Heart Failure with Reduced Ejection Fraction

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KEYWORDS

• Heart failure with reduced ejection fraction • Guideline-directed medical therapy
• Left ventricular systolic dysfunction • Heart transplantation

KEY POINTS

- Heart failure with reduced ejection fraction (HFrEF) is defined as clinical heart failure with a left ventricular ejection fraction $\leq$40%.
- Guideline-directed management and therapy (GDMT), which includes RAAS inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors, forms the foundation of HFrEF medical treatment. The best outcomes to date for HFrEF are associated with the full implementation of evidence-based management and therapy.
- Treatment plans should incorporate the benefits of cardiology referral for additional diagnostic evaluation and treatment approaches to halt the progression of heart failure. Early diagnosis and optimization of comorbidities, including diabetes, hypertension, and coronary artery disease, is essential for improving clinical outcomes in HFrEF.
- Advanced therapies on the GDMT foundation, including cardiac resynchronization therapy, implantable cardioverter-defibrillators, and mechanical circulatory support, where appropriate, constitute optimal medical therapy for patients with persistent symptoms.
- Heart transplantation is a successful and viable option for end-stage disease. Palliative care may represent the best care when disease-modifying interventions are not successful.

INTRODUCTION/BACKGROUND

Heart failure with reduced fraction (HFrEF) is characterized by impaired left ventricular contractility, resulting in reduced cardiac output, and is associated with significant morbidity, mortality, and healthcare costs.[1,2] Recent advances in pharmacologic and device therapies offer the best outcomes to date, with modeling exercises sourced from clinical trial data indicating marked improvement in survival from

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Abbreviations	
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ARBs	angiotensin receptor blockers
ARNI	angiotensin receptor antagonist/neprilysin inhibitor
BNP	B-type natriuretic peptide
CRTs	cardiac resynchronization therapy
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GDMT	guideline-directed medical therapy
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
ICDs	implantable cardioverter-defibrillator
ID	iron deficiency
JHFS	Japanese Heart Failure Society
LV	left ventricular
LVEF	left ventricular ejection fraction
MRAs	mineralocorticoid receptor antagonists
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PA	pulmonary artery
RAAS	renin-angiotensin-aldosterone system
SGLT	sodium-glucose cotransporter

5-year mortality rates of approximately 50% to 10-year rates at approximately 50%.[3,4] There is a robust opportunity to modify the natural history for those with symptomatic left ventricular dysfunction, and failure per se is no longer an inevitability. Early identification, comprehensive risk stratification, and implementation of evidence-based therapies facilitate the best possible outcomes.[5]

DIAGNOSIS AND DEFINITIONS

Heart failure (HF) is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. The universal definition of HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality with obligatory corroboration by objective evidence of congestion—either elevated natriuretic peptide levels and/or objective clinical evidence of pulmonary or systemic congestion.[6] Similarly, the diagnosis of HFrEF requires clinical symptoms of HF (dyspnea, fatigue, fluid retention) and objective evidence of reduced left ventricular ejection fraction (LVEF) less than or equal to 40%. The diagnosis of HFrEF must meet this troika of symptoms, left ventricular (LV) dysfunction, and objective evidence of congestion.[7]

Various predicate definitions of HF reflect the progression of knowledge endorsed by a series of clinical practice guidelines: American College of Cardiology Foundation/American Heart Association (AHA) (2013) describes it as “a complex clinical syndrome” stemming from any structural or functional impairment of the heart, with dyspnea and fatigue and fluid retention as cardinal manifestations; European Society of Cardiology (ESC) (2016) characterized HF by typical symptoms alongside possible signs caused by structural and/or functional cardiac malfunction leading to decrease in the heart pumping function and/or increased filling pressure; and Japanese Circulation Society/Japanese Heart Failure Society (JHFS) (2017) more succinctly defined HF as a clinical syndrome comprising of signs and/or exercise capacity decline

resulting from reduced heart pumping ability.[8–10] The current universal definition now supersedes all foregoing descriptions.

The clinical syndrome of HF is identified by a well-recognized cluster of signs and symptoms: difficulty breathing, fluid retention/swelling, tiredness, activity intolerance, and limited exercise capacity. Signs consistent with HF harken to the bedside experience and require adroit clinical acumen: jugular venous distension, pulmonary rales, proto-diastolic heart signs, hepatic congestion, dependent edema (including presacral edema in those who are mostly recumbent), reduced peripheral circulation and the bedside ability to classically distinguish *wet and warm* from *cold and wet* leading to markedly different acute treatment algorithms.

