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EXPERT CONSENSUS DECISION PATHWAY

2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

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OVERVIEW

The 2021 Update to the 2017 American College of Cardiology (ACC) Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction[1] provided a practical, streamlined resource for clinicians managing patients with heart failure with reduced ejection fraction (HFrEF). The expert consensus decision pathway (ECDP) provided guidance on introducing the numerous evidence-based therapies, improving adherence, overcoming treatment barriers, acknowledging contraindications and situations for which little data exist, affording expensive therapies, treating special cohorts, and making the transition to palliative care. Rather than focusing on extensive text, the document provided practical tips, tables, and figures to make clear the steps, tools, and provisos needed to treat the patient with HFrEF successfully and expeditiously. Many of the pivotal issues addressed in the ECDP were not the substance of clinical trials; rather, they represent the challenge of clinical practice.

Since publication of the 2021 ECDP, new data have developed that necessitate an update to the ECDP, including publication of the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.[2] This update thus serves as updated guidance to clinicians based on contemporary knowledge. The treatment of HFrEF can feel overwhelming, and many opportunities to improve patient outcomes are being missed; hopefully, this ECDP will streamline care to realize the best possible patient outcomes in HF (heart failure).

1. INTRODUCTION

The prevalence of HF is escalating rapidly, with a projected increase of 34% in upcoming decades.[3,4] Compounding this, HF is a syndrome that consumes

substantial health care resources, inflicts considerable morbidity and mortality, and adversely affects quality of life. Important breakthroughs have redefined opportunities to change the natural history of HF with a broad range of medical therapies, devices, and care strategies.

The purpose of this document is to update the 2021 ECDP with further data from recent studies and to provide succinct, practical guidance for managing patients with HFrEF. The format of the 10 Pivotal Issues in the prior versions of this ECDP was preserved, and their associated treatment algorithms and tables have been updated to accommodate the evolving evidence. The Preface and Methods sections are accessible online in the Supplemental Appendix.

Ten Pivotal Issues in HFrEF

1. How to initiate, add, or switch therapies with consideration of newer evidence-based guideline-directed treatments for HFrEF.
2. How to achieve optimal therapy given multiple drugs for HF, including augmented clinical assessment (eg, imaging data, biomarkers, and filling pressures) that may trigger modifications in guideline-directed therapy.
3. When to refer to an HF specialist.
4. How to enhance care coordination.
5. How to improve medication adherence.
6. How to tailor treatment in specific patient cohorts: African-American patients, older adults, and patients with frailty.
7. How to manage patients' costs and increase access to HF medications.
8. How to manage the increasing complexity of HF.
9. How to manage common comorbidities.
10. How to integrate palliative care and the transition to hospice care.

2. ASSUMPTIONS AND DEFINITIONS

To limit inconsistencies in interpretation, specific assumptions (eg, treatment effects in varied populations) were considered by the writing group in development of the ECDP. References are supplied when applicable or appropriate.

2.1. General Clinical Assumptions

1. Although many topics are generalizable to all patients with HF, the focus of this effort is on patients with HFrEF. The reader is directed to the 2023 ACC ECDP on Management of HFpEF for more focused details on care for this population.[5]
2. Although some of the recommendations may be relevant to patients hospitalized with acute HF or in those with left ventricular ejection fractions (LVEFs) higher than 40%, this document focuses primarily on the management of patients with chronic HFrEF with LVEF ≤40% in the ambulatory setting and without symptoms or signs of clinical instability. For a patient presenting with symptoms of orthopnea or uncomfortable peripheral edema, the initial therapy would include diuretic agent therapy with early follow-up to ensure progress toward decongestion; following that, the steps outlined in this document would apply. For more information on care of worsening HF/congestion, the reader is directed to the ACC ECDP on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized with HF.[6]
3. The expert consensus Writing Committee endorses the evidence-based approaches to HF therapy and management enumerated in the 2022 AHA/ACC/HFSA HF guideline.[2]
4. These algorithms assume the clinician will seek input as needed from a pharmacist, a cardiologist, an HF specialist, and/or a disease management program, and/or other relevant specialists (eg, endocrinologists or nephrologists) to guide clinical management.
5. In all cases, patient preferences and values, in addition to evidence-based clinical judgment, should guide clinical decision-making.
6. At any point in time, these suggestions and algorithms may be superseded by new data.

2.2. Definitions

AHA/ACC/HFSA Stages of HF:

- Stage A: At risk for HF but without symptoms, structural heart disease, or cardiac biomarkers of stretch or injury (eg, patients with hypertension, atherosclerotic cardiovascular disease, diabetes, metabolic syndrome and obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or positive family history of cardiomyopathy).
- Stage B: Structural heart disease but no prior or current signs or symptoms of HF. Structural heart disease may include reduced left or right ventricular function, left ventricular (LV) hypertrophy, chamber enlargement, wall motion abnormalities, or valvular heart disease. Additionally, evidence for increased filling pressures by invasive hemodynamic measurements or imaging as well as elevated concentrations of B-type natriuretic peptide (BNP)/N-terminal pro-B-type natriuretic peptide (NT-proBNP) or high-sensitivity cardiac troponins.
- Stage C: Structural heart disease with prior or current symptoms of HF.
- Stage D: Marked HF symptoms that interfere with daily life, with recurrent hospitalizations despite attempts to optimize GDMT.

GDMT: Guideline-directed medical therapy, representing treatment options supported for use by clinical practice guidelines.

HFrEF: Clinical HF and LVEF ≤40%.

New York Heart Association (NYHA) functional classification:

- Class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
- Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
- Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
- Class IV: Unable to perform any physical activity without symptoms of HF, or symptoms of HF at rest.

Optimal therapy: GDMT provided at either the target or the highest-tolerated dose for a given patient.

Target doses: Doses targeted in clinical trials.

3. PATHWAY SUMMARY GRAPHIC

Figure 1 is an update of the 2017 ACC ECDP Summary Graphic outlining the 10 pivotal issues about HFrEF.

4. DESCRIPTION AND RATIONALE: ANSWERS TO 10 PIVOTAL ISSUES IN HF

4.1. How to Initiate, Add, or Switch to Evidence-Based Guideline-Directed Therapy for HFrEF

Although loop diuretic agents are an important part of the treatment of congestion in the individual with HFrEF, once approaching or achieving euvolemia, it is critical to add and optimize therapies proven to reduce morbidity and mortality. Established pharmacological therapies for chronic HFrEF include renin-angiotensin inhibitors such as angiotensin II receptor/neprilysin inhibitors (ARNIs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), along with evidence-based beta-blockers, sodium-glucose cotransporter (SGLT) inhibitors, mineralocorticoid antagonists, loop diuretic agents, hydralazine/isosorbide dinitrate (HYD/ISDN), ivabradine, and vericiguat. With the exception of loop diuretic agents, all of these therapies have been shown in randomized controlled trials to improve symptoms, reduce hospitalizations, and/or prolong survival.[2,7] In contrast, use of digoxin as a treatment for HFrEF lacks contemporary data; most of its use in modern HFrEF management focuses on its role as a rate control agent for atrial fibrillation (AF) in those with low blood pressure.

Since the publication of the 2021 ECDP, more data have emerged to support early and rapid initiation and titration of the "4 pillars" of GDMT to maximize the early benefits of improvement in patient-reported outcomes, reduction in HF hospitalizations, reduction in mortality, and improved adherence to GDMT.[8-14] When using the therapeutic standard of a 4-drug regimen (ARNI, beta-blocker, mineralocorticoid antagonist, SGLT inhibitor), there is an aggregate treatment effect that includes increasing years of survival and years free from cardiovascular (CV) death or HF hospitalizations.[15] As an example, 4-class medication initiation reduced the hazard of CV death or hospital admission for HF significantly (HR: 0.38; 95% CI: 0.3-0.47) compared with therapy with just an ACE inhibitor/ARB plus a beta-blocker.[15-18]

Another important development since the publication of the 2021 ECDP is the growing recognition of the safety and urgency of initiating therapies rapidly. As an example, the STRONG-HF (Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial showed that among patients admitted to the hospital with acute HF, high-intensity management that included rapid uptitration of GDMT and close follow-up, with a goal of reaching target doses within 6 weeks of discharge after hospitalization, was safe, well-tolerated, and associated with a reduced risk of 180-day all-cause death or HF readmission compared with usual care.[18,19]

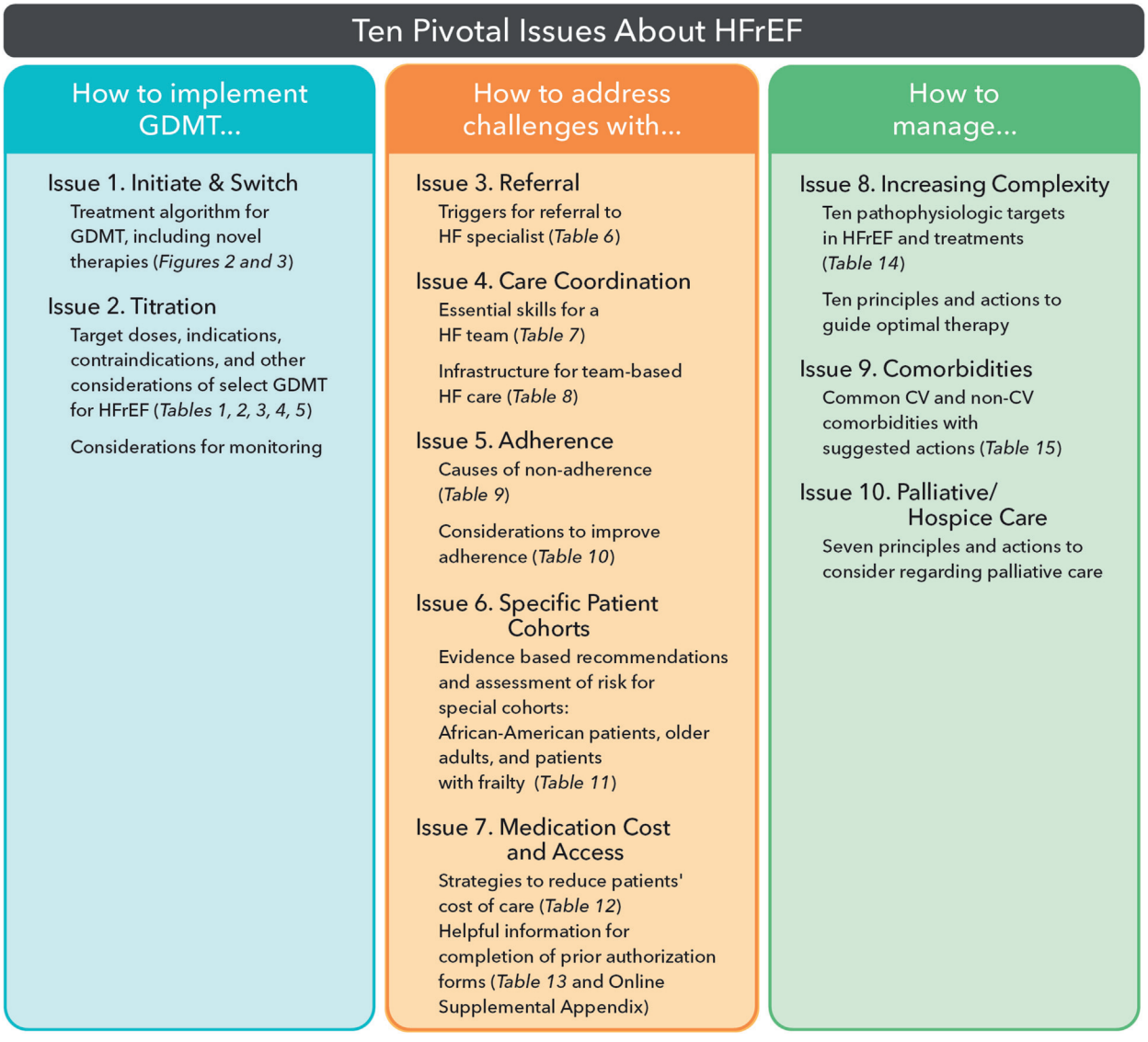
Finally, the VICTORIA (Vericiguat Global Study in Patients With Heart Failure and Reduced Ejection Fraction) trial showed that in higher-risk patients with HFrEF already on GDMT with worsening symptoms, the oral soluble guanylyl cyclase stimulator vericiguat was superior to placebo in reducing the risk of HF hospitalization and/or CV death.[20] Subsequently, vericiguat was given a Class 2b recommendation in the updated 2022 AHA/ACC/HFSA HF guideline.[2] In light of these developments, an update on when and how to add, switch, and titrate all HFrEF therapies to maximally tolerated and, ideally, target doses (Figure 1, Table 1) was deemed important.

HF is a complex clinical syndrome typically associated with multiple comorbidities; most patients are on multiple medications. No clinical trials have specifically evaluated the potential for greater benefit or excessive risk of indicated therapies among patients with multimorbidity. To assess tolerability of medications and best assess the trajectory of HF, it is often necessary for patients to have more frequent follow-ups, especially after initiation or titration of therapy. These follow-ups may be in-person or virtual on a case-by-case basis and depending on patient stability and adjustment(s) made.

4.1.1. Initiating GDMT

Recommendations for starting GDMT in a patient with a new diagnosis of symptomatic HFrEF are detailed in Figure 2.

FIGURE 1 **Ten Pivotal Issues About HFrEF**



CV = cardiovascular; GDMT, guideline-directed medical treatment; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.

In a patient with new-onset Stage C HFrEF, a common question is which medication class to initiate first, and a common second question is how rapidly to add additional agents and titrate medication doses. There is no optimal order of initiation and/or titration, so the Writing Committee recommends that clinicians will need to approach each patient in an individual fashion to decide on which agents to titrate and when to do so. The Writing Committee also recommends that regardless of the sequencing of agents, careful initiation and titration of GDMT should be early and as rapid as possible with a goal to use the 4 key medication classes in each patient.

