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Guideline for heart failure with reduced ejection fraction

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Definition and Pathway

Heart failure with reduced ejection fraction (HFrEF) is defined as clinical heart failure and left ventricular ejection fraction less or equal to 40%. Trials have shown that initiating therapies rapidly in the novo heart failure has demonstrated improvement or recovery of some patients' ejection fraction. Current guidelines recommend that for chronic HFrEF every patient should be taking renin-angiotensin inhibitors such as angiotensin II receptor/neprilysin inhibitors (ARNI), angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), beta-blocker (BB), sodium-glucose cotransporter 2 (SGLT2) inhibitors, mineralocorticoid antagonists (MRA), loop diuretic agents, and hydralazine/isosorbide dinitrate. Except for loop diuretic agents, all these therapies have been shown in randomized controlled trials to improve symptoms, reduce hospitalizations, and/or prolong survival. The STRONG-HF trial concluded that we could reduce risk of all-cause death in the 6 months after hospitalization or avoid readmission when compared with usual care if we have intensive management which included rapid up-titration of guideline directed medical therapy (GDMT) in patient with acute heart failure exacerbation and close follow-up, to reach target doses within 6 weeks of discharge after hospitalization. Some medications that have being studied and can be added if a patient has worsening symptoms even on GDMT are ivabradine, vericiguat, and digoxin. Vericiguat in the trial VICTORIA prove to reduce the risk of HF hospitalization and/or CV death. The SHIFT trial reveal that ivabradine reduces the risk of hospitalization for worsening heart failure in patients with reduced ejection fraction and a persistently elevated heart rate. From these medications, digoxin lacks contemporary data but is well known that it induces an increase in intracellular sodium that will drive an influx of calcium in the heart and cause an increase in contractility.

We have created **Figure 1** to facilitate visualization on how to initiate, titrate, and/or switch evidence-based GDMT for HFrEF Stage C (defined as structural heart disease with prior or current symptoms of HF) as well as target dose of medications (**Table 1**).

Table 1. Target dose of GDMT

Medication	Target dose (high-intensity)
ARNI	
Sacubitril/Valsartan	97/103 mg twice daily
ACEi	
Lisinopril	20 - 40 mg once daily
Enalapril	10 - 20 mg twice daily
Captopril	50 mg 3 times daily
ARB	
Losartan	50 - 150 mg once daily
Valsartan	160 mg twice daily
Candesartan	32 mg once daily
Beta-Blockers	
Bisoprolol	10 mg once daily
Carvedilol	25 - 50 mg twice daily
Metoprolol succinate	200 mg once daily
MRA	
Spironolactone	25 - 50 mg once daily
Eplerenone	50 mg once daily

Figure 1: GDMT for HFrEF stage C:

HFrEF stage C: four pillars of treatment

1. ARNI superior to ACEi/ARB

- ARNI and its starting dose:

Sacubitril/valsartan: 24/26mg bid or 49/51mg bid based on previous ACEi/ARB equivalent.

- ARNI should not be administered within 36 hours of switching from or to an ACEi.*

- ACEi/ARBs and their starting dose:

Lisinopril: 2.5-5 mg qd
Enalapril: 2.5 mg bid
Captopril: 6.25 mg tid
Candesartan: 4-8 mg qd
Losartan: 25-50 mg qd
Valsartan: 20-40 mg qd

- ACEi/ARB are only used for those with contraindications to ARNI.

- Increase dose and assess tolerability every 1-2 weeks until maximum tolerated or target dose achieved.
- Monitor blood pressure (BP) and basic metabolic panel (BMP) for initiation and titration.

2. Beta-blockers

- Evidence-based beta blockers and their starting dose:

Bisoprolol: 1.25 mg qd
Carvedilol: 3.125 mg bid
Metoprolol succ: 12.5-25 mg qd

- Increase dose every 2 weeks until maximum tolerated or target dose achieved.
- Monitor for bradycardia, orthostasis, hypotension, and/or signs of congestion after initiation and up titration.

3. Mineralocorticoid receptor antagonists

- MRAs and their starting dose:

Eplerenone: 25 mg qd
Spironolactone: 12.5-25 mg qd

- Increase dose every 2 weeks until maximum tolerated or target dose achieved.
- Monitor BMP at 1 week after initiation and up titration for potassium abnormalities.
- Follow up monitoring qmonth for 3 months and q3months for a year.

4. SGLT2 inhibitor

- SGLT2 inhibitors and their starting/target dose:

Dapagliflozin: 10 mg qd
Empagliflozin: 10 mg qd

- Ensure eGFR 25 or more for dapagliflozin before initiation.
- There is no need for monitoring BMP for electrolyte abnormalities.