Classification by ejection fraction: Ejection fraction (EF), as a description of end-diastolic volume variation from systole to diastole, as established by E. Braunwald, remains the cornerstone of phenotype determination for LV dysfunction.[11] The American College of Cardiology (ACC)/AHA 2022 guidelines reaffirmed HFrEF as a clinical syndrome characterized by structural or functional cardiac abnormalities that result in a LVEF less than or equal to 40%.[12] The 2013 ACC/AHA guidelines introduced specific terminology, including "HFpEF-borderline" for patients whose EF falls between 41% to 49%, and "HFpEF-improved" for individuals whose EF increased from lower values to exceed 40%, categorizing both under HFpEF. Furthermore, Heart Failure Association/ESC and guidelines have established a third classification—HF with midrange EF (HFmrEF) or mildly reduced EF—for those with EFs ranging from 41% to 49%. Remarkably, normal EF varies by sex as women consistently exhibit higher EF. Practically, any EF less than 60% is deemed abnormal and extends the indication for specific evidence-based therapies (eg, sodium-glucose cotransporter 2 inhibitors and the angiotensin receptor antagonist/neprilysin inhibitor [ARNI]).[12] Future assessments of ventricular function, including global longitudinal strain and replacement fibrosis, offer the potential for not only better characterization but also improved prognostication for clinical outcomes.

Biomarkers in heart failure diagnosis: Natriuretic peptides like B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) show elevated levels in most HF types and play a crucial role in establishing a HF diagnosis across numerous clinical contexts,[13] mainly when uncertainty exists. Current clinical practice guidelines assign these biomarkers (NT-proBNP and BNP) the highest recommendation classification for confirming or ruling out HF. Clinical practice guidelines instruct the best utility for biomarker assessment but the best takeaway is the additive value, that is, incorporation in the totality of clinical assessment and the deployment of an *a priori* Bayesian model of diagnostic yield based on the pretest likelihood of disease (with best use in those cases of intermediate likelihood).

Staging and Functional Classification

Stage A represents individuals at risk for HF but without symptoms, structural heart disease, or cardiac biomarkers indicating stretch or injury (hypertension, atherosclerotic cardiovascular disease, diabetes, metabolic syndrome, obesity, exposure to cardiotoxic substances, and genetic variants associated with cardiomyopathy).[6]

Stage B encompasses patients with structural heart disease, but no previous or current HF signs or symptoms. Structural heart disease may include reduced left or right ventricular function, LV hypertrophy, chamber enlargement, wall motion abnormalities, or valvular heart disease. A presumptive stage B2 includes evidence of increased filling pressures detected through invasive hemodynamic measurements or imaging, and/or elevated natriuretic peptides. These patients benefit from early treatment

with renin-angiotensin-aldosterone system (RAAS) inhibitors and beta-adrenergic blocker therapy.

Stage C refers to structural heart disease with previous or current HF symptoms. Stage C2 represents those with recurrent (but not persistent) symptoms, including repeat hospitalization, despite treatment with evidence-based therapy.

Stage D describes severe persistent HF symptoms that disrupt daily activities, with recurring hospitalizations despite attempts to optimize guideline-directed medical therapy.

Treatment approaches involve addressing risk factors (stage A), managing risk and structural heart disease to prevent HF (stage B), and alleviating symptoms while reducing morbidity and mortality (stages C and D).

New York Heart Association (NYHA) functional classification includes:

- Class I: No physical activity limitations. Daily physical activity without any HF symptoms.
- Class II: Slight physical activity restrictions. Comfortable when resting, but ordinary physical activity causes HF symptoms.
- Class III: Significant physical activity limitations. Comfortable when resting, but less than ordinary activity triggers HF symptoms.
- Class IV: Unable to perform any physical activity without experiencing HF symptoms, or symptoms that occur even at rest.

The NYHA classification system evaluates the symptoms and functional abilities of patients experiencing symptomatic HF (stage C) or advanced HF (stage D).