For the person with de novo HFrEF, therapies should be initiated with a goal of reaching target or maximally tolerated doses of the 4 key medication classes as soon as possible, and ideally no longer than 3 months. In many individuals, some GDMT may already be in place, and the Writing Committee recommends initiation and titration of missing key therapies as rapidly as possible,

TABLE 1 Starting and Target Doses of GDMT for HF (Choice and timing of each therapy and who should have them added are discussed in the text)*

	Starting Dose	Target Dose
Beta-blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5-25 mg daily	200 mg daily
ARNI		
Sacubitril/valsartan	24/26 mg to 49/51 mg twice daily	97/103 mg twice daily
ACE inhibitors		
Captopril	6.25 mg 3× daily	50 mg 3× daily
Enalapril	2.5 mg twice daily	10-20 mg twice daily
Lisinopril	2.5-5 mg daily	20-40 mg daily
Ramipril	1.25 mg daily	10 mg daily
ARBs		
Candesartan	4-8 mg daily	32 mg daily
Losartan	25-50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily
Mineralocorticoid antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5-25 mg daily	25-50 mg daily
SGLT inhibitors		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily
Sotagliflozin	200 mg daily	400 mg daily
Vasodilators		
Hydralazine	25 mg 3× daily	75 mg 3× daily
Isosorbide dinitrate†	20 mg 3× daily	40 mg 3× daily
Fixed-dose combination isosorbide dinitrate/hydralazine‡	20 mg/37.5 mg (one tab) 3× daily	2 tabs 3× daily
Ivabradine		
Ivabradine	2.5-5 mg twice daily	Titrate to heart rate 50-60 beats/min. Maximum dose 7.5 mg twice daily
Oral soluble guanylyl cyclase stimulator		
Vericiguat	2.5 mg daily	10 mg daily

*Digoxin remains indicated for HFrEF, but there are no contemporary data to warrant additional comment in this document. The reader is referred to already available guideline statements.[2]

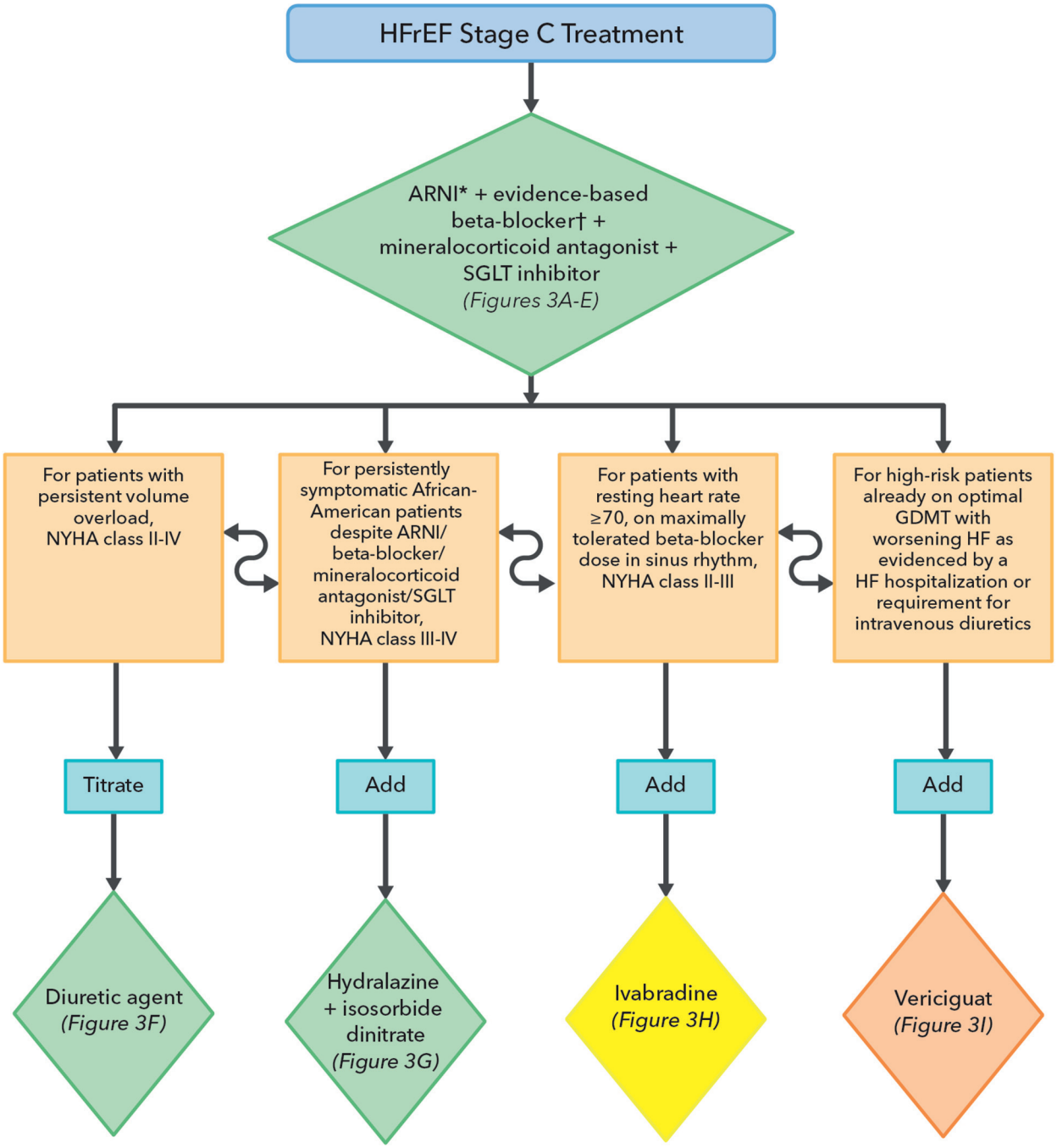
†Isosorbide mononitrate is not recommended by the 2022 ACC/AHA/HFSA HF guideline.[2]

‡The 2022 ACC/AHA/HFSA HF guideline[2] considers either the fixed-dose combination or the separate combination of isosorbide dinitrate and hydralazine as appropriate guideline-directed therapy for HF.

ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; SGLT = sodium-glucose cotransporter; tab = tablet.

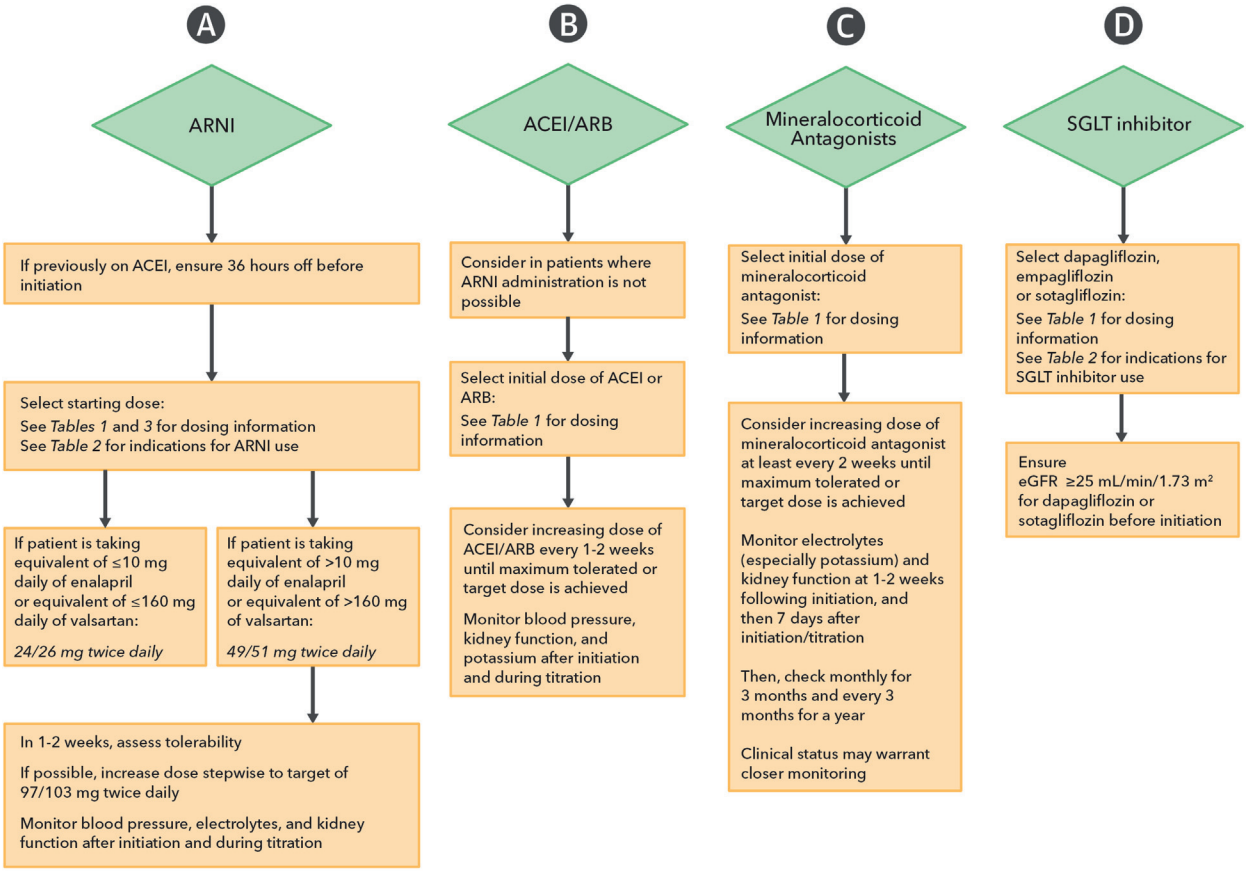
with a goal of reaching target or maximally tolerated doses in an even shorter period. These recommendations are because the STRONG-HF trial showed safety and efficacy of a goal of 50% of target doses by hospital discharge and 100% of target doses by 2 weeks following discharge from the hospital, focusing on an approach that used mostly ACE inhibitors/ARBs, evidence-based beta-blockers, and mineralocorticoid antagonists. Importantly, the STRONG-HF trial had very limited use of ARNI, and SGLT2 inhibitor use was not prioritized. Accordingly, recognizing the challenges introduced by the additional complexity of GDMT and potential hemodynamic impact of the preferred ARNI class, a longer time horizon may be necessary. The Writing Committee affirms potential value from more rapid titration, if safely possible. In some cases, the

FIGURE 2 **Treatment Algorithm for Guideline-Directed Medical Therapy**



*ACE inhibitors/ARBs should only be considered in patients with contraindications, intolerance, or inaccessibility to ARNI. In those instances, please consult Figure 3 and the text for guidance on initiation. †Carvedilol, metoprolol succinate, or bisoprolol. Colors correspond to ACC/AHA Class of Recommendation. Green = Class 1 (strong); Yellow = Class 2a (moderate); Orange = Class 2b (weak). ARNI = angiotensin receptor/neprilysin inhibitors; ACC = American College of Cardiology; AHA = American Heart Association; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association; SGLT = sodium-glucose cotransporter.

FIGURE 3 GDMT, Including Newer Therapies, in the ECDP for Chronic HF



ARNIs are the preferred renin-angiotensin system inhibitor and should be used as first-line therapy whenever possible. For patients in whom ARNI administration is not possible, an ACE inhibitor/ARB is recommended. *Carvedilol, metoprolol succinate, or bisoprolol. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitors; CBC = complete blood count; eGFR = estimated glomerular filtration rate; SGLT = sodium-glucose cotransporter.

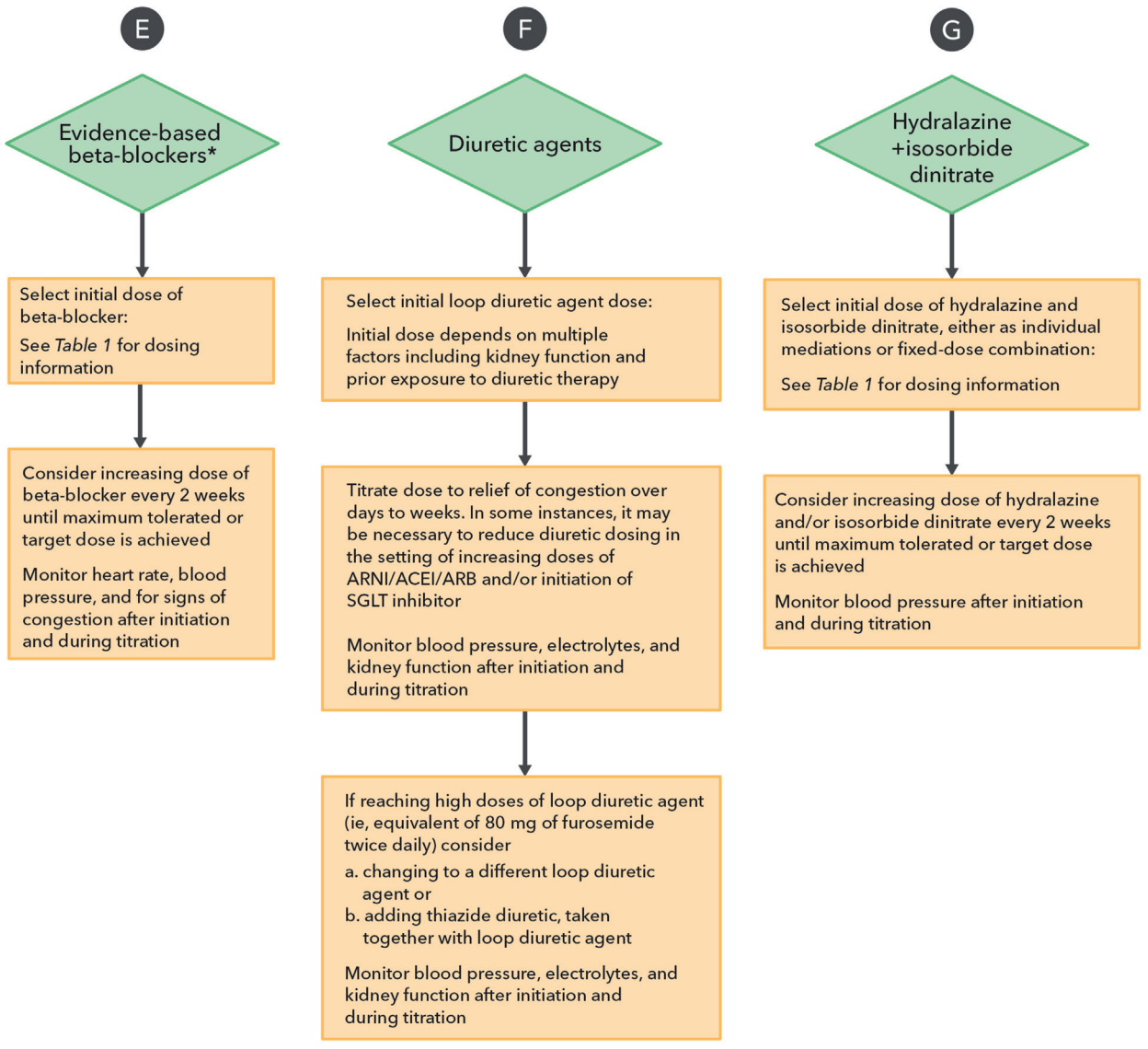
Continued on the next page

combination of 4 classes of GDMT can be started at the same time at low doses, and more than 1 titration at a time may be done. In other cases, sequencing of individual medications or various combinations may be necessary.

Recent results from clinical trials examining initiation of ARNI in those without ACE inhibitor or ARB pretreatment suggest that this strategy is well-tolerated and effective, improves health status, and generates considerable reverse cardiac remodeling. Accordingly, the Writing Committee affirms its previous stance of directly initiating ARNI whenever possible to avoid delays in optimizing GDMT.[14,21,22]

The initiation and titration of GDMT may require consideration of the individual patient phenotype. For example, initiation of an ARNI (**Table 1**, **Figures 2 and 3**) is often better tolerated when the patient is still congested ("wet"), whereas beta-blockers are better tolerated when the patient is less congested ("dry") with an adequate resting heart rate; beta-blockers should not be newly initiated in patients with decompensated signs or symptoms but can be continued with decompensated HF. Only evidence-based beta-blockers should be used in patients with HFrEF (**Table 1**, **Figures 2 and 3**). Titration of ARNI/ACE inhibitor/ARB and beta-blockers is discussed in Section 4.2. When used at guideline-recommended doses,

FIGURE 3 Continued



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mineralocorticoid antagonists, SGLT inhibitors, and vericiguat have minimal, if any, blood pressure-lowering effect.

4.1.2. Angiotensin Receptor/Neprilysin Inhibitor

Sacubitril/valsartan is 1 of the "4 pillars" of medical care for HFrEF. The 2022 AHA/ACC/HFSA HF guideline[2] recommends sacubitril/valsartan as a Class I, Level of Evidence: A therapy to reduce the risk of HF hospitalization and CV mortality in patients with symptomatic chronic HFrEF (**Figures 2 and 3**, **Table 2**).

