pressure is 140/84 mmHg. Her lungs sound clear and the most recent laboratory results show a stable/controlled serum potassium, and an eGFR of 64 ml/min/1.73m2. She in on the following medications: sacubitril/valsartan 24/26 mg BID, metoprolol succinate 200 mg daily, metformin 500 gm daily, and rosuvastatin 20 mg daily. Given her history and physical exam, which of the following is/are appropriate medication recommendations to make to YZ's current drug therapy?

a. Add furosemide to correct fluid status
b. Add spironolactone to regimen for addition HF benefit and correct fluid status
c. Add dapagliflozin for addition HF benefit and correct fluid status
d. A and C are correct
e. A, B, and C are all correct

9. Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
   a. Yes
   b. No

10. On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety of your patients.

11. On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

12. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.

13. How useful was the educational material?
   a. Very useful
   b. Somewhat useful
   c. Not useful

14. How effective were the learning methods used for this activity?
   a. Very effective
   b. Somewhat effective
   c. Not effective

15. Learning assessment questions were appropriate.
   a. Yes
   b. No

16. Were the authors free from bias?
   a. Yes
   b. No

17. If you answered "no" to question 16, please comment (email info@pswi.org).

18. Please indicate the amount of time it took you to read the article and complete the assessment questions.

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10) _____
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17) _____
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