MEDICATIONS AND DEVICES MANAGEMENT

Initial Management: Clinical implementation prioritizes diuretic administration and decongestion strategies as first-line interventions for patients with HF. Medication initiation should closely follow diuretic administration and begin with patient stabilization, with particular attention to care transitions and postdischarge management coordination.[14]

The treatment of risk factors and comorbidities such as hypertension, diabetes, obesity, or coronary artery disease constitutes appropriate management of Stage A HF or pre-HF. The goal is to retard the likelihood of advancement from Stages A/B to C/D, but data do not fully endorse that continuum.

Pharmacological Options: The cornerstone of HFrEF management, that is, guideline directed management and therapy (GDMT) consisting of 4 primary medication classes:

1. RAAS inhibitors (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], or ARNI)
2. Beta-blockers
3. Mineralocorticoid receptor antagonists (MRAs)
4. sodium-glucose cotransporter 2 (SGLT2) inhibitors

Sequential initiation and dose optimization of these medications has shown substantial mortality benefits compared to historical treatments. The PARADIGM-HF[15] trial demonstrated the superiority of sacubitril/valsartan over enalapril in reducing cardiovascular mortality and HF hospitalizations. The DAPA-HF[16] and EMPEROR-Reduced[17] trials established SGLT2 inhibitors as a new pillar of HFrEF therapy, with significant reductions in the composite of cardiovascular death or HF hospitalization.[13]

Key Contemporary Heart Failure Trials Supporting Current Treatment Guidelines on the Foundation of Renin-Angiotensin-Aldosterone System-Inhibition, Sympathetic Nervous System Inhibition (Beta Blockers) and Mineralocorticoid Antagonism

Current guideline-directed therapy for HFrEF includes 4 medication classes, with SGLT2 inhibitors being the most recent additions (**Table 1**). While loop diuretics play an essential role in managing fluid overload in patients with HFrEF, once the patient approaches or achieves normal fluid status, it becomes essential to introduce and optimize medications through an evidence-based approach.[13]

Underutilized Approved Treatments

- *Hydralazine/isosorbide dinitrate:* For various reasons, hydralazine/isosorbide dinitrate therapy, though indicated for certain HF patients, is often overlooked in eligible individuals, currently defined by self-identified Black or African American race. The benefits, demonstrated in the A-HeFT and ancillary studies are irrefutable (43% relative reduction in mortality and 33% relative reduction in HF hospitalization and positive impact on health status),[18] but the requirement to address race assignment in clinical medicine limits use.
- *Ivabradine:* Heart rate independently predicts outcomes in HFrEF. A meta-analysis of beta-blocker trials suggests that heart rate reduction in normal sinus rhythm directly correlates with improved outcomes.[19] Although evidence-based beta-blocker therapy is the recommended guideline-directed medical therapy and lowers heart rate in HFrEF, some patients cannot tolerate higher beta-blocker doses and continue to have elevated heart rates.[20] Additionally, patients on target doses occasionally maintain persistent resting heart rates above 70 beats per minute.
- *Vericiguat:* Vericiguat, an oral soluble guanylyl cyclase stimulator, directly binds and activates soluble guanylyl cyclase and increases cyclic guanine monophosphate production. Cyclic guanine monophosphate has several potentially therapeutic effects in HF patients, including blood vessel dilation, improvement in blood vessel lining function, as well as reduction in scarring and structural changes of the heart. The VICTORIA trial demonstrated that in higher-risk patients with HFrEF (LVEF<45%) already receiving guideline-directed medical therapy with worsening symptoms (as evidenced by a HF hospitalization or need for intravenous diuretics).[21] This agent may be suitable for the described Stage C2 patient.

Additional Heart Failure Trials

This is **Table 2** Additional heart failure trials.

Optimizing Multi-drug Therapy and Monitoring

- To maximize the benefits of guideline-directed medical therapy in patients with chronic HFrEF, medications must be quickly started and adjusted to the highest tolerated doses. Medication doses exceeding those investigated in randomized clinical trials, even if well-tolerated, have not demonstrated additional benefits and are generally not advised while many patients will do quite well and subtarget doses. It is very important to individualize medical therapy, particularly for long-term use (**Table 2**).
- Dose adjustment strategies with the aim of achieving target or maximum tolerated doses of guideline-directed medical therapy. This process may be facilitated through virtual healthcare or specialized medication adjustment clinics.