Neprilysin, also known as neutral endopeptidase, is a zinc-dependent metalloprotease that inactivates several vasoactive peptides, including the natriuretic peptides, adrenomedullin, bradykinin, and substance P, each of which has an important role in the pathogenesis and progression of HF.[23] Because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors raise angiotensin levels, which explains the rationale for coadministration of an ARB. Neprilysin inhibitors are not combined with an ACE inhibitor due to a higher risk of angioedema.[24]

Sacubitril/valsartan[17,25] was tested in patients with chronic HFrEF in a randomized controlled trial, PARADIGM HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in

FIGURE 3 Continued

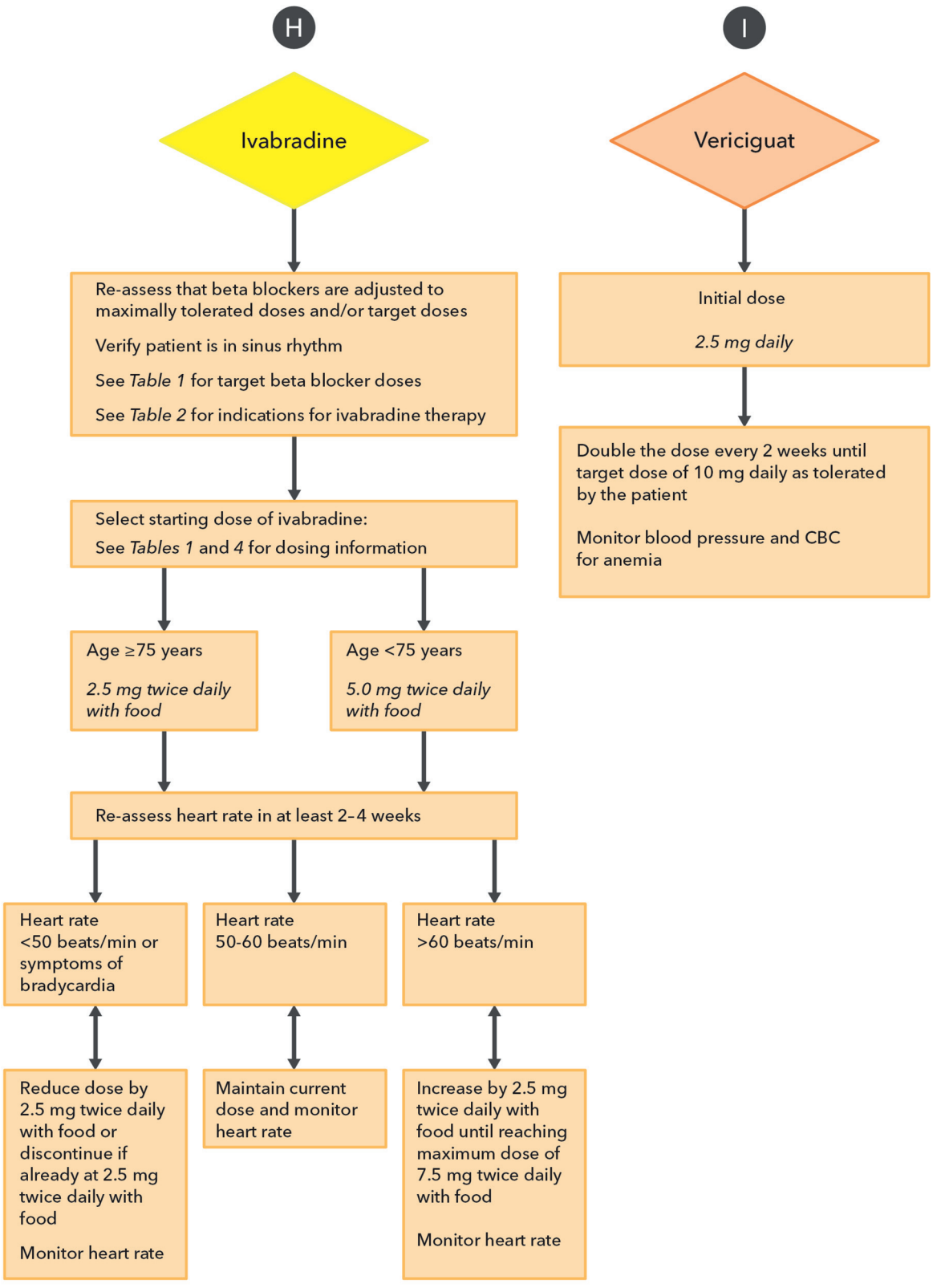


TABLE 2 Indications for ARNI, Ivabradine, SGLT Inhibitor, and Vericiguat Use

Indications for Use of an ARNI in HFrEF
■ NYHA functional class II-IV HF
■ Administered in conjunction with a background of GDMT for HF in place of an ACE inhibitor or ARB
Indications for Use of Ivabradine in HFrEF
■ LVEF ≤35%
■ On maximum tolerated dose of beta-blocker
■ Sinus rhythm with a resting heart rate ≥70 beats/min
■ NYHA functional class II or III HF
Indications for Use of an SGLT Inhibitor in HFrEF
■ HFrEF (EF ≤40%) with or without diabetes
■ NYHA functional class II-IV HF
■ Administered in conjunction with a background of GDMT for HF
Indications for Use of Vericiguat
■ HFrEF (LVEF <45%)
■ On maximum tolerated GDMT
■ Worsening HF symptoms

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SGLT = sodium-glucose cotransporter.

HF). The trial enrolled patients with NYHA functional class II to IV symptoms with an ejection fraction (EF) ≤40% (modified to ≤35% 1 year into the trial), stable on doses of ACE inhibitors/ARBs, and on other background GDMT. Patients with a history of angioedema, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, symptomatic hypotension or systolic blood pressure <100 mm Hg, or current decompensated HF were excluded. The trial began with a sequential run-in period to ensure that every patient who was randomized could tolerate target doses of both sacubitril/valsartan and the comparator enalapril. Of the 10,513 candidates screened, 2,079 were not randomized due to inability to achieve target-dose therapy on enalapril or sacubitril/valsartan. Most patients enrolled in PARADIGM-HF had NYHA functional class II to III symptoms (<100 patients with NYHA functional class IV symptoms).

PARADIGM-HF demonstrated an absolute 4.7% reduction in the primary outcome of CV death or HF hospitalization (HR: 0.80; 95% CI: 0.73-0.87; $P < 0.001$) in patients treated with sacubitril/valsartan vs enalapril. The number of patients who would need to be treated to prevent 1 primary endpoint over 27 months was 21. These differences in outcomes included a 20% reduction in sudden cardiac death, presumably due to reverse cardiac remodeling and improved EF.

Symptomatic hypotension was more common with sacubitril/valsartan (14.0% vs 9.2%; $P < 0.001$) but was not associated with worsening of kidney function. Angioedema was numerically higher but not statistically significantly different from enalapril in the sacubitril/valsartan group. The 2022 AHA/ACC/HFSA HF guideline[2] recommended an ARNI, ACE inhibitor, or ARB to reduce morbidity and mortality in patients with chronic HFrEF and that patients with NYHA functional class II to III symptoms who can tolerate an ACE inhibitor or ARB should transition to an ARNI to further reduce morbidity and mortality (Class I, Level of Evidence: B-R).[2,7,10,11] ARNIs have been associated with improvements in surrogates such as diastolic function, LV function, natriuretic peptide concentrations, burden of ventricular arrhythmias, and hard endpoints, including quality of life, costs, hospital days, and HF hospitalizations.[11,13,14,26-30] In the PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for HF) study, after 12 months of therapy with sacubitril/valsartan, the median LVEF increased from 28.2% to 37.8% (difference: 9.4%; 95% CI: 8.8%-9.9%; $P < 0.001$), whereas the median LV end-diastolic volume index decreased from 86.93 mL/m^2 to 74.15 mL/m^2 (difference, −12.25 mL/m^2 [interquartile range: −12.92, −11.58 mL/m^2]; $P < 0.001$) and the median LV end-systolic volume index decreased from 61.68 to 45.46 mL/m^2 (difference: −15.29 mL/m^2; 95% CI: −16.03 to −14.55 mL/m^2; $P < 0.001$). Indexed left atrial volume by body surface area and the E/e′ ratio also decreased significantly.[14] These results were demonstrated in important subgroups not represented in the PARADIGM-HF trial, such as those with *de novo* HF or naive to ACE inhibitors/ARBs, those with lower NT-proBNP concentrations at enrollment, or those not attaining the target dose during the study. The results from PROVE-HF were further substantiated by evidence from the randomized EVALUATE-HF (Effects of Sacubitril/Valsartan vs Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction) trial, which demonstrated that compared with enalapril, sacubitril/valsartan treatment improved echocardiographic parameters of reverse cardiac remodeling as early as 12 weeks.[31]

Emphasizing the preference for ARNIs over ACE inhibitors or ARBs, the PROVE-HF study demonstrated that improvement in LVEF was accompanied by a reduction in the presence and severity of mitral regurgitation (MR). Given increased use of percutaneous edge-to-edge repair of the mitral valve as an adjunct to GDMT, these results emphasize the importance of optimizing medical therapy, including ARNI, before deciding on such management; in PROVE-HF, 44% of those eligible for mitral valve clipping would no longer qualify after treatment with sacubitril/valsartan.[32] In a similar fashion, the PROVE-HF

TABLE 3 Dose Adjustments of Sacubitril/Valsartan for Specific Patient Populations

Population	Initial Dose
High-dose ACE inhibitor *>10-mg total daily dose of enalapril or therapeutically equivalent dose of another ACE inhibitor* *High-dose ARB* *>160-mg total daily dose of valsartan or therapeutically equivalent dose of another ARB*	**49/51 mg twice daily**
De novo initiation of ARNI *Low- or medium-dose ACE inhibitor* *≤10-mg total daily dose of enalapril or therapeutically equivalent dose of another ACE inhibitor*	**24/26 mg twice daily**
Low- or medium-dose ARB *≤160-mg total daily dose of valsartan or therapeutically equivalent dose of another ARB*	
ACE inhibitor/ARB-naive	
Severe kidney impairment (eGFR <30 mL/min/1.73 m²)*	
Moderate hepatic impairment (Child-Pugh class B)	
Elderly patients (age ≥75 y)	

*This population was not studied in the PARADIGM-HF trial. The statement is consistent with U.S. Food and Drug Administration–approved labeling indications.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; eGFR = estimated glomerular filtration rate; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF.

investigators also reported on the potential impact of LVEF increase on eligibility for implantable cardioverter-defibrillator (ICD) placement. Among individuals with an LVEF ≤35% initiated on sacubitril/valsartan, following 12 months of ARNI treatment, 61% had an LVEF >35%.[33]

A frequent question is whether use of a mineralocorticoid antagonist is mandatory before initiation of an ARNI. As there are no data to suggest that a mineralocorticoid antagonist is mandatory before ARNI therapy, lack of treatment with a mineralocorticoid antagonist should not delay initiating or switching a patient to an ARNI. Guidance for the transition from an ACE inhibitor or ARB to an ARNI is detailed in **Figures 2 and 3** and in **Tables 1, 2, 3, and 4**.

In a patient without contraindications to ARNI (eg, no prior angioedema), when making the transition from an ACE inhibitor to an ARNI, a 36-hour washout period should be strictly observed (to avoid angioedema); this delay is not required when switching from an ARB to an ARNI.[34]

An ideal time to consider GDMT initiation and/or optimization is during hospitalization for HFrEF, and the reader is directed to the 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure.[6] Although discussion of hospital-based initiation of ARNI is outside of the scope of this document, it is important to prioritize titration of GDMT for patients during the hospital-to-home transition. The PIONEER-HF (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute HF Episode) trial established that the initiation of ARNI during an acute decompensated HF hospitalization is feasible[22] after the patient has been hemodynamically stabilized; in PIONEER-HF, up to 25% of patients developed hypotension when treated with sacubitril/valsartan. Ensuring that patients are not volume-depleted at the time of initiation may help to avoid this issue. Notably, the TRANSITION (Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event) study demonstrated that about one-half of patients could achieve the target dose within 10 weeks after in-hospital initiation or soon after discharge.[21] Accordingly, following the patient's discharge from the hospital, ongoing efforts toward GDMT optimization (including titration to target doses whenever possible) should continue. And, most recently, the STRONG HF trial demonstrated that for individuals hospitalized with acute HF, intensive and rapid initiation and titration of GDMT supported by in-person follow-up after hospitalization was safe, was tolerated, and resulted in a reduction in 180-day HF hospitalizations and/or CV deaths.[35]

Clinicians should be advised that ARNIs may exert a greater blood pressure-lowering effect compared with ACE inhibitors/ARBs. Therefore, for patients with lower blood pressure (eg, systolic blood pressure ≤100 mm Hg), careful administration and follow-up are advised. In patients who are not obviously congested and have otherwise stable clinical profiles, decreasing the dose of loop diuretic agents may mitigate the hypotensive effects of sacubitril/valsartan.[36] Last, the LIFE trial randomized HFrEF patients with NYHA functional class IV symptoms to ARNI vs ARB and showed no statistically significant difference in NT-proBNP levels with sacubitril/valsartan compared with valsartan alone, no difference in clinical outcomes, and an increase in hyperkalemia events.[37] In addition, nearly one-half of the trial participants were unable to tolerate ARNI. Thus, the role of ARNIs may be limited in more advanced HFrEF. Nonetheless, the Writing Committee recommends its use in those who can tolerate it, with careful monitoring for adverse side effects, such as hyperkalemia.

4.1.3. Initiation of an ARNI *De Novo* Without Prior Exposure to an ACE Inhibitor or ARB

Some patients will meet all criteria for initiation of an ARNI but have not yet been treated with an ACE inhibitor or ARB. Recent data from clinical studies,[10-12] along with aggregate clinical experience, suggest that directly initiating an ARNI, rather than a pretreatment period with an ACE inhibitor or ARB, is a safe and effective strategy. In a

TABLE 4 Contraindications and Cautions for Sacubitril/Valsartan, Ivabradine, SGLT Inhibitors, and Vericiguat

Contraindications	Cautions
A. Sacubitril/Valsartan	
■ Within 36 h of ACE inhibitor use ■ Any history of angioedema ■ Pregnancy ■ Lactation (no data) ■ Severe hepatic impairment (Child-Pugh class C) ■ Concomitant aliskiren use in patients with diabetes ■ Known hypersensitivity to either ARBs or ARNIs	■ Kidney impairment: • Mild-to-moderate (eGFR 30-59 mL/min/1.73 m^2): no starting dose adjustment required • Severe* (eGFR <30 mL/min/1.73 m^2): reduce starting dose to 24 mg/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97 mg/103 mg twice daily, as tolerated ■ Hepatic impairment: • Mild (Child-Pugh class A): No starting dose adjustment required • Moderate (Child-Pugh class B): Reduce starting dose to 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated ■ Renal artery stenosis ■ Systolic blood pressure <100 mm Hg ■ Volume depletion
B. SGLT Inhibitors	
■ Not approved for use in patients with type 1 diabetes due to increased risk of diabetic ketoacidosis ■ Known hypersensitivity to drug	■ For HF care, dapagliflozin or sotagliflozin, eGFR <25 mL/min/1.73 m^2 ■ Pregnancy ■ Increased risk of mycotic genital infections ■ May contribute to volume depletion. Consider altering diuretic agent dose if applicable ■ Ketoacidosis in patients with diabetes: • Temporary discontinuation for at least 3 days before scheduled surgery is recommended to avoid potential risk for ketoacidosis • Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level ■ Acute kidney injury and impairment in kidney function: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses ■ Urosepsis and pyelonephritis: Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated ■ Necrotizing fasciitis of the perineum (Fournier gangrene): Rare, serious, life-threatening cases have occurred in both female and male patients; assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise
C. Ivabradine	
■ HFpEF ■ Presence of angina with normal EF ■ Hypersensitivity ■ Severe hepatic impairment (Child-Pugh class C) ■ Acute decompensated HF ■ Blood pressure <90/50 mm Hg ■ Sick sinus syndrome without a pacemaker ■ Sinoatrial node block ■ Second- or third-degree block without a pacemaker ■ Persistent AF or flutter ■ Atrial pacemaker dependence	■ Sinus node disease ■ Cardiac conduction defects ■ Prolonged QT interval ■ Resting heart rate <60 beats/min
D. Vericiguat	
■ Patients with concomitant use of other soluble guanylate cyclase stimulators ■ Pregnancy	■ Patients with anemia ■ Patients with symptomatic hypotension ■ Concomitant use with PDE-5 inhibitors is not recommended due to the potential for hypotension

*This population was not studied in PARADIGM-HF. The statement is consistent with U.S. Food and Drug Administration–approved labeling indications.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF; PDE-5 = phosphodiesterase-5; SGLT = sodium-glucose cotransporter.

prospective study comparing the tolerability of different initiation strategies for sacubitril/valsartan,[34] patients with *de novo* HFrEF or those who were naive to ACE inhibitors/ARBs demonstrated no unexpected adverse effects compared with those already taking an ACE inhibitor/ARB. In a similar fashion, in an open-label prospective study of patients eligible for ARNI therapy, the PROVE-HF study demonstrated tolerability and significant reverse cardiac remodeling among those with *de novo* HFrEF or those naive to ACE inhibitors/ARBs, who had an average 12% increase in LVEF by 1 year. These results are also supported by data from studies of acute HFrEF that indicate efficacy and tolerability for those not previously treated with an ACE inhibitor/ARB.[12,38] In a prespecified subanalysis from PIONEER-HF, patients with *de novo* HF who underwent in-hospital initiation of an ARNI had a greater reduction in natriuretic peptide concentrations, a comparable safety profile, and a significant

improvement in early clinical outcomes compared with those on enalapril[22]; such improvement in early clinical outcomes would be lost in a scenario of ACE inhibitor/ARB pretreatment.