Special indications:

- Persistent volume overload NYHA II-IV
: titrate **diuretics** ***(****Select initial loop diuretic agent dose depending on kidney function and prior exposure to diuretic therapy. Titrate dose over days-weeks. If reaching high doses of loop diuretic dosing (equivalent of 80mg furosemide twice daily) consider changing to different diuretic agent or adding thiazide diuretic taken together with loop diuretic.*
- Persistently symptomatic African-American NYHA III-IV
: add **hydralazine + isosorbide dinitrate :** Initial dose 20/37.5 mg tid. Titrate every 2 weeks to target dose of 40/75 mg tid. Monitor for hypotension.

* Recommendation due to significantly increased risk of angioedema.

With the initiation of GDMT, clinical reassessment every 1 to 3 weeks is recommended until safely titrated to target dose. This would take on average 2~4 months for stabilization. During the initial and follow up assessment, volume status, symptoms, labs, and/or imaging tests are recommended. **Tables 2 and 3** illustrate when to use echocardiogram, brain natriuretic peptide (BNP) and pulmonary artery pressure to complement our clinical assessment.

Table 2: Complementary additional tests to guide GDMT

Exam	When	Consider
Echocardiogram	Initial, and 3-6 months into GDMT	The interval would be earlier if high-risk features (I-NEED-HELP acronym below) are present such as low EF or markedly elevated BNP, and later if it is expected or LV remodeling to take further time. Repeat echocardiogram could be indicated if any change in clinical status.
BNP or pro-BNP	When diagnosing HF, and repeat in every assessment when titrating GDMT	Severe kidney dysfunction may interfere with the interpretation of BNP, so BNP interpretation should always be interpreted within the context of drugs and other comorbidities.
Pulmonary artery pressure (PAP)	Not routinely done.	Can be useful in patients with refractory symptoms, worsening kidney function, or repeated hospitalizations to guide HF therapy changes and select candidates for advanced therapies. Ways to measure pulmonary artery pressure are implantable CardioMEMS™ Heart Sensor in ambulatory HF patients and intrathoracic impedance monitoring via pacemakers.

Table 3: I-NEED-HELP Acronym for high-risk features assessment

I	Inotropes (previous or ongoing need)
N	NYHA IIIB/IV or persistently elevated BNP
E	End-organ dysfunction
E	Left ventricular ejection fraction < 20%
D	Defibrillator shocks (recurrent, appropriate)
H	Hospitalization > 1 (over the last year)
E	Persistent edema or increasing diuretic requirements
L	Consistently low blood pressure, SBP < 90-100 mmHg
P	Prognostic medication – inability to uptitrate or need to reduce or discontinue medications.

When do we need to refer to a heart failure specialist?

Referral to a HF specialist or program is critical in certain clinical scenarios to optimize therapies and evaluate advanced HF treatments. Key triggers for referral include:

1. New-onset HF for etiology evaluation and management.
2. Chronic HF with high-risk features such as persistent symptoms, low systolic BP, or worsening renal function.
3. Poor response to guideline-directed medical therapy after 3 months.
4. Need for a second opinion regarding HF etiology.
5. Annual reviews for patients with established advanced HF.
6. Consideration for clinical trial participation.

How can we optimize patient care and coordination?

- Manage complex treatment regimens involving medications, devices, and lifestyle changes.
- Handle all comorbidities, which are common in HF patients, especially the elderly.
- Avoid involving multiple clinicians across various care settings, as it can increase the risk of healthcare inefficiencies and problems arising from miscommunication.
- Adopt team-based approaches, which have shown better outcomes in terms of death rates, hospitalizations, and quality of life.
- Employ tools such as electronic health records, patient portals, and remote monitoring devices to enhance care coordination and patient engagement.

How can we improve patient adherence to treatment?

- Recognize that nonadherence is common and address it on each encounter. Consider social determinants of health (SDOH).
- Shift from a hierarchical approach to a shared decision-making model that emphasizes patient empowerment.
- Utilize various interventions such as patient education, medication management, clinical pharmacist consultations, cognitive-behavioral therapies, medication reminders, social worker consultation to address SDOH, and incentives.
- Implement systematic approaches and policies to support adherence, including the use of electronic health records, patient portals, and remote monitoring technologies.
- Employ strategies tailored to individual patients to address specific barriers to adherence, such as socioeconomic factors and health literacy.

For more information, please visit:

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