Table 1
Key contemporary heart failure trials supporting current treatment guidelines

Trial Demographics	PARADIGM-HF[15]	DAPA-HF[16]	EMPEROR-Reduced[17]
Ages	≥18 y, NYHA II-IV	≥18 y, NYHA II-IV	≥18 y, NYHA II-IV
LVEF	<35%	≤40%	≤40%
Natriuretic peptides	BNP ≥100–150 pg/mL or NT-proBNP ≥400–600 pg/mL (higher threshold for nonhospitalized patients)	NT-proBNP ≥400–900 pg/mL (higher for nonhospitalized or AF patients)	NT-proBNP thresholds vary by LVEF (600–5000 pg/mL, higher for AF)
History	HF hospitalization within 12 mo	HF diagnosis ≥2 mo	NYHA II-IV for ≥3 mo
Therapy	Sacubitril/valsartan	Dapagliflozin	Empagliflozin
Finding	Reduced cardiovascular mortality and HF hospitalizations compared to enalapril	Reduced worsening HF or cardiovascular death, improved symptoms regardless of diabetes status	Reduced cardiovascular death or HF hospitalization, slowed kidney function decline

Table 2
Additional heart failure trials

Trial Demographics	VICTORIA[25]	GALACTIC-HF[22,a]	AFFIRM-AHF[23,b]	HEART-FID[24,b]
Ages	≥18 y, NYHA II-IV	18–85 y, NYHA II-IV	≥18 y	≥18 y
LVEF	<45%	≤35%	≤50%	≤40% ambulatory
Inclusion Criteria: Natriuretic peptides or ID	*Natriuretic peptides*: BNP >300–500pg/mL or NT-proBNP >1000–1600pg/mL (higher for AF)	*Natriuretic peptides*: NT-proBNP ≥400–1200pg/mL or BNP ≥125–375pg/mL (higher for AF)	*ID:* Serum ferritin of <100 ng/mL, or 100–299 ng/mL with transferrin saturation of <20%	*ID*: Serum ferritin level of <100 ng/mL or a level of 100–300 ng/mL with a transferrin saturation of <20%
History	HF hospitalization within 6 mo or IV diuretics within 3 mo	Current HF hospitalization or urgent ED visit/ hospitalization within 12 mo	Current hospitalization for HF as the index with IV diuretics	Hospitalization for HF or elevated natriuretic peptide
Therapy	Vericiguat	Omecamtiv mecarbil	Intravenous Ferric Carboxymaltose	Intravenous Ferric Carboxymaltose
Finding	Reduced composite of cardiovascular death or HF hospitalization in high-risk patients	Modest reduction in composite of HF events or cardiovascular death, greatest benefit in patients with LVEF ≤28%	Reduction in recurrent hospitalizations without effect on cardiovascular death	No difference in a hierarchical composite of death, HF hospitalizations, and 6-min walk distance

Abbreviations: ED, emergency department; ID, iron deficiency.

[a] Omecamtiv is not Food and Drug Administration (FDA)-approved, though clinical trials are ongoing to test the benefit of myosin activation further.

[b] The European guidelines now recommend intravenous iron therapy for symptomatic heart failure patients with iron deficiency regardless of anemia status. The FDA approved IV ferric carboxymaltose for HF class II/III to improve exercise capacity.

- Prompt and rapid optimization of guideline-directed medical therapy particularly at the time of hospitalization or an episode of urgent care is recommended because improvements in patient-reported outcomes and reductions in HF hospitalizations and deaths occur shortly after starting these medications. Multiple medications may be initiated and/or adjusted simultaneously, and in certain situations, all 4 drug classes might be started concurrently (**Fig. 1**).