Because of this totality of data, a *de novo* ARNI approach is now preferred, with close follow-up, serial assessments (blood pressure, electrolytes, and kidney function), and consideration of the risk of angioedema or hypotension (**Figures 2 and 3** and **Tables 1, 2, 3, and 4**). For those with contraindications to even low-dose ARNI (eg, systolic blood pressure <100 mm Hg), consideration should be given for an ACE inhibitor/ARB at very low doses.

When making a recommendation to initiate an ARNI (either as a switch or as *de novo* treatment), the Writing Committee recommends that the decision occurs within a framework of shared decision-making (https://www.cardiosmart.org/topics/heart-failure/assets/decision-aid/drug-options-for-patients-with-heart-failure). The Writing Committee is aware that an ARNI may not be easily accessible to all patients with HFrEF due to cost and insurance challenges (see the discussion on costs of care in Section 4.7). Although an ARNI is the preferred renin-angiotensin antagonist in HFrEF, an ACE inhibitor/ARB should be used to reduce morbidity and mortality in patients with HFrEF in such cases where the decision is not to use an ARNI. Patients who are initiated on an ARNI and later find it cost-prohibitive should be transitioned to an ACE inhibitor/ARB.

4.1.4. SGLT Inhibitors

SGLT inhibitors (including SGLT1/2 or SGLT2 inhibitors) are a core therapy in the "4 pillars" of medical care for HFrEF. The 2022 AHA/ACC/HFSA HF Guideline[2] recommends SGLT inhibitors as a Class I, Level of Evidence: A therapy to reduce the risk of HF hospitalization and CV mortality, irrespective of the presence of diabetes, in patients with symptomatic chronic HFrEF (**Figures 2 and 3**, **Table 2**). The contraindications to SGLT inhibitors are enumerated in **Table 4**. Although the mechanism of benefit from these agents in HFrEF remains uncertain, treatment with SGLT inhibitors leads to osmotic diuresis and natriuresis, decreases in arterial pressure and stiffness, and a shift to ketone-based myocardial metabolism.[39] Further benefits may be due to reduction of preload and afterload blunting of cardiac stress/injury with less hypertrophy and fibrosis, exerting favorable effects on autophagy and myocardial remodeling.[40,41]

The first study to demonstrate a benefit of SGLT inhibitors for HFrEF care examined the role of dapagliflozin in patients with HFrEF. The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) study demonstrated that among 4,744 patients with HFrEF, the risk of worsening HF or death from CV causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of type 2 diabetes (T2D) (16.3% in the dapagliflozin group vs 21.2% in the placebo group; HR: 0.74; 95% CI: 0.65-0.85; $P < 0.001$). In addition, dapagliflozin demonstrated a significant reduction in each of the individual components of the composite endpoint, with a 30% decrease in the risk of experiencing a first episode of worsening HF (hospitalization for HF/urgent HF visit) and an 18% decrease in the risk of CV death.[18] The DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients with HF) study demonstrated that dapagliflozin increased the proportion of patients with HFrEF who experienced clinically meaningful improvements in HF-related health status or natriuretic peptide concentrations, regardless of the presence of diabetes.[42] In addition, the trial also showed that treatment with dapagliflozin attenuated long-term decline in eGFR.[43] For empagliflozin, the EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) trial randomized 3,730 patients with chronic HFrEF to empagliflozin vs placebo. Empagliflozin significantly reduced the composite endpoint of CV death or HF hospitalization in adults with and without diabetes (19.4% in the empagliflozin group vs 24.7% in the placebo group; HR: 0.75; 95% CI: 0.65-0.86; $P < 0.001$). The trial also showed that treatment with empagliflozin slowed the decline in eGFR over time.[19] A subsequent meta-analysis of DAPA-HF and EMPEROR-Reduced suggested that the effects of empagliflozin and dapagliflozin on hospitalization for HF were consistent and that these agents reduced all-cause and CV death and improved kidney outcomes in patients.[44] More recently, the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes And Worsening Heart Failure) trial reported that sotagliflozin, an SGLT1/2 inhibitor, reduced events among individuals with diabetes mellitus hospitalized for HF who were treated during or soon after hospitalization. Among the 1,222 study participants in this trial, the average LVEF was 35%, with a majority of participants with HFrEF. Treatment with sotagliflozin was associated with a 29% reduction in worsening HF or CV death during an average 18 months of follow-up. In light of these results plus the aggregate findings from SGLT inhibitor trials, the U.S. Food and Drug Administration recently granted an indication for sotagliflozin to reduce CV events in patients with HF.[45]

Beyond reducing CV events, SGLT inhibitors may have other benefits, including improvement in health status, reduction in loop diuretic agent dosage,[46] and reduced episodes of hyperuricemia and clinical gout.[47] Furthermore, SGLT inhibitors have minimal blood pressure-lowering effects[48,49]; as such, they may be one of the preferred options for individuals with lower blood pressures who are intolerant to other GDMT choices. Last, the

use of SGLT inhibitors reduces risk for hyperkalemia in those treated with mineralocorticoid antagonists and minimizes risk for the latter GDMT being discontinued.[50]

The dosing for SGLT inhibitors is detailed in **Table 1**, whereas cautions and contraindications for SGLT inhibitors are enumerated in **Table 4**. Treatment with an SGLT inhibitor may increase diuresis (particularly in those with hyperglycemia); adjustment in loop diuretic agents may be necessary to avoid volume depletion in this setting.

Considerable clinician confusion exists about initiation of SGLT inhibitors in the setting of impaired kidney function. The Writing Committee recognizes that the glucosuric effects of SGLT inhibitors may be less pronounced in those with markedly reduced eGFR; however, this does not attenuate the CV benefits of SGLT inhibitors for HFrEF.[51] Pivotal trials examining SGLT inhibitors in HFrEF typically had lower eGFR cutoffs of 20 to 30 mL/min/1.73 m^2; however, recent label updates now have lower limits of 25 mL/min/1.73 m^2 for dapagliflozin and sotagliflozin, and no lower bound cutoff for empagliflozin. Following initiation of an SGLT inhibitor, a drop in eGFR is expected in many individuals (because of an increase in afferent glomerular arteriolar tone). Clinicians should not necessarily adjust or discontinue medications solely based on this expected change. In the clinical trials of dapagliflozin and empagliflozin, study participants with an eGFR below 20 mL/min/1.73 m^2 nonetheless continued treatment, with considerable benefits.[52] Closer monitoring of such individuals is advised; however, in most cases, SGLT inhibitors should be continued. In contrast, in studies of sotagliflozin, the drug was discontinued if the eGFR dropped below 15 mL/min/1.73 m^2, so data with this agent in individuals with end-stage kidney disease are lacking.

Despite previous concerns about risk for limb amputation among those with diabetes treated with SGLT-2 inhibitors, this therapy has been repeatedly shown to be safe, even in those with peripheral arterial disease.[2,7,53] Similar to ARNI, the Writing Committee recognizes the potential financial burden related to drug costs of SGLT inhibitors; the reader is directed to the discussion on costs of care in Section 4.7.

4.1.5. Ivabradine

Heart rate independently predicts outcomes in HFrEF. A meta-analysis of beta-blocker trials suggests that heart rate lowering in sinus rhythm is directly related to improved outcomes.[54] Although evidence-based beta-blocker therapy is the indicated GDMT to reduce heart rate in HFrEF, some patients cannot tolerate higher beta-blocker doses and remain with higher heart rates. Furthermore, patients receiving target doses occasionally continue to have persistent resting heart rates over 70 beats/min.[54]

TABLE 5 Recommended Starting Dose of Ivabradine

Population	Initial Dose
Maximally tolerated beta-blocker dose with persistent resting heart rate ≥70 beats/min	5 mg twice daily with meals
History of conduction defects Age ≥75 y	2.5 mg twice daily with meals

Ivabradine is an adjunct to reduce the heart rate in patients with chronic HFrEF with an LVEF ≤35% and in sinus rhythm. Ivabradine specifically inhibits the I_f current involved in sinoatrial nodal activity and reduces the heart rate of patients in normal sinus rhythm without lowering blood pressure. In the SHIFT (Systolic HF Treatment with the I_f Inhibitor Ivabradine) trial of 6,505 subjects with stable, chronic, predominantly NYHA functional class II and III HFrEF, ivabradine therapy, when added to GDMT, resulted in a significant reduction in HF hospitalizations (672 [21%] placebo vs 514 [16%] ivabradine; HR: 0.74; 95% CI: 0.66-0.83; $P < 0.0001$).[55] Benefits were noted especially for those patients with contraindications to beta-blockers, for those on beta-blocker doses ≤50% of GDMT targets,[56] and in those with resting heart rate ≥77 beats/min at study entry.[57] It is important to emphasize that ivabradine is indicated only for patients mainly in sinus rhythm, not in those with persistent or chronic AF, those experiencing 100% atrial pacing, or those who are unstable. A history of paroxysmal AF is not a contraindication to ivabradine; in the SHIFT study, nearly 10% of patients had a history of paroxysmal AF. In this study, there was a requirement for sinus rhythm at least 40% of the time. From a safety standpoint, patients treated with ivabradine had greater rates of bradycardia and transient blurring of vision.[55]

The Writing Committee reaffirms the importance of titrating evidence-based beta-blockers to target dose whenever possible. However, for those in whom this is not possible, the 2022 AHA/ACC/HFSA HF guideline[2] articulates a Class IIa, Level of Evidence: B-R recommendation supporting ivabradine therapy[7,53] to reduce the risk of HF hospitalization in patients with HFrEF (LVEF ≤35%) already receiving GDMT (including a beta-blocker at the maximally tolerated dose), and who are in sinus rhythm with a heart rate >70 beats/min at rest (**Figures 2 and 3**, **Tables 1, 2, and 5**). The drug is added and titrated to a heart rate between 50-60 beats/min if possible.

The contraindications to ivabradine are enumerated in **Table 4**. Caution should be exercised for those at risk for excessive bradycardia. Because of a higher risk of ischemic complications, ivabradine should not be used in patients with a history of activity-limiting angina pectoris.[58]

4.1.6. Vericiguat

Vericiguat, an oral soluble guanylyl cyclase stimulator, directly binds and stimulates soluble guanylyl cyclase and increases cyclic guanine monophosphate production. Cyclic guanine monophosphate has several potentially therapeutic effects in patients with HF, including vasodilation, improvement in endothelial function, as well as decrease in fibrosis and remodeling of the heart.[59] The VICTORIA (Vericiguat Global Study in Patients With Heart Failure and Reduced Ejection Fraction) trial showed that in 5,050 higher-risk patients with HFrEF (LVEF <45%) already on GDMT with worsening symptoms (as evidenced by an HF hospitalization or need for intravenous diuretic agents), vericiguat was superior to placebo in reducing the risk of HF hospitalization and/or CV death (897 of 2,526 patients [35.5%]) in the vericiguat group and 972 of 2,524 patients [38.5%] in the placebo group; HR: 0.90; 95% CI: 0.82-0.98; $P = 0.02$).[20]

In the 2022 AHA/ACC/HFSA HF guideline,[2] vericiguat was given a Class 2b, Level of Evidence: B-R recommendation because it may be considered in select high-risk patients with HFrEF and recent worsening HF to reduce HF hospitalization and CV death.

4.1.7. Consensus Pathway Algorithm for Initiation and Titration of HFrEF Therapies

Figures 2 and 3 depict a strategy for initiating and titrating evidence-based therapies for patients with HFrEF. As noted previously, after a diagnosis of HFrEF, initiation of ARNI, evidence-based beta-blocker, mineralocorticoid antagonist, and SGLT inhibitor is advised. Subsequent adjustment of therapies should occur frequently, with a goal to rapidly achieve target doses. Simultaneous initiation and titration of more than one therapy is encouraged where possible; some patients may tolerate more rapid titration of GDMT. For individuals not receiving any GDMT at the time of their HFrEF diagnosis, clinicians should aim to achieve optimal 4-drug GDMT no longer than 3 months following an initial diagnosis of HF. For those on partial GDMT, the timeline should be shorter. During follow-up, the clinical status of the patient, blood pressure, and kidney function (and electrolytes) should be assessed frequently. Structured medication titration plans embedded in disease management programs that articulate a strategy for drug initiation and strategies for follow-up were shown to be useful in obtaining target doses of GDMT.[60]

During follow-up, in addition to electrolyte and kidney function measurement, reassessment of natriuretic peptide concentrations may support therapeutic decision making (eg, adjustments to diuretic agent doses),[61] and predict cardiac remodeling response to GDMT.[62] Reassessment of ventricular function should occur 3 to 6 months after target (or maximally tolerated) doses of GDMT are achieved to determine the need for device therapies such as ICDs and/or cardiac resynchronization therapy (CRT). For those at higher risk of sudden death (eg, with ischemic cardiomyopathy, LVEF <30%, evidence for ventricular ectopy), the time to follow-up imaging might be shorter, whereas in those at lower risk (eg, with nonischemic cardiomyopathy, LVEF 30%-40%), time to follow-up might be longer.[2,7] In patients who already have such devices, reimaging might be deferred even further.

4.1.8. Mitral Regurgitation and the Use of Transcatheter Mitral Valve Repair

Surgical treatment should be considered as first-line therapy in cases of severe primary (ie, structural) chronic MR resulting in HFrEF.[63] For severe functional MR, the rise of transcatheter edge-to-edge repair of the mitral valve has demonstrated benefit. In 2018, 2 large randomized clinical trials of percutaneous mitral valve repair were published. The MITRA-FR (Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary MR) and COAPT (CV Outcomes Assessment of the MitraClip Percutaneous Therapy for HF Patients With Functional MR) trials reported divergent results. Whereas no benefit from percutaneous clipping of the mitral valve was observed in MITRA-FR, the COAPT study investigators reported that, in a population with maximally tolerated GDMT and device therapy, there was a reduction in HF hospitalization and mortality in symptomatic HF patients with grade 3 to 4+ MR.[64,65]

Substantial differences exist between MITRA-FR and COAPT, but one primary difference relates to the requirement in COAPT for optimized GDMT before the use of percutaneous mitral valve edge-to-edge reapposition. Optimal GDMT leads to reversal of cardiac remodeling, reduction of LV volumes,[10] and a concomitant reduction in functional MR[66]; in a recent study, initiation of sacubitril/valsartan reduced potential eligibility for mitral repair by 44%.[32]

The treatment for moderate or severe chronic functional MR should always incorporate optimization of GDMT and participation in team management decisions before the use of percutaneous transcatheter repair. Although percutaneous mitral valve repair is of benefit in patients with optimized GDMT and persistent symptoms with severe MR, it is essential that GDMT is optimized before referral for the procedure to ensure the greatest likelihood that patients will receive the combined benefits both therapies.

4.1.9. Patients in Whom New Therapies May Not Be Indicated

Contraindications may preclude the initiation of some agents for some patients. Additionally, after being presented with all evidence for and against these therapies, a well-informed patient may make a personal judgment, in terms of benefits and risks, and decide against initiation. This may be also the case when evaluating an individual whose life expectancy is short (<1 year) due to advanced HF or other comorbidities, where intolerances to therapies are more common. Shared decision making is important in this situation.

4.2. How to Achieve Optimal Therapy Given Multiple Drugs for HF, Including Augmented Clinical Assessment That May Trigger Additional Changes in GDMT (eg, Imaging Data, Biomarkers, and Filling Pressures)

4.2.1. Target Doses

To achieve the maximal benefits of GDMT in patients with chronic HFrEF, therapies must be rapidly initiated and titrated to maximally tolerated doses.[17,67-69] Doses of GDMT higher than those studied in randomized clinical trials, even if tolerated, are not known to provide incremental benefits and are generally not recommended.

Strategies for titration are detailed in **Figures 2 and 3**. Rapid achievement of target or maximally tolerated doses of GDMT is the goal. This may be facilitated using virtual care or in the context of GDMT titration clinics.[70]

Early and rapid optimization of GDMT is recommended because improvement in patient-reported outcomes and reduction in HF hospitalizations and mortality occurs early after initiation of GDMT.[15] More than 1 drug may be started and/or titrated at the same time and, in certain circumstances, all 4 classes may be started at once.

Beta-blocker doses should be adjusted every 1 to 2 weeks[71] in a patient with no evidence of decompensated HF and no contraindications to higher doses. Longer time periods may be needed for frail patients or those with marginal hemodynamic status, whereas more rapid titration may be reasonable in clinically stable patients. Following adjustment, patients should be cautioned that there may be a transient worsening of HF symptoms such as dyspnea, fatigue, erectile dysfunction, or dizziness.