Devices Implantable Cardioverter-Defibrillator (ICDs) and Cardiac Resynchronization Therapy (CRTs): Given the correct awareness of GDMT, that is, guideline-directed management and therapy, device therapies fall into this realm. ICDs demonstrated survival benefits initially for secondary prevention in cardiac arrest survivors (Antiarrhythmics Versus Implantable Defibrillators, Cardiac Arrest Study Hamburg, Canadian Implantable Defibrillator Study trials) established breakthrough mortality benefits in patients with reduced EF ($\leq$30–35%) across various clinical scenarios as preemptive strategies to reduce deaths attributable to sudden cardiac death.[25–27] Whether this now decades old clinical trial result demonstrating clear benefit remains as strong in the setting of contemporary GDMT is uncertain. The DANISH trial showed benefit only for sudden cardiac death reduction in nonischemic cardiomyopathy. Economic analyses consistently demonstrate cost-effectiveness for ICD therapy with ratios generally below $60,000 per life-year added when survival increased by greater than 1.4 years, inferring the necessity for careful risk assessment and candidacy review.[28]

CRT benefits emerged from landmark trials (MIRACLE, COMPANION, CARE-HF, REVERSE, MADIT-CRT, RAFT) showing improvements in mortality, hospitalization, and quality of life metrics across HF populations.[29–31] The greatest benefits occurred in patients with left bundle branch blockmorphology and QRS durations $\geq$150 ms, that is, electrical remodeling, though some benefits extended to 120 ms–149 ms QRS durations. Economic evaluations confirmed cost-effectiveness, particularly in populations with larger expected mortality reductions. Benefits extended to specific

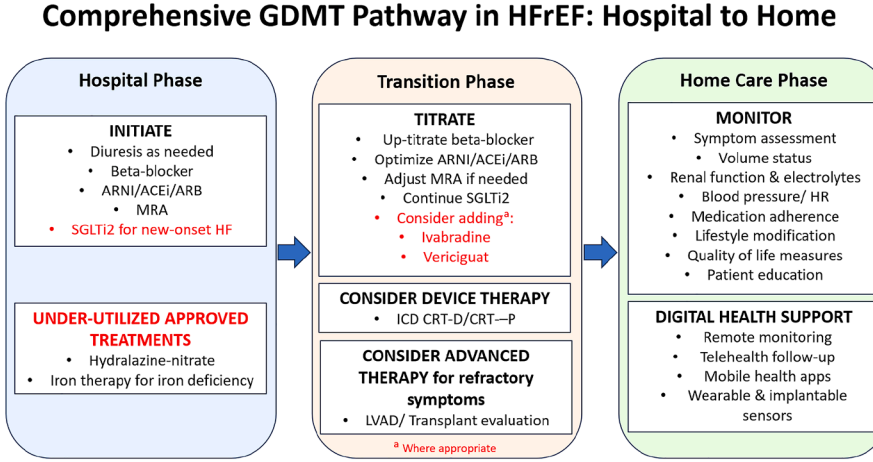

Fig. 1. Recommendations for initiation and titration of GDMT in HFrEF from the hospital phase of care to home: initiate/titrate/monitor. ARNI, angiotensin receptor-neprilysin inhibitor; GDMT, guidelines-directed medical therapy; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

populations, including those with LVEF 35% to 50% (BLOCK-HF), atrial fibrillation (AF) (MUSTIC AF, RAFT, SPARE), and those with high ventricular pacing burden.[32–34]

Functional Mitral Regurgitation Interventions: The MITRA-FR and COAPT trials examining percutaneous mitral valve clipping yielded contradictory outcomes, with MITRA-FR (showing no benefit in the composite endpoint of death/HF hospitalization), while COAPT (demonstrated significant reductions in HF hospitalizations and all-cause mortality).[35–37] Several parameters differentiated these studies collectively, suggesting that percutaneous mitral valve repair benefits carefully selected patients with significant functional MR despite maximally tolerated medical/device therapy, with patient selection representing the critical outcome determinant.

Implantable Pulmonary Artery Pressure Monitoring Devices: The CardioMEMS HF system and similar remote pulmonary artery (PA) pressure monitoring devices are changing how HF is managed. These implantable systems track daily pressure readings and send the PA pathophysiological data to care providers.[38] This allows the care team to observe early warning signs of HF before the symptoms become noticeable. With this proactive approach guided by actionable information, they can adjust medications or treatments in real-time, helping to lower hospital visits and making a palpable difference in overall quality of life.[39]

Advanced Therapies: For patients experiencing persistent symptoms despite exhaustive medical and device interventions, several advanced therapeutic pathways exist. Heart transplantation offers a definitive solution when viable, while LV assist devices serve either as permanent support (destination therapy) or as a temporary measure until transplantation becomes possible. This is also a patient population suitable for enrollment in clinical trials exploring novel therapeutics. For individuals deemed unsuitable candidates for these advanced care approaches, palliative care provides focused symptom management to maintain quality of life. And for some, hospice care is the best and most humane option. The selection among these options depends on individual patient factors, including age, comorbidities, and personal preferences regarding treatment goals.