An ARNI is the preferred renin-angiotensin inhibitor in the absence of hypotension, electrolyte/kidney instability, or prior angioedema on an ACE inhibitor or ARB. If use of an ARNI is not feasible, then an ACE inhibitor or ARB should be used, barring contraindication. ARNI (or ACE inhibitor/ARB) may be titrated similarly to beta-blockers, with monitoring of kidney function, potassium, and blood pressure; more rapid titration is also reasonable in clinically stable patients. For those taking an ARNI, doses can be increased every week to allow time for adjustment to the vasodilatory effects of the combined inhibition of the angiotensin receptor and neprilysin while also monitoring kidney function, potassium, and especially blood pressure. For optimal titration of an ARNI, lower loop diuretic agent doses may be necessary to permit titration; in this circumstance, careful attention to potassium concentrations is needed, as the kaliuretic effects of loop diuretic agents may no longer be present, and restriction of supplemental and/or dietary potassium may be necessary.

Mineralocorticoid antagonists are added in as part of the therapy for patients with symptomatic chronic HFrEF who are already receiving beta-blockers and an ARNI (or ACE inhibitor/ARB) and who do not have contraindications to this therapy.[2] It is not necessary to achieve target or maximally tolerated doses of other drugs before adding mineralocorticoid antagonists, and these agents may be added in combination with other GDMT such as SGLT inhibitors; treatment with an SGLT inhibitor reduces risk for hyperkalemia and allows for persistence of mineralocorticoid antagonist therapy.[50] The doses of mineralocorticoid antagonists used in clinical trials, which are typically below those that might influence blood pressure, are sufficient for clinical efficacy. Adherence to the guideline recommendations for monitoring of kidney function and potassium is required.[53]

SGLT inhibitors should be added, barring contraindications.[18,44,72,73] Achieving target or maximally tolerated doses of other drugs is not necessary before adding SGLT inhibitors and, as mentioned earlier, these agents may be added in combination with other therapy initiations (eg, together with spironolactone). These agents are used in a fixed dose; titration is not required. SGLT inhibitors are uniquely well-tolerated by those with lower blood pressures, making this class (and mineralocorticoid antagonists) important treatment options for this circumstance. The loop diuretic agent dose may need to be adjusted based on close monitoring of weight and symptoms.[74] In patients using insulin or insulin secretagogues (such as sulfonylureas), coordinating care through the inclusion of endocrinology specialists and primary care providers may be helpful to minimize the risk of hypoglycemia in patients with diabetes.

For several reasons, HYD/ISDN-indicated therapy for HF is often neglected in eligible patients.[75,76] However, given the benefits of this combination (43% relative reduction in mortality and 33% relative reduction in HF hospitalization) and the favorable impact on health status,[77] African-American patients who remain symptomatic should receive these drugs once target or maximally

tolerated doses of beta-blocker, ARNI/ACE inhibitor/ARB, mineralocorticoid antagonist, and SGLT inhibitors are achieved.[2] This combination of drugs is especially important for those patients with NYHA functional class III to IV symptoms. In patients whose heart rate remains ≥70 beats/min on target or maximally tolerated doses of beta-blockers, ivabradine[2] can be added and titrated at 2 weeks to lower the heart rate. Finally, in select high-risk patients with HFrEF and worsening HF, vericiguat can be considered and titrated every 2 weeks until the target dose is achieved.

4.2.2. Barriers to Medication Titration

Although the Writing Committee emphasizes the importance of comprehensive efforts to establish quadruple therapy for the care of HFrEF, in some instances, it may not be possible to initiate or titrate GDMT to the target doses achieved in clinical trials. Patients seen in clinical practice may differ substantially from those enrolled in trials. For example, patients seen in clinical practice are typically older; may experience more side effects, including hypotension; and are likely to have more comorbidities that will limit titration. Although data are lacking, it is logical to assume that below-target doses of multiple classes of GDMT are likely more effective in reducing risk than large doses of 1 or 2 agents. Furthermore, patients should be educated that receiving some GDMT is still far more important than receiving none; those receiving fewer than 4 drugs are still considerably better off than those receiving none.

Abnormal kidney function and/or hyperkalemia are common barriers to initiation and titration of GDMT. In patients with hyperkalemia, education regarding a low-potassium diet should be provided as a first step, as this often helps to address the issue. Use of SGLT inhibitors should be prioritized in this setting, because these agents help to mitigate hyperkalemia. In addition, newer potassium binders (patiromer and sodium zirconium cyclosilicate) are now approved by the U.S. Food and Drug Administration and may be considered. In the DIAMOND (Patiromer for the Management of Hyperkalemia in Participants Receiving RAASi Medications for the Treatment of Heart Failure) trial, patients with HFrEF and a history of renin-angiotensin-aldosterone inhibitor-induced hyperkalemia were randomized to patiromer vs placebo. Before randomization, eligible patients had a run-in phase during which patiromer was started and GDMT optimized. After the run-in phase, patients were randomized to either continue or stop patiromer. Patiromer maintained lower serum potassium levels and was associated with a lower incidence of severe hyperkalemia (>5.5 mEq/L). Patiromer allowed for 85% of participants to be optimized on GDMT.[78]

For patients with established kidney disease, more caution may be necessary when starting and escalating GDMT. In patients with moderate kidney impairment (eGFR ≥30 and <60 mL/min/1.73 m^2), no adjustment is needed when deciding the starting dose of the ARNI sacubitril/valsartan. In those with severe kidney impairment (eGFR <30 mL/min/1.73 m^2), the starting dose of sacubitril/valsartan should be reduced to 24/26 mg twice daily (**Table 1**). ACE inhibitors/ARBs are generally considered safe in patients with severe kidney impairment, although definitive data are lacking. Mineralocorticoid antagonists are contraindicated in patients with severe kidney impairment (eGFR <30 mL/min/1.73 m^2, or creatinine >2.5 mg/dL in men or creatinine >2 mg/dL in women) or with potassium >5.0 mEq/L (**Figure 2**). SGLT inhibitors may be initiated down to an eGFR of 20 mL/min/1.73 m^2 (empagliflozin), 30 mL/min/1.73 m^2 (dapagliflozin), or 25 mL/min/1.73 m^2 (sotagliflozin), and if the eGFR drops below this value, discontinuation is not mandatory.

Kidney function and potassium should be assessed within 1 to 2 weeks after initiation or dose increase of an ARNI/ACE inhibitor/ARB. In patients with preserved kidney function or mild to moderate kidney impairment, kidney function and potassium after initiation and titration of mineralocorticoid antagonists should be assessed within 1 to 2 weeks. The schedule for subsequent monitoring should be dictated by the clinical stability of kidney function and volume status but should occur at least monthly for the first 3 months and every 3 months thereafter.[2]

During the initiation and titration of agents that affect kidney function, a decrease in eGFR of >30% or the development of hyperkalemia should alert the clinician that a reduction in doses may be necessary. However, clinicians should recognize that short-term, transient changes in eGFR are to be expected during intense diuretic agent therapy or with the initiation of a renin-angiotensin-aldosterone inhibitor and do not predict longer-term adverse outcomes nor necessitate dose reduction.[79] Similarly, initial mild reduction in eGFR after SGLT inhibitor initiation often occurs before longer-term kidney function preservation.[19] In patients with evidence of hypovolemia, the dose of diuretic agents should be reduced. The ARNI dose may also need to be reduced in the setting of kidney insufficiency or hypotension. Hyperkalemia may also require changes in medical therapy. In clinical trials of SGLT inhibitors for patients with chronic HFrEF, experience is somewhat lacking in those with <20 mL/min/1.73 m^2, but consensus has developed around continuing these agents even below this eGFR threshold.

Socioeconomic barriers to care may undermine the ability to achieve GDMT. For example, the cost of

therapies poses a substantial barrier to care, particularly for ARNI, SGLT inhibitors, ivabradine, and vericiguat (see the discussion on costs of care in Section 4.7). In such cases, if all solutions are exhausted, optimizing care with the most financially manageable program is recommended. Assessments for prior authorizations and patient assistance programs should be addressed immediately upon prescribing medications. Similarly, some patients have a limited ability to attend frequent office visits for GDMT optimization. For example, homebound patients or those with limited ability to travel may be unable to have blood pressure, heart rate, or kidney function assessed in a timely fashion. In these cases, options such as virtual care and home visiting nurse services may aid in remote optimization of GDMT.[80] Useful guidance exists regarding the use of virtual visits to allow for medical access, monitoring of symptoms/signs, and adjustments of GDMT.[81]

4.2.3. Clinical Assessment

Figure 4 details a reasonable strategy for patient evaluation and management following a diagnosis of HFrEF.

After GDMT is initiated and titrated with the goal of achieving clinical trial doses or maximally tolerated doses, patients with chronic HFrEF should be evaluated regularly. For most patients, a reasonable interval is every 3 to 6 months, although many may require more frequent follow-up to monitor clinical stability and revisit opportunities for further GDMT titration. Cardiac rehabilitation is helpful to support drug titration, monitor symptoms, improve health status, and increase exercise tolerance, but remains underused in terms of both prescription and access.[82] Virtual care to allow for outpatient GDMT titration has been useful in certain patients[83] and will play an increasingly larger role in HF, particularly for medication titration.

High-risk features (conveniently summarized by the acronym "I NEED HELP" in **Figure 4** and **Table 6**) should trigger consideration for referral for an advanced HF consultation.[84,85] Features triggering referral to advanced HF care are also discussed in Section 4.3 and **Table 6**.

4.2.4. When to Order an Echocardiogram

An echocardiogram is recommended in the evaluation of the patient with incident HF to assess LVEF, diastolic function, chamber size, ventricular wall thickness, valvular abnormalities, and hemodynamic parameters, including estimated right ventricular systolic pressure, central venous pressure, and LV filling pressures. Once optimal doses of GDMT have been achieved for 3 to 6 months, repeat imaging can be useful in making decisions regarding device therapy (ICD, CRT, or transcatheter mitral valve repair) or referral for advanced therapies (ventricular assist device or transplant). In some patients, it may be reasonable to wait longer for such decisions if there is an expectation that LV remodeling might further progress. For example, in the PROVE-HF study, increases in LVEF and reduction in LV volumes continued over 12 months in some patients.[14] However, certain high-risk features, such as markedly elevated NT-proBNP or a lower starting LVEF, might lead to earlier reimaging to make further therapy decisions, because such individuals might not develop sufficient reverse remodeling to justify delaying device placement.[86] Repeat imaging may also be considered at the time of important changes in clinical status.[2,7] Routine surveillance echocardiograms (eg, annually) in the absence of change in clinical status or some other signal of risk are unwarranted. If echocardiography does not provide an assessment of LVEF, guidelines recommend other modalities, including radionuclide ventriculography or magnetic resonance imaging.[2,7]

When recovery of LVEF to >40% is noted in the setting of prior HFrEF, outcomes improve[87]; despite this fact, ongoing titration of GDMT to target dose is always advised even for those with evidence of recovering LVEF. Clinicians are often faced with the question of whether to continue GDMT or reduce/eliminate it in patients with LVEF recovery to a "normal" range. The TRED-HF (Withdrawal of Pharmacological Treatment for Heart Failure in Patients With Recovered Dilated Cardiomyopathy) study examined this question, finding that nearly 50% of subjects withdrawn from GDMT had a relapse of their cardiomyopathy within 6 months.[88] Therefore, in the absence of a defined, reversible cause for HFrEF (eg, tachycardia-mediated cardiomyopathy), current GDMT should be continued.[89]

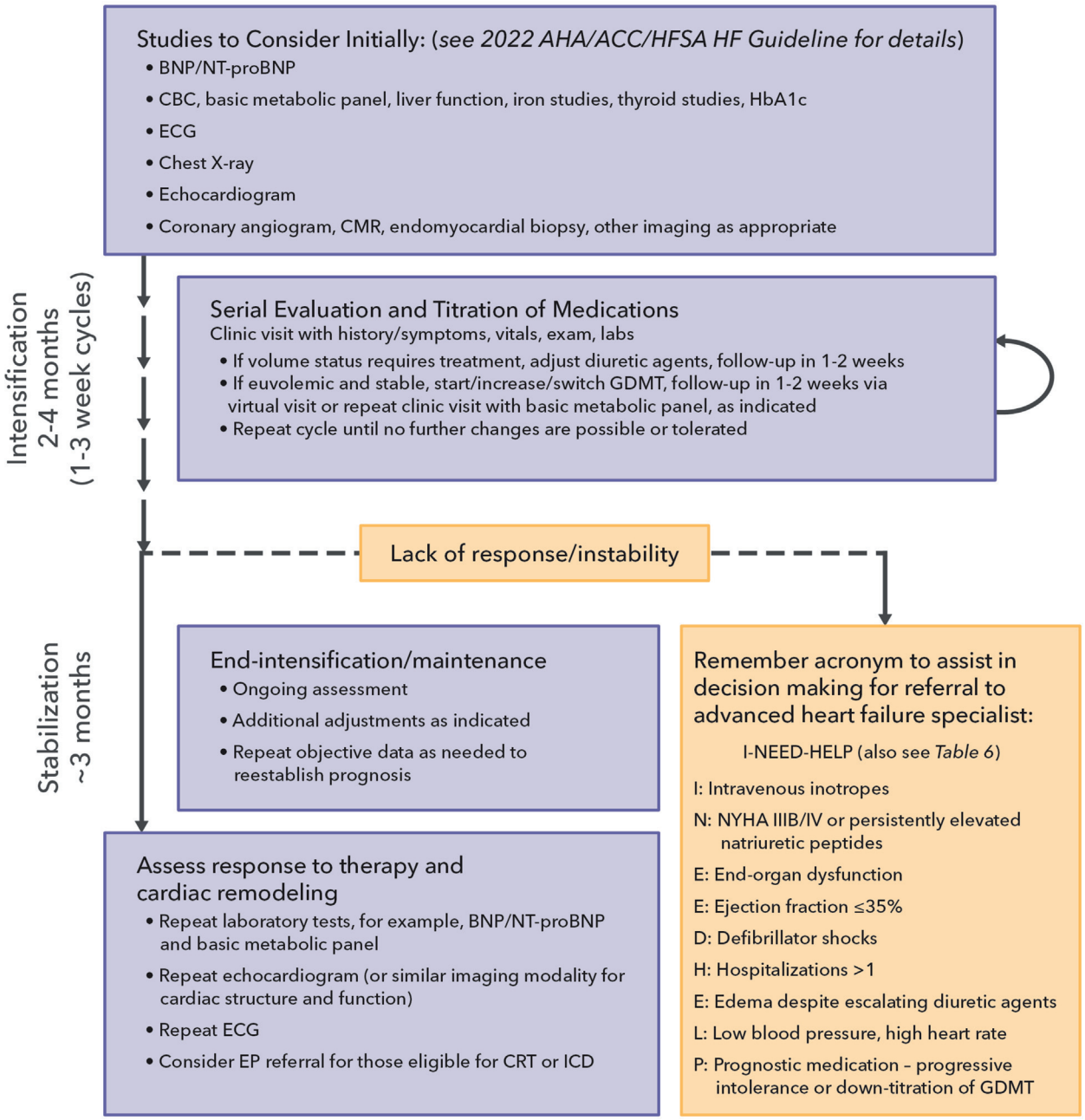
4.2.5. Biomarkers—When to Order Natriuretic Peptides

BNP and NT-proBNP are the most studied biomarkers in HF. They play a role in diagnosis and prognostication: higher concentrations of BNP or NT-proBNP in an ambulatory patient with HFrEF inform high risk, particularly when the concentrations are rising. Current clinical practice guidelines give a Class I recommendation to measure BNP or NT-proBNP to support a clinical diagnosis of HF, assess disease severity, or establish prognosis.[2,7]

Trends in natriuretic peptide concentrations inform prognosis as well as the potential presence and severity of congestion and trajectory of LV remodeling, and they also closely track with health status.[62] Thus, a measurement of BNP or NT-proBNP at each clinical evaluation may inform clinical decisions (eg, diuretic agent dosing); more frequent measurement might be appropriate in certain circumstances, such as during rapid medication titration or in the setting of symptom instability.