Management of Comorbidities in HF: Cardiovascular comorbidities in HFrEF patients require targeted interventions based on association strength and evidence quality. Coronary artery disease management involves revascularization for suitable candidates, while atrial fibrillation requires anticoagulation, possible ablation, or AV nodal procedures with CRT implantation following established guidelines. Valvular conditions—mitral regurgitation and aortic stenosis—demand multidisciplinary structural heart team involvement, with transcatheter intervention considered for select MR patients after GDMT optimization. Hypertension and dyslipidemia, despite uncertain direct associations with outcomes, warrant management per current guidelines for prevention benefits. Peripheral and cerebrovascular diseases, moderately associated with HF outcomes, should follow their respective management protocols despite limited specific HF evidence.

Noncardiovascular comorbidities significantly impact HF trajectories and require systematic management.[40] Diabetes necessitates endocrinologist consultation, regular creatinine and albuminuria monitoring, SGLT inhibitor therapy, and adherence to current standards. Nutritional interventions emphasize low-salt, plant-forward diets, while hyperkalemia management includes dietary modifications and potassium binders to optimize GDMT. Additional considerations include cautious obesity management (noting glucagon-like peptide-1 agonist benefits in HFpEF), smoking cessation for pulmonary disease, thyroid disorder treatment, and appropriate vaccination against viral infections—all requiring specialty consultation and guideline-directed approaches.

CLINICAL MANAGEMENT STRATEGIES

Management Strategies for Heart Failure Patients

- Initial treatment involves diuretic therapy with prompt follow-up to ensure progressive decongestion.[41]
- Despite recognizing the critical importance of establishing comprehensive quadruple therapy for treating HFrEF, sometimes initiating or adjusting guideline-directed medical therapy to reach the target doses achieved in clinical trials may not be feasible.
- During the introduction and dose adjustment of medications affecting kidney function, a reduction in the estimated glomerular filtration rate exceeding 30% or developing elevated potassium levels should signal clinicians to consider dose reduction or a slowing in the rate of up-titration. However, healthcare providers should note brief, temporary changes in kidney function measurements are expected during intensive diuretic treatment or when starting RAAS inhibitors and do not predict long-term negative outcomes nor require dose modifications.
- A sensible approach for patient assessment and care following HFrEF diagnosis involves regular evaluation after guideline-directed medical therapy is started and adjusted to reach clinical trial doses or maximally tolerated levels. Recurrent evaluations every 3 to 6 months represent a reasonable target. However, many patients may need more frequent check-ups to monitor clinical stability and revisit opportunities for further medication adjustments. Cardiac rehabilitation is an evidence-based strategy in HFrEF benefitting cardiovascular mortality and morbidity, yet it is poorly deployed. The benefits include medication titration, tracking symptoms, enhancing the quality of life, and building exercise capacity. Telemedicine allowing outpatient medication adjustment is a reasonable alternative for certain patients and will assume an increasingly prominent role in HF management, particularly for medication optimization.
- Key processes include initiating, adjusting doses, optimizing treatment regimens, promoting medication adherence, and utilizing clinical judgment for echocardiography, NT-proBNP measurements, and other biomarker tests as deemed appropriate.

Multi-Team-Based Approach: Optimal care delivery incorporates coordinated team-based approaches with integrated information systems. Consider integrating pharmacist support for medication management optimization across a continuum or outpatient and inpatient teams.

Most HF patient care is delivered by practitioners outside cardiology, including primary care physicians, general internal medicine or family medicine providers, hospital-based clinicians, emergency department clinicians, and other specialists. Facilitate referral to HF specialists when appropriate. Key considerations for noncardiologists include: (1) the fundamental importance of appropriately identifying and managing patients with HF risk factors to prevent or postpone HF development; (2) understanding that patients with pre-HF conditions, such as asymptomatic individuals with high natriuretic peptide measurements, will likely benefit from cardiology referral for additional diagnostic evaluation and treatment approaches to halt HF progression; (3) recognizing that proper diagnosis and early intervention should not be overlooked or postponed in patients exhibiting HF symptoms or/and signs and should be considered for referral to HF specialists (**Fig. 2**).