Patients whose natriuretic peptide concentrations do not fall with GDMT ("nonresponders") have a worse

FIGURE 4 Testing and Medication Titration Following Diagnosis of HFrEF



BNP = B-type natriuretic peptide; CBC = complete blood count; CMR = cardiac magnetic resonance; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; EP = electrophysiologist; GDMT = guideline-directed medical therapy; HbA1c = glycosylated hemoglobin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; IV = intravenous; NT-proBNP = N terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

prognosis, more congestion, and more deleterious LV remodeling.[10,90,91] In the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in HF) trial, among patients with HFrEF, lowering NT-proBNP to <1,000 pg/mL was associated with significant reverse remodeling and improved outcomes.[92] Similarly, in the PROVE-HF study, the speed and magnitude of NT-proBNP–lowering after ARNI initiation were associated

with greater degrees of reverse cardiac remodeling and improved outcomes.[10,87] In the setting of worsening symptoms,[93] reassessment of BNP or NT-proBNP may be informative. Therefore, measurement of BNP or NT-proBNP is useful to monitor risk, assist in decision-making regarding the ordering of imaging studies to evaluate LV remodeling, and to provide helpful objective data regarding decision-making for referral to an advanced HF specialist (**Figure 4** and **Table 6**).

Although rising BNP concentrations are correlated with adverse outcomes, this relationship can be confounded when using sacubitril/valsartan. Due to neprilysin inhibition, concentrations of BNP may modestly rise in patients treated with sacubitril/valsartan. Such concentrations may ultimately decrease with chronic therapy.[94] In contrast, NT-proBNP concentrations typically decrease much more consistently than do BNP concentrations, because NT-proBNP is not a substrate for neprilysin.[95] Clinicians should interpret natriuretic peptides in the context of GDMT; caution is advised when attempting to interpret BNP values in the context of ARNI treatment, and NT-proBNP measurement may be preferable in this setting. Severe kidney dysfunction may also interfere with the interpretation of natriuretic peptide concentrations.

4.2.6. Filling Pressure Assessment—When and How to Measure Filling Pressures

Whereas routine pulmonary artery catheterization is not recommended to manage congestion, invasive hemodynamic and filling pressure assessment may occasionally be useful to support decision-making. For example, in patients who have refractory symptoms despite perceived adequate use of diuretic agents, those who develop worsening kidney function with attempts to increase doses of diuretic agents, or those with repeated hospitalization for congestion, a better understanding of filling pressures and hemodynamics might assist in pivotal changes in HF therapies (2022 AHA/ACC/HFSA HF Guideline Class of Recommendation 2a).[2] Pulmonary artery catheterization results may also help select candidates for advanced therapies, including transplantation or mechanical circulatory support.

Recent attention has focused on the use of implantable sensors to guide filling pressure assessment in ambulatory patients with HF.[96] In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients) study, patients with NYHA functional class III HF symptoms were randomly assigned to receive a wireless, implantable, pulmonary artery pressure (PAP) monitor vs usual care.[97] Patients who were managed with data from implantable PAP monitoring experienced more changes in GDMT and diuretic agent doses.[98] In addition, those managed with implantable PAP monitoring had a 28% relative reduction in HF hospitalization (0.49 events/patient/y in the treatment arm vs 0.69 events/patient/y in the control arm; $P < 0.001$). Such improvement was seen in patients with both HFrEF and HF with preserved EF. The reduction in PAP and hospitalization can still be seen after 2 years of PAP-guided management.[99] This suggests that in well-selected patients with recurrent congestion, this highly specialized monitoring strategy may guide therapeutic decision-making. The recent GUIDE-HF (Hemodynamic-Guided Management of HF) trial[100] did not show a similar benefit as the CHAMPION trial, but the trial was confounded by the COVID-19 pandemic. When the GUIDE-HF investigators examined outcomes among patients monitored before the COVID-19 pandemic, they noted a lower HF hospitalization rate among monitored patients (relative risk for HF events among monitored patients compared with control patients: 0.76; 95% CI: 0.61-0.95; $P = 0{\cdot}014$). More recent data from the MONITOR-HF (Remote Hemodynamic Monitoring of PAPs in Patients With Chronic Heart Failure) trial suggested that hemodynamic monitoring with the CardioMEMS device improved quality of life and reduced HF hospitalizations among those treated with GDMT.[101] This suggests that monitoring with implantable sensors may continue to be an important strategy for HF patients. A team-based approach may be necessary to best deploy this monitoring strategy (see Section 4.8).

Another HF-monitoring approach is thoracic fluid assessment by intrathoracic impedance monitoring via pacemakers. Impedance values correlate with pulmonary capillary wedge pressure to identify potential volume overload before HF hospitalization.[102] In patients already targeted to receive an ICD or CRT with a defibrillator implant, such impedance monitoring capabilities may provide additional insight, although definitive outcomes data supporting this are limited.

Patients on optimal GDMT who have either high-risk features (Section 4.3 and **Table 6**) or a poor response to therapy should be considered for referral to an advanced HF specialist, as discussed in the next section.

4.3. When to Refer to an HF Specialist

Appropriate and timely referral to an HF specialist and/or HF program is essential in certain clinical scenarios to optimize therapies and evaluate appropriateness for advanced HF therapies (**Table 6**).[2,7,85,103] Referrals should be made for consultation and, if indicated, for comanagement as well as consideration of advanced therapies (heart transplantation,[104] CRT, or mechanical circulatory support), recognition and management of specific or unusual cardiomyopathies, or annual review.[2,7,105-111] Clinical triggers for referral (**Table 6**) include assistance in evaluation of a new diagnosis of HFrEF, persistent or

TABLE 6 Triggers for HF Patient Referral to a Specialist/Program

Clinical Scenario	
	1. New-onset HF (regardless of EF): Refer for evaluation of etiology, guideline-directed evaluation and management of recommended therapies, and assistance in disease management, including consideration of advanced imaging, endomyocardial biopsy, or genetic testing for primary evaluation of new-onset HF
	2. Chronic HF with high-risk features, such as development or persistence of 1 or more of the following risk factors: • Need for chronic intravenous inotropes • Persistent NYHA functional class III-IV symptoms of congestion or profound fatigue • Systolic blood pressure ≤90 mm Hg or symptomatic hypotension • Creatinine ≥1.8 mg/dL or BUN ≥43 mg/dL • Onset of atrial fibrillation, ventricular arrhythmias, or repetitive ICD shocks • 2 or more emergency department visits or hospitalizations for worsening HF in the prior 12 months • Inability to tolerate optimally dosed beta-blockers and/or ARNI/ACE inhibitors/ARBs and/or mineralocorticoid antagonists • Clinical deterioration, as indicated by worsening edema, worsening symptoms, rising biomarkers (BNP, NT-proBNP, others), worsened exercise testing, decompensated hemodynamic status, or evidence of progressive remodeling on imaging • High mortality risk using a validated risk model, such as the Seattle Heart Failure Model, for further assessment and consideration of advanced therapies
	3. Persistently reduced LVEF ≤35% despite GDMT for ≥3 months: Refer for consideration of device therapy in those patients without prior placement of ICD or CRT, unless device therapy is contraindicated or inconsistent with overall goals of care
	4. Second opinion needed regarding etiology of HF; for example: • Coronary ischemia and the possible value of revascularization • Valvular heart disease and the possible value of valve repair • Suspected myocarditis • Established or suspected specific cardiomyopathies (eg, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, Chagas disease, restrictive cardiomyopathy, cardiac sarcoidosis, amyloid, aortic stenosis)
	5. Annual review needed for patients with established advanced HF in which patients/caregivers and clinicians discuss current and potential therapies for both anticipated and unanticipated events, possible HF disease trajectory and prognosis, patient preferences, and advanced care planning
	6. Assessment of patient for possible participation in a clinical trial

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CRT = cardiac resynchronization therapy; EF = ejection fraction; GDMT = guideline-directed medical therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SGLT = sodium-glucose cotransporter.

worsening symptoms, adverse clinical events, adverse drug reactions, or other features suggesting that the patient is at high risk for disease progression or death.[84,112-115]

4.4. How to Optimize Care Coordination

Delivering optimal patient-centered HF care is complex. The range of treatments available, particularly those for patients with HFrEF, include multiple medications, cardiac devices, surgery, and lifestyle adaptations, all of which require education, monitoring, and engagement. For example, patients with HFrEF frequently require consultative care delivered by electrophysiology specialists to implant, monitor, and adjust devices such as ICDs or CRT devices. As outlined in Section 4.9, the complexity of HF care is further exacerbated by the frequent coexistence of both cardiac and noncardiac comorbidities in patients with HF. Comorbidities are particularly common in the elderly. More than 50% of patients with HF on Medicare have 4 or more non-CV comorbidities and more than 25% have 6 or more.[116] The care needs for comorbidities can complicate—and in some cases prevent—the optimal use of HF therapies. Finally, the medical complexity inherent in most patients with HF generally requires the involvement of multiple clinicians across many care settings (eg, hospitals, rehabilitation facilities, and ambulatory clinics). This raises the risk of inefficiencies in care delivery, miscommunication, potential drug-drug interactions and drug-disease interactions, and missed opportunities to achieve optimal HF outcomes.

As new medications and devices become available that require optimal communication between multiple parties, including the patient, care coordination is especially important. For example, when caring for patients with HF who have comorbid T2D and are being considered for SGLT inhibitors, possible approaches include a “consultative” approach or a “team” approach. In a consultative approach, the CV specialist consults with the diabetes clinician and/or the patient in the provision of their care.[117] In a team approach, an interprofessional, multidisciplinary group of clinicians (eg, primary care, endocrinologists, cardiologists, pharmacists, nurses, advanced practice professionals, and dieticians) consider novel therapies collectively.[117] Regardless, all approaches to HFrEF management need to be patient-centered, use shared decision-making, and involve communication across disciplines.[117]

Randomized trials have demonstrated the superiority of the team-based approach over usual care in patients with HF[118-121] with respect to the risks of death, hospitalization, lengths of stay, and quality of life.[122-125] These outcomes are generally attributed to greater adherence to GDMT, higher proportions of patients receiving effective medication doses, and earlier recognition of HF signs and symptoms.[126,127] Team-based HF care is thus

TABLE 7 Essential Skills for an HF Team

■ HF diagnosis and monitoring for progression
■ Treatment prescription, titration, and monitoring
■ Patient and caregiver education on disease and treatments
■ Lifestyle prescription (eg, diet, exercise), education, and monitoring
■ Access to genetic testing and counseling programs
■ Psychological and social support assessment, treatment, and monitoring
■ Palliative and end-of-life counseling and care
■ Coordination of care for concomitant comorbidities
■ Nutritional counselling

HF = heart failure.

recommended in the most recent ACC/AHA/HFSA HF guideline.[2]

Necessary skills for care teams include proficiency in monitoring for HF progression and exacerbation, care coordination, treatment prescription and monitoring, and education for patients and their caregivers (Table 7).

Effective team-based HF care may be possible with small teams if the requisite skills are available. Composition of care teams may continue to evolve. For example, transcatheter mitral valve intervention programs require collaboration with cardiology, cardiac surgery, anesthesiology, imaging, nursing, and social services. They also require other medical professionals to be involved with preprocedural patient selection, intraprocedural management, postprocedural in-hospital and postdischarge care, and follow-up outcome reporting.

Referral of HFrEF patients to team-based HF medication optimization clinics focused on rapidly initiating and titrating quadruple GDMT to target doses can minimize clinical inertia and capitalize on reductions in hospitalizations and mortality.[128] A study by Coons et al[129] comparing persons with HFrEF receiving usual care vs referral to a medication optimization clinic noted that patients with HFrEF receiving usual care were 3 times more likely to incur a HF hospitalization than patients managed in a medication optimization clinic. Each program will define the roles and responsibilities of various care team members in an effort to effectively communicate and obtain optimal patient outcomes.[130] In addition, recent innovations in HF care delivery, such as group visits, remote specialist video consultation, and telemonitoring programs, may also be useful.[131-136] Remote programs to monitor patients with HF for early signs of clinical decompensation have also been growing.[137,138] Potential infrastructure components to support team-based HF care are detailed in Table 8.

Electronic health records are essential to communication and coordination of care and may provide a means by which to identify individuals receiving inadequate GDMT.[139] Patient monitoring and engagement tools that can detect early signs of HF decompensation and encourage adherence to effective therapies are also important adjuncts. Many recent technological innovations in this area, such as implantable PAP monitoring devices,[97] wearable activity monitors,[140] and smartphone and other mobile applications,[141] have the potential to improve monitoring and patient engagement.[141] These advances have been accompanied by new billing codes for remote monitoring activities. However, as previously noted, these innovations need more evidence to support broader use so the focus should remain on effectiveness and evidence, rather than the form of these tools. In addition, these programs will require a clear and effective way for care teams to receive, analyze, and act on the information. Low-tech approaches, such as daily weights and algorithms for management of HF, may be sufficient for some patients to assist in self-management. In all cases, understanding who receives and acts upon the data is as important as having established programs for monitoring patient-generated data. Patient and caregiver educational tools also support team-based HF care. Recent advances in optimizing health literacy and empowering patient engagement and self-management in HF care are promising in this respect.[142,143] Ongoing monitoring of team-based care implementation, outcomes, and safety through periodic data collection, analysis, benchmarking, and—as needed—process improvements are an essential aspect of optimal team-based HF care.

4.5. How to Improve Adherence

4.5.1. Medication Nonadherence

Patient adherence is fundamental to the therapeutic effectiveness of GDMT. Medication adherence is defined as the extent to which medications are taken as prescribed, such that nonadherence is not dichotomous, but rather a spectrum of types and degrees of discordance with medication prescription.[144] Estimates of significant nonadherence in patients with HFrEF vary from 20% to 50%,[145-148] with some difference by drug.[76] Such nonadherence is associated with worse outcomes in HF.[149,150] In addition to nonadherence, a large proportion of patients with HFrEF do not receive target doses of medical therapies,[151] even in the absence of documented intolerance. In a subanalysis from the VICTORIA trial,[152] there was an evaluation of medication data at baseline on 5,040 individuals with HFrEF. This analysis demonstrated the following: 1) for beta-blockers, basic adherence was 93.1% but was 45.4% with dose-corrected data; and 2) for mineralocorticoid antagonists, basic adherence was 70.3%. For triple therapy (ARNI/ARB/ARNI + beta-blocker + mineralocorticoid antagonists), basic adherence was 59.7%, and dose-corrected adherence was only 25.5%.

TABLE 8 Potential Infrastructure Components to Support Team-Based HF Care

Modality	Potential Benefits	Challenges
Electronic health records	■ Reduction in errors ■ Decision support (eg, ACC TreatHF mobile app) ■ Accurate medication reconciliation to facilitate guideline adherence ■ Patient portal to facilitate patient/caregiver engagement, including patient-reported outcomes and other patient-generated data (if available)	■ Ease of access ■ Interoperability with other electronic data repositories ■ Data accuracy, including missing data
Patient monitoring devices: (eg, scales, implanted devices, bioimpedance devices, wearable hemodynamic sensors)	■ Early warning and a reduction in morbidity	■ Accuracy ■ False alert ■ Cost-effectiveness ■ Infrastructure/resource needs, including accurate data management and triage
Wearable activity monitors	■ Physical activity coaching/adherence ■ Early detection of arrhythmias (eg, AF)	■ Accuracy
Smartphones or other mobile technologies	■ Activity tracking ■ Dietary records ■ Weight management ■ Communication with HF team ■ Prompts for medication and lifestyle adherence	■ Need for more useful apps or other mobile technologies, including support systems in place for providing equipment and training for use ■ Potential privacy issues

ACC = American College of Cardiology; AF = atrial fibrillation; HF = heart failure.

Reasons for nonadherence are complex,[153,154] as outlined in Table 9. Unintentional nonadherence is thought to be more common than intentional nonadherence.[144,155] As Table 9 shows, the ability of patients to follow treatment plans in an optimal manner is frequently compromised by more than one barrier.[156,157] It is the responsibility of the clinician to assess reasons for reduced adherence and attempt to meet the needs of the patient.

Patients with HF, especially those with HFrEF, have indications for multiple medication therapies. In addition, the HF population has a rising prevalence of comorbidities that necessitate their own pharmacological therapies. As a result, patients with HF are prescribed an average of 6 different medications totaling more than 10 daily doses.[158,159] Consequently, interventions that target adherence in HF must be multidisciplinary, multifactorial, and personalized to the needs of the patient.

TABLE 9 Reasons for Nonadherence (World Health Organization)

Patient	■ Perceived lack of effect ■ Poor health literacy ■ Disabilities without affording appropriate accommodations ■ Mental health disorders (depression, anxiety) ■ Social isolation ■ Cognitive impairment (eg, dementia)
Medical condition	■ High HF regimen complexity ■ Impact of comorbidities (eg, depression) ■ Polypharmacy due to multiple comorbidities
Therapy	■ Frequency of dosing (eg, hydralazine, nitrates) ■ Polypharmacy ■ Side effects
Socioeconomic	■ Difficult access to pharmacy ■ Lack of social support ■ Homelessness
Health system	■ Poor communication ■ Silos of care ■ No automatic refills ■ Difficulty navigating patient assistance programs ■ Unaffordable cost of care, including medication costs

HF = heart failure.

4.5.2. General Approaches to Improving Adherence

Regularly assessing adherence helps guide individual approaches and tailor the intensity and type of adherence interventions. Notably, however, clinicians tend to overestimate actual adherence, and no perfect measure of adherence exists.

The past decade has seen a transition away from a hierarchical approach to medication adherence and more toward a shared approach, with greater focus on systems solutions (Table 10).

As such, the language has shifted from patient "compliance" to "adherence" and now to "activation," "engagement," and "empowerment."[160] Within this new paradigm, patients are seen as needing support, whereas blame is counterproductive and inappropriate in medical records. Shared decision-making, holistic approaches to multiple chronic conditions, cost transparency, personal responsibility, and behavioral theories underlie many of the evolving approaches to enhancing medication adherence.[161,162] Six categories of interventions have been identified: patient education; medication regimen management; clinical pharmacist consultation for chronic disease comanagement; cognitive behavioral therapies; medication-taking reminders; and incentives to promote adherence.[147] A systematic review and meta-analysis of

TABLE 10 Ten Considerations to Improve Adherence

1. Capitalize on opportunities when patients are most predisposed to adherence • In-hospital/predischarge initiation following decompensation
2. Consider the patient's perspective • Start with the goals of therapy (feeling better and living longer) and then discuss how specific actions (medication initiation, intensification, monitoring, and adherence) support those goals (example: ACC's My Heart Failure Action Plan) • Use decision aids when available (example: CardioSmart Heart Failure Resources) • Ask patient how they learn best and provide education accordingly • Use culturally sensitive patient education materials • Focus on a patient-centered outcome (ie, treatment satisfaction, treatment burden, and mental health)
3. Simplify medication regimens whenever possible, especially in older adults
4. Consider costs and access • Become familiar with and advocate for systems that help make cost-sharing automatic, immediate, and transparent • Prescribe lower-cost medications if of similar efficacy • Facilitate access to copay assistance upon prescription • Address prior approvals upon prescription (Document the frequency of these issues, delays in care, and adverse events to help change public policies.) • Discuss out-of-pocket copays proactively • Prescribe 90-day quantities for refills
5. Communicate with other clinicians involved in care, ideally facilitated by electronic health records
6. Educate using practical, patient-friendly information • Provide a written explanation of the purpose of each medication prescribed • Plan pharmacist visits for complex medication regimens • Use the "teach-back" principle to reinforce education • Education the patient and their identified social network
7. Recommend tools that support adherence in real time • Pill boxes to be filled by patient or care partner a week at a time • Alarms for each time of the day medications are due • Smartphone or other mobile health applications that provide an interactive platform for education, reminders, warnings, and adherence tracking • Use of telehealth to increase access to care
8. Consider behavioral supports • Motivational interviewing • Participate in engaged benefit designs
9. Anticipate problems • Communicate common adverse effects • Provide instructions on when to call for refills or report problems • Remind patients using pharmacy assistance programs that refills/reorders are not automatic • Request pharmacy to synchronize refills • Incorporate social support or caregivers in the management
10. Monitor adherence and target patients at risk • Inquire patients directly (eg, "How many times in a week do you miss taking your medications?" "Have you run out of your medications recently?") • Carry out medicine reconciliation at visits, with focus on discrepancies • Ask the patient to bring all the pill bottles to the office visit • Assess remaining dosage units (ie, count excess remaining tablets) • Monitor pharmacy fills, using available clinical databases, or automated alerts for failed fills and refills • Review available drug levels (eg, digoxin, INR) or concentrations of BNP/NT-proBNP • Plan home-based nursing visits for appropriate patients

ACC = American College of Cardiology; BNP = B-type natriuretic peptide; INR = international normalized ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

771 intervention trials on medication adherence demonstrated that the most effective interventions were delivered face-to-face by pharmacists and administered directly to patients, with a specific focus on habit-based interventions.[163] In a systematic review of 57 studies,[164] interventions to enhance adherence for patients with HF were associated with lower mortality (relative risk: 0.89; 95% CI: 0.81-0.99) and hospital readmission (odds ratio: 0.79; 95% CI: 0.71-0.89).

A virtual multidisciplinary care approach may contribute to decrease therapeutic inertia, and allow the patient to reach faster therapeutic goals. A systematic review of 27 studies of mobile health interventions for CV diseases, including HF,[165,166] found that mobile health significantly improved adherence to medical therapy (OR: 4.51; $P < 0.00001$). Smartphone-based remote monitoring between patients and nurses with messaging and e-learning can facilitate information sharing, patient engagement, continuity of care, and ease in communication.[167] In addition, use of remote telerehabilitation is feasible in patients with HFrEF with lack of access to outpatient cardiac rehabilitation.[168-170] A prospective controlled trial demonstrated 80% adherence or partial adherence to telerehabilitation, without adverse events reported during supervised exercise.[169]

4.5.3. Systems and Policies to Promote Adherence

Individual patients and clinicians must be supported by systems that help the right patient get the right therapy at the right time.[171] Automated screening and assessment

TABLE 11 Specific Patient Cohorts in HF Care

Patient Cohorts	Description	Evidence-based Recommendations	Risks	Uncertainties
African-American patients	Self-identified	GDMT	■ ACE inhibitors and ARBs: possibly higher risk of angioedema compared with White patients ■ ARNI: Risk of angioedema may not be different from White patients.	Expected outcomes of ARNI, SGLT inhibitors, and/or ivabradine in those treated with HYD/ISDN; ARNI remains recommended as first-line therapy before HYD/ISDN.
Older adults	Age ≥75 y	■ GDMT, but recognize that this population is excluded from many trials supporting GDMT ■ Consider starting with lower doses of GDMT	■ Potential falls ■ Worsening of kidney function ■ Polypharmacy ■ Comorbidity ■ Depression ■ Financial toxicity	■ Efficacy of lower-dose GDMT on outcomes ■ Greater risk of hypotension? ■ Greater risk of hyperkalemia?
Patients living with frailty	Meets established frailty criteria[187]	GDMT as tolerated	■ Uncertain response to GDMT ■ Possibly increased risk for adverse drug reactions	Unclear impact on natural history among patients with pre-existing frailty

Examples of populations that have been relatively understudied in HFrEF trials include African-American patients, older adults (age ≥75 years), and patients with frailty.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; GDMT = guideline-directed medical therapy; HF = heart failure; HYD/ISDN = hydralazine/isosorbide dinitrate.

tools can identify and target patients who are at the greatest risk for nonadherence (eg, those with dementia, depression, homelessness, or drug use).[172] Health information technologies increasingly can collect pooled data on prescription fills at pharmacies through insurance claims databases and share these data among care providers and across settings. This offers the potential to characterize patient medication adherence in real time and automatically identify problems. Electronic health record-based algorithms to identify and optimize use of GDMT are already in use for these purposes.[173-175]

Cost contributes to suboptimal adherence to GDMT, especially with ARNIs and SGLT inhibitors; accordingly, individuals with HF often experience significant financial toxicity.[176]

Several other mechanisms can help to optimize adherence:

1. Integration of pharmacists, patient navigators, and registered nurses in collaborative practice may help with optimization of GDMT.[129,177-183]
2. Lower prescription insurance copays to limit out-of-pocket costs for patients have been associated with small increases in patient prescription fills and adherence.[146,176,184,185] Value-based insurance designs that tailor cost-sharing to value are promising.
3. The CMS Innovation Center's Beneficiary Engagement and Incentives Models aim to support patient adherence (https://www.cms.gov/newsroom/fact-sheets/beneficiary-engagement-and-incentives-models-shared-decision-making-model).
4. Advocacy through CV societies and community leaders to improve legislation to implement policies and laws to lower drug costs and broaden insurance coverage.

4.6. What is Needed in Specific Patient Cohorts: African-American Populations, Older Adults, and Patients Living With Frailty

Randomized clinical trials typically enroll only a subset of patients with HFrEF, resulting in limited demographic, economic, and clinical diversity. Consequently, there is uncertainty about the benefits and risks of HFrEF therapies in patients not resembling those studied. As a result, only approximations of risks and benefits can guide therapy in the least-studied populations (Table 11).[186,187] Given that race and ethnicity are social constructs, trials are also often missing factors that contribute to study outcomes, particularly social determinants of health, bias, and structural racism.

African-American Patients

ARNIs, SGLT inhibitors, ivabradine, and vericiguat were tested in clinical trial populations with few patients who identified as African American. In fact, the landmark ivabradine study SHIFT included almost no African-American patients.[18,55,188] Nonetheless, no significant differences in the efficacy of ARNIs, SGLT inhibitors, nor soluble guanylyl cyclase stimulators have been observed by race. Given the established benefits in the general public, we recommend that African-American patients receive these newer medications as part of their HF GDMT.

A key therapy among African-American patients with HFrEF is HYD/ISDN, although the consideration of this combination therapy should not supersede use of ARNIs, evidence-based beta-blockers, mineralocorticoid antagonists, and SGLT inhibitors. The combined benefit of HYD/ISDN, in addition to these 4 classes, is less clear–

nevertheless, this lack of clarity should not prevent their use. If extra GDMT is needed for care of an African-American person with HFrEF, we recommend consideration of HYD/ISDN prescriptions, with the acknowledgment that its addition on top of GDMT could increase the risk of hypotension. Additionally, the risk of angioedema with ACE inhibitors is higher in African-American patients, but data are less clear with ARNIs.[189-191]

Clinical guidance for treating HF in African-American patients includes:

1. Establish GDMT with an ARNI (or ACE inhibitor/ARB if ARNI is not available), a beta-blocker (carvedilol, metoprolol succinate, or bisoprolol), an SGLT inhibitor, and a mineralocorticoid antagonist; if stable, follow with titration of HYD/ISDN (starting at a low dose, but aim for doses used in the pivotal randomized trials [**Table 1**, **Figure 3G**]). For those with persistent NYHA functional class III to IV symptoms, titration should proceed with careful blood pressure monitoring and close monitoring of other side effects (eg, headache, dizziness).
   (Note: HYD/ISDN are available as a fixed-dose combination or as individual medications. The AHA/ACC/HFSA HF guideline considers either form acceptable in this context)
2. Avoid ARNIs in settings of any history of angioedema.
3. If the heart rate remains above goal in sinus rhythm, ivabradine may be considered; however, given the paucity of data in African Americans, optimize beta-blocker dosing preferentially.
4. Use of an SGLT inhibitor is indicated as concomitant treatment for HFrEF in African-American patients.
5. Social barriers to GDMT and optimal HFrEF management should be assessed and, where present, addressed to avoid health inequities in HFrEF outcomes.[192] African-American patients have a higher risk of developing and dying from HF.[193,194]
6. African-American patients are less likely to receive care from a cardiologist than White patients.[195] The 2022 AHA/ACC/HFSA HF Guideline[2] has Class I recommendations to identify patients at risk for disparities and address etiologies at the clinic and hospital levels.[2] Strategies should address social determinants of health, bias, and structural racism.[192]
7. All treatment decisions should be determined in the context of an informed, culturally competent, shared decision-making discussion with the patient that considers the risks and benefits of treatment.

Older adults

Older adults, especially the very elderly, represent yet another conundrum for treatment of HF. The upper range for inclusion in HF clinical trials has typically been age 75 ± 5 years; in essence, there are very few randomized data for drugs or devices in patients older than 80 years of age. Subgroup analyses from pivotal studies of GDMT suggest that the 4 classes of Class I therapies have generally consistent efficacy in older individuals. Accordingly, target doses for GDMT should be attempted in older patients, with close surveillance for any adverse drug reactions. The pharmacokinetic profile for GDMT as a function of age is not known, and higher risks of adverse events[186] have been described in older populations. Optimal doses for older patients may be lower than those studied in trials or tolerated in younger patients. Furthermore, medication and dosing decisions should be made in a holistic context of the patient. At times, "deprescribing," or the process of medication withdrawal or dose reduction to correct or prevent medication-related complications, may be an appropriate action.[196] Similar to other vulnerable populations, financial toxicity related to cost of GDMT may be a particular issue for elderly individuals.

Frailty

Frailty is a specific pathophysiological entity with variable prevalence but may approach up to 45% of patients with HF. It amplifies cachexia, muscle wasting, and neurological decline.[197] Furthermore, it increases the risk for HF and, when HF is already present, exaggerates both morbidity and mortality. No evidence exists to suggest that any current therapies should be withheld or doses modified in the setting of frailty. Potential interventions include multidomain rehabilitation along with cognitive and nutritional support programs to accompany standard GDMT for HFrEF.[198,199] Standard assessments of frailty are available (eg, Clinical Frailty Scale, PRISMA-7 questionnaire, and so on).[187]

4.7. How to Manage Patients' Costs and Access to HF Medications

The economic burden of HF is substantial and is expected to increase markedly in parallel with increases in HF prevalence and in escalating costs of medical care. Between 2012 and 2030, total direct medical costs for HF are projected to increase from $21 billion to $53 billion,[200] whereas total costs (including indirect outlay) are estimated to increase from $30.7 billion to $69.8 billion.[201] After hospital costs, the cost of CV medications is the second most important cost for patients with HF, accounting for 15.6% of direct costs.[202] In a study by Karter et al,[203] it was noted that patients who paid $20.00 or more for each prescription were twice as likely to not pick up their medication from the pharmacy as those who received medications at no cost. Disease and medication-related costs create a financial barrier for many patients, which is compounded by the fact that most patients with

HF also have several comorbidities requiring additional medications. For example, diabetes is present in over 40% of all patients with HF, and polypharmacy for diabetes treatment is also growing rapidly.[204] The Writing Committee recommends periodic reassessment of access and affordability of all GDMT to ensure persistence of treatment.

Cost Reduction Measures

A variety of cost reduction measures should be considered in patients with HF (Table 12). Whenever possible, generic equivalents for GDMT should be considered. Pricing for common generic HF drugs (digoxin, carvedilol, and lisinopril) varies widely, even within a limited geographic area.[205] This variability in pricing could potentially have negative implications for adherence, encouraging patients to "shop around" for the best price, increasing time and travel costs, and leading patients to obtain drugs at multiple pharmacies. The use of multiple pharmacies prevents the efficiencies of having a single pharmacist overseeing all of a patient's medications, identifying potential drug interactions, performing medication synchronization, assessing adherence, providing disease management programs, and ensuring that vaccinations are current. As such, patients and clinicians should be encouraged to work with pharmacists, social workers, and/or patient navigators to help identify copay assistance programs and request price matching, when possible, should another pharmacy be found to have the medication at a lower cost. In addition, price-checker tools (eg, Pharmacy Checker) can be used to assist patients in locating the retailers with the lowest cost medications.