Advanced Care Pathways: For patients who demonstrate resistance or intolerance to GDMT, an evaluation for advanced therapeutic interventions, including transplantation candidacy, mechanical circulatory support implementation, or palliative care

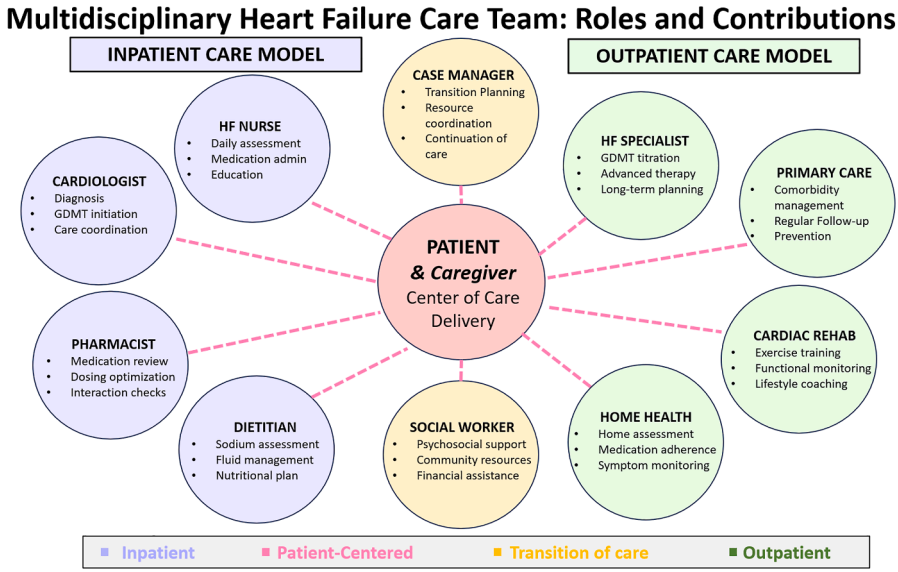

Fig. 2. The roles of the team members in the care cycle: HF nurse, primary care, nutrition team, defined by their roles and contribution to the care model.

services is appropriate.[42] Patients experiencing advanced HF and engaging in shared decision-making discussions should receive referrals to specialized HF management teams. These specialized teams conduct comprehensive reviews of HF treatment protocols, evaluate eligibility for advanced therapeutic interventions, and implement palliative care strategies—including palliative inotropic support when aligned with the patient's expressed care objectives.[43]

A holistic approach to HFrEF should include a heart-healthy diet low in sodium, saturated fats, and processed foods while emphasizing fruits, vegetables, whole grains, and lean proteins to support cardiac function and manage weight.[44] Lifestyle modifications such as stress management, adequate sleep, and medication adherence, combined with supervised cardiac rehabilitation that includes aerobic and resistance training, create a comprehensive treatment strategy that addresses both the physiological and psychological aspects of HF management.[45] Regular exercise through a structured cardiac rehabilitation program has been shown to significantly improve exercise capacity and reduce mortality and hospitalization rates in HFrEF patients, with studies demonstrating lower risk of death compared to nonrehabilitation groups.[46]

In-Hospital Initiation of Evidence-Based Heart Failure Therapies

A designated follow-up analysis from PIONEER-HF revealed that heart failure patients receiving their first diagnosis who started angiotensin receptor-neprilysin inhibitor treatment while hospitalized showed greater decreases in heart failure biomarkers than those beginning treatment after leaving the hospital.[47] This observation indicates that prompt hospital-based initiation of guideline-recommended medications may enhance patient results and speed up clinical recovery.