Many health systems have financial assistance programs to help patients navigate financial hurdles associated with out-of-pocket medication-related expenses. Health systems often use charitable donations and, if eligible, can elect to participate in drug cost-savings programs, such as the 340B Drug Pricing Program or pharmaceutical company-sponsored patient assistance programs, to reduce or eliminate medication-related costs for patients in need (HRSA, 340B Health, AHA). The Public Health Service Act of 1992, or 340B Drug Pricing Program, is operated by the Health Resources and Services Administration Office of Pharmacy Affairs (HRSA OPA) to allow eligible entities, such as Medicare/Medicaid disproportionate share hospitals and safety net providers, to purchase discounted medications for patients within their system. These covered entities can determine the critical needs of the patients they serve and choose how the savings will be applied. Assisting patients who are uninsured with costs associated with obtaining GDMT therapies or reducing the cost of medications for patients with high-deductible copayments or with minimal ability to pay out-of-pocket for GDMT based on low-income status are examples of programs that could be supported by a 340B Patient Assistance Program at a covered entity. In addition, the Inflation Reduction Act of 2022 (P.L. 117-169) will be contributing to reduced medication for Medicare beneficiaries.[206]

TABLE 12 Strategies to Reduce Patients' Cost of Care

■ Coordinate care (including labs and imaging) among clinicians to minimize unnecessary duplication
■ Consider limitations of medication coverage (insurance, Medicaid, etc.) when prescribing
■ Use generic equivalents for GDMT whenever possible
■ Work with a pharmacist, social worker, or patient navigator to identify and navigate Patient Assistance Programs
■ Request price matching if a drug is found at a lower cost at another pharmacy
■ Determine eligibility for health system participation in 340B Drug Pricing Program to reduce medication-related costs for targeted vulnerable patient populations

GDMT = guideline-directed medical therapy

Medication Access Measures

Newer HFrEF therapies are often expensive, with higher monthly costs and copays, and more time and effort are frequently required to obtain them. For example, prior authorization from payers is often required before these medications will be covered, which can serve as a significant barrier to GDMT. In 2017, the ACC and a coalition of 16 medical organizations called for reform of the prior authorization process and utilization management requirements that increase clinical workload and limit patient access to care (see: https://www.acc.org/-/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Latest-in-Cardiology/Advocacy-and-Policy/PA-Reform-Principles.pdf?la=en&hash=55B06B5BD008D6B05AAD2E874F96667DF9366344).[207]

Managing approvals for medications may be time-consuming; tips for managing such processes are outlined in Table 13.

Although cost-effectiveness analyses of sacubitril/valsartan, ivabradine, dapagliflozin, empagliflozin, and vericiguat showed an incremental cost-effectiveness ratio that compares favorably to other accepted CV therapies when they were first adopted or approved,[208-212] these studies consider societal cost but not the fiscal impact on the individual patient, which may be considerable. Pharmacists can help navigate insurance coverage and patient assistance programs. Standard requests through patient assistance programs allow for 90-day supplies with 3 refills to provide coverage for 1 year. However, income verification and reordering procedures are among the most challenging aspects of patient assistance programs for patients and clinicians.[213] Likewise, patients and clinicians need to be cognizant of reordering procedures, which becomes especially important if doses are

TABLE 13 Helpful Information for Completion of Prior Authorization Forms*

Patient Criteria
■ Include HF phenotype: HFrEF; HFpEF
■ Identify NYHA functional class
■ Include recent measurement of LVEF with source documentation if requested
■ Identify the treatment requested or the additional testing required, with indications supported by evidence and/or guideline statements where applicable; clinical judgment, especially for testing requests, is an appropriate rationale
■ Address previous therapies used and the rationale for switching to or adding the requested treatment
■ Address known contraindications to use, adverse effects, and steps intended to minimize the risks of drugs or procedures
■ Document, when appropriate, that delays or interruptions in therapy may cause harm to the patient
■ Work with local pharmacy resources and pharmacy professionals to jointly address prior authorization requirements; do not hesitate to appeal decisions that are contrary to the best patient care. Provide evidence-based literature when available as supporting documentation Document all steps taken in the patient's health record.

*Required information may vary depending on payer and state.

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction, LVEF= left ventricular ejection fraction; NYHA = New York Heart Association.

changed—refills/reorders are not always sent and, unfortunately, refills/reorders cannot be requested before the 60-day postapproval date. This may create a confusing situation for the patient and lead to errors in drug dosing. It is best practice to wait until after the patient has been initiated on and titrated to the target dose of GDMT and demonstrated drug tolerability before applying to pharmaceutical company-based patient assistance programs. The Supplemental Appendix provides product-specific information on assistance in payment for newer HF therapies and appropriate use criteria to assist in the prior authorization process. Finally, evolving policies around out-of-pocket limits may affect decision-making.

4.8. How to Manage the Increasing Complexity of HF Management

Addressing Social Determinants of Health

The 2017 and 2021 HF ECDPs were motivated by an increasingly complex management environment and the need to assist clinicians in navigating it.[1,214] The evidence surrounding new HF treatments has continued to evolve, prompting this update. Social determinants of health (SDOH) are increasingly recognized as drivers of outcomes in HFrEF.[215-217] As such, the 2022 AHA/ACC/HFSA HF guideline[2] provided a Class 1 recommendation to target SDOH, in addition to traditional risk factors, to narrow and/or eliminate disparities in HFrEF.[2] SDOH are the circumstances in which, and the systems under which, people are born, acculturate, live, work, and age[218] and include education access and quality, economic stability, neighborhood and built environment, social and community context, and health care access and quality, which are influenced by bias and structural racism (Healthy People 2030).[219] Social determinants closely interface with structural determinants of health, which are the "social, economic, and political mechanisms which generate social class inequalities"(AAFP, WHO). Awareness of the impact and implementation of strategies to address SDOH should undergird all aspects of contemporary HFrEF care.

Methods to address SDOH in HFrEF start with data capture and documentation. The Writing Committee recommends that clinicians discuss patients' SDOH with each encounter and document the findings in the health record. Topics explored should include but not be limited to educational attainment, household income, insurance status, zip code, food/nutrition insecurity, social support systems, health literacy, and race/ethnicity. Approximations of SDOH are available from Census Tract data and allow for at least semiquantitative estimates of the social burden. Multiple validated surveys can be used to assess SDOH, as found in the Rural Health Information Hub and the Agency for Healthcare Research and Quality-SDOH website.[220,221] It is very important to confirm SDOH factors at each encounter, given that social circumstances can and do change, which can lead to the reclassification of risk in patients with HFrEF.

Most importantly, care teams should develop strategies to address SDOH and to reassess for appropriate management. Centers can start with developing repositories of resources for patients and use those resources based on identified needs. These should include components like cost-mitigating resources for GDMT, partnerships with access points to nutritious foods, and educational resources specifically geared toward understanding HFrEF.[218] Last, resources should be allocated to identify those at high social risk so that targeted interventions may be implemented to improve outcomes.

GDMT Management

As detailed in Table 14, the modulation of 12 pathophysiological targets has now been shown to improve symptoms and/or outcomes for patients with HFrEF.

The large and growing target and therapy list in HFrEF significantly complicates HF management for both patients and their care teams. However, several guiding principles can improve decision-making for and adherence to GDMT, which, in turn, is likely to improve patient outcomes.

Principle 1: GDMT is the foundation of HF care, and the GDMT with the highest expected benefit should be prioritized.

Based on large, randomized trials for HFrEF, ARNI, evidence-based beta-blockers, mineralocorticoid

TABLE 14 Important Pathophysiological Targets in Chronic, Hemodynamically Stable HFrEF and Treatments

Target	Therapy
Renin-angiotensin-aldosterone system	ARNIs/ACE inhibitors/ARBs, mineralocorticoid antagonists
Sympathetic nervous system	Beta-blockers
Natriuretic and other vasodilator peptides	Neprilysin inhibitor (ARNI)
Sodium-glucose cotransporters	SGLT1/2 and SGLT2 inhibitors
Balanced vasodilation and oxidative stress modulation	HYD/ISDN
Elevated heart rate	Beta-blocker, ivabradine
Guanylyl cyclase	Soluble guanylyl cyclase stimulators
Relief of congestion	Diuretic agents
Ventricular arrhythmias	Implantable cardioverter-defibrillators
Ventricular dyssynchrony due to conduction abnormalities	Cardiac resynchronization therapy
Mitral regurgitation	Surgical or percutaneous mitral valve repair
Reduced aerobic capacity	Aerobic exercise training

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; HYD/ISDN = hydralazine/isosorbide dinitrate; SGLT = sodium-glucose cotransporter.

antagonists, and SGLT inhibitors are first-line medications for all populations. HYD/ISDN is also a first-line medication for self-identified African-American patients after initiating optimal doses of first-line medications. Ivabradine is a second-line medication for select populations, as is vericiguat.

Principle 2: Target doses are associated with best outcomes.

Attempt to rapidly achieve target doses of all recommended therapies in the absence of contraindications and/or intolerance. Titration should occur even if the patient appears stable or their symptoms and/or EF improve. Failure to tolerate titration should prompt consideration for referral to an advanced center.

Principle 3: Start GDMT immediately and titrate during each encounter.

Delayed initiation of GDMT is associated with never initiating GDMT.[222] The goal is to finish initiation and titration by 2 to 3 months (or sooner). Although GDMT may be added sequentially, in many cases, simultaneous start of multiple agents (or all 4) may be possible.

Principle 4: Attention to the clinical, social, and financial barriers to achieving GDMT should be prioritized.

This includes addressing bias, structural racism, and SDOH routinely during encounters. Multidisciplinary care should be targeted to the individual patient's barriers. This should be reevaluated for success at the clinic and hospital levels at routine intervals. Consider early referral to an HF team for assistance.

Principle 5: Diligent management of volume status will reduce patient symptoms.

Congestion drives symptoms and hospitalizations. If the volume status is unclear, consider performing right heart catheterization and/or referral to an HF specialist. Chronic ambulatory PAP monitoring may be considered in patients with hospitalizations in the past year who have persistent symptoms with minimal exertion.

Principle 6: Tolerability and side effects depend, in part, on how and when GDMT is prescribed.

Scenario: *Worsening kidney function or hyperkalemia.*

Available data support a survival benefit even with low doses of GDMT. Use less than target doses of an ARNI/ACE inhibitor/ARB and discontinue the mineralocorticoid antagonist if estimated creatinine clearance is <30 mL/min or serum potassium is >5.0 mEq/L, despite all efforts to address hyperkalemia. SGLT inhibitors are beneficial, even below approved creatinine clearance thresholds.

Scenario: *Symptomatic hypotension.*

Symptomatic hypotension may be due to overdiuresis, use of non-CV drugs with hemodynamic effects (eg, anticholinergic agents, treatments for prostate enlargement, others), autonomic dysfunction, or simultaneous administration of multiple HF medications. All of these should be addressed before deciding to lower doses of evidence-based therapies. After excluding other causes of hypotension, use best-tolerated doses of GDMT, accepting that less data exist for the impact of lower doses in HF management. Clinical comorbidities and clinical judgement should be used to guide which GDMTs are reduced. For persistent hypotension, consider referral to an advanced HF specialist.

Scenario: *Hypokalemia*

When possible, consider increasing the dose of mineralocorticoid antagonist (if appropriate kidney function) in lieu of adding oral potassium.

Principle 7: Primary prevention ICDs and CRT should be considered after consistent use of optimal doses of all GDMTs for at least 3 to 6 months, followed by reassessment of EF and other indications for device therapy.

Principle 8: Transcatheter mitral valve repair may be considered in symptomatic patients with chronic, moderate-severe to severe MR despite optimal doses of all GDMTs.

Principle 9: Focus on the patient's symptoms, functional capacity, and cardiac function. Maintain surveillance of the patient's health status using validated symptom questionnaires (eg, the Kansas City Cardiomyopathy Questionnaire). This could be achieved during cardiac rehabilitation, which should be used to improve patient-reported outcomes, reduce hospitalizations, and improve aerobic fitness.

Principle 10: The value of a therapy to a patient is the combination of benefits and burdens as they relate to that patient's values, goals, and preferences. Shared decision-making will help patients and the health care team reach the best treatment plan for the individual patient.

Principle 11: Team-based care is critical to optimizing GDMT and may include frequent follow-up visits, telehealth visits, and remote monitoring.

Use multidisciplinary teams that include advanced-practice professionals, clinical nurses, and pharmacists to help titrate GDMT. Team management also facilitates serial assessments and longitudinal care, including management of comorbidities.

4.9. How to Manage Common Comorbidities

Patients with HF, particularly older patients, frequently have other CV and non-CV comorbidities that affect their prognosis. Examples of relevant comorbid conditions include hypertension, diabetes, coronary artery disease, atrial fibrillation, chronic kidney disease, anemia/iron deficiency, sleep disorders, and chronic lung disease, among others. The presence of multiple chronic conditions is associated with increased symptom burden, may contribute to progression of underlying disease, and often plays a role in a large proportion of hospitalizations in patients with HF. Some comorbid conditions, for example chronic kidney disease and atrial fibrillation, have bidirectional relationships with HF, whereby the presence of one may increase the risk of the other, and the prognosis may be worse if both are present simultaneously. Furthermore, comorbid conditions can greatly influence how HF therapies are used and the extent to which they can be optimized; limitations imposed by kidney dysfunction illustrate this issue. To optimally manage patients and improve clinical outcomes, clinicians must increasingly consider diagnosis and treatment of relevant comorbidities alongside the use of evidence-based HF therapies. Given the complex relationships between HF and many of these conditions, however, it is challenging to outline specific recommendations or practical approaches to therapeutic strategies that can be applied broadly or in all scenarios. Additional evidence and large-scale trial data are needed. For these reasons and others, appropriate referral to clinicians with experience treating various comorbidities is a particularly important aspect of management that lays the foundation for effective team-based care.

Specific management recommendations can be made in some situations. Table 15 classifies comorbidities between CV and non-CV processes and provides guidance on appropriate management options, when possible, as well as references for disease- or condition-specific guidelines, if available.[223-237] Of these, 3 conditions that deserve particular mention are diabetes, viral respiratory infections, and anemia/iron deficiency.[238,239]

Diabetes is common and is strongly associated with the risk of both incident HF and adverse clinical outcomes. It is also closely linked to other relevant comorbid conditions such as hypertension, coronary artery disease, and chronic kidney disease. Treatment of patients with T2D with SGLT inhibitors improves glycemic control and also significantly reduces HF events in patients with established CV disease or CV risk factors.[240-242] Among patients with chronic kidney disease, SGLT inhibitors also decrease the risk of kidney disease progression in a manner additive to renin-angiotensin-aldosterone system inhibitors.[243]

Viral infections (eg, influenza, pneumonia, and COVID-19) are often perceived as primarily respiratory in nature. However, they also have multiorgan impacts that can strongly influence the outcomes of patients with HF. In particular, viral infections of this nature have a significant impact on the heart.[244-249] Sympathetic stimulation and proinflammatory cytokines from the infection lead to increased myocardial oxygen demand, myocardial depression, and myocarditis myocyte necrosis.[250] Vaccination for each of these conditions has shown marked improvements in mortality and hospitalization outcomes for heart failure patients.[251-253] The Standards for Adult Immunization Practices emphasize the crucial role that all clinicians play in influencing their patients to receive these important annual vaccinations.[254] Although often regarded as a primary care role, the role of the HF team in recommending and/or providing vaccination can highly influence HF patient outcomes. Several resources have been developed to support patients and educate them on the link between CV outcomes and vaccination.[255]

Anemia is one of the most common non-CV comorbidities in patients with HF and is independently associated with mortality in this population.[256] Studies investigating the use of erythropoietin-stimulating agents to treat anemia in patients with HF, including a large, randomized trial in >2,000 patients, have demonstrated no benefit in rehospitalization or mortality but a significant increase in thromboembolic events, including

TABLE 15 Common Cardiovascular and Noncardiovascular Comorbidities Encountered in Patients With HFrEF

Comorbidity	Association With Heart Failure Outcomes	Clinical Trial Evidence for Modulating Comorbidity	Suggested Action
Cardiovascular			
Coronary artery disease	Strong	Strong	■ Revascularize in appropriate patients with HFrEF and suitable coronary anatomy
Atrial fibrillation/ flutter	Strong	Strong	■ Anticoagulate if indicated ■ Consider AF ablation[223] or AV nodal ablation with CRT implantation in selected patients ■ Treat according to the current ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation[224]
Mitral regurgitation	Strong	Intermediate	■ Multidisciplinary management, including structural heart team[225,226] ■ Consider transcatheter intervention in carefully selected patients with symptomatic HF and secondary MR after GDMT optimization[227] ■ Treat according to the current ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease[225] and ACC ECDP on the Management of MR[226]
Aortic stenosis	Strong	Strong	■ Multidisciplinary management, including structural heart team ■ Treat according to current ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease[225]
Hypertension	Uncertain	Strong for prevention	■