In a parallel finding, the SOLOIST-WHF study demonstrated that sotagliflozin, which inhibits both SGLT1 and SGLT2, reduced cardiovascular events in diabetic heart

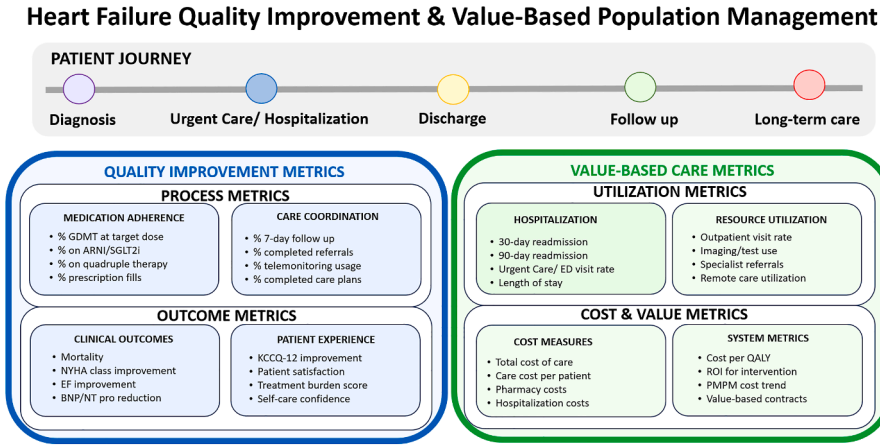

Fig. 3. Heart failure patient journey and metrics dashboard: a crossover between values based in HF and population management. KCCQ, Kansas City cardiomyopathy questionnaire; PMPM, per member per month; QALY, quality adjusted life year; ROI, return on investment.

failure patients when administered either during hospitalization or soon after discharge from the hospital.[48] SOLOIST-WHF reinforces the emerging view that hospitalization provides a vital opportunity to implement potentially life-preserving medications.

The STRONG-HF trial added further support by showing that escalation of GDMT therapy during hospitalization, coupled with monitoring after discharge, markedly lowered the combined outcome of death and HF rehospitalization versus standard care.[49] Interestingly, patients under intensive treatment experienced superior quality of life gains and fewer complications despite receiving more aggressive medication adjustments.

TRANSITION investigated whether starting sacubitril/valsartan in-hospital or postdischarge was safe and effective for stabilized patients previously admitted for acute HF decompensation.[50] The study found similar safety outcomes and successful treatment establishment with both approaches, offering timing flexibility while confirming in-hospital initiation as a feasible strategy.

Real-world evidence from the OPTIMIZE-HF registry showed that patients who received evidence-supported beta-blockers and ACE inhibitors/ARBs during hospitalization experienced significantly reduced 60 to 90-day death rates and fewer readmissions.[51,52] This extensive practical dataset confirmed that not starting these treatments during hospital stays represented a lost chance to improve outcomes after discharge.[53]

Taken together, these investigations establish that hospitalization should not be viewed solely as a stabilization period, but rather as an ideal moment to establish a foundation of comprehensive guideline-directed medical therapy that can later be refined in outpatient settings, leading to better clinical outcomes and decreased healthcare system burden (**Fig. 3**).

SUMMARY

HFrEF remains a significant clinical challenge, but more hope and optimism exist today based on a robust evidence base. The challenge is implementation, and the requirement is multidisciplinary management. Early diagnosis, comprehensive risk

stratification, and guideline-directed care can substantially improve outcomes. Optimization of GDMT, including RAAS inhibitors, beta-blockers, MRAs, and SGLT2 inhibitors, remains the foundation of treatment. Device therapy and advanced interventions should be considered for appropriate patients with refractory symptoms. Future directions include personalized medicine approaches based on HF phenotypes and novel therapies targeting underlying pathophysiology.

CLINICS CARE POINTS

- Initiate all 4 pillars of GDMT (RAAS inhibitors, beta-blockers, MRAs, and SGLT2 inhibitors) as soon as possible after diagnosis of HFrEF.
- Consider switching from ACE inhibitor/ARB to ARNI (sacubitril/valsartan) in patients with persistent symptoms despite optimal medical therapy, or preferably initiate ARNI as first-line therapy. In some patients, the combination of nitrates and hydralazine may be indicated.
- For patients with clear indication and especially those with persistent symptoms despite optimal medical therapy, refer for evaluation for device therapy (ICD, CRT) as a component of GDMT or advanced HF therapies for worsening symptoms and a declining prognosis.
- Screen for and aggressively manage comorbidities, including coronary artery disease, AF, diabetes, and ID.
- Implement a patient-centered approach with shared decision-making regarding goals of care, especially for patients with advanced disease.
- Remain aware of the value-based proposition in the management of HF.
- Frameshift the clinical paradigm away from failure per se and consider all opportunities to advance care and improve outcomes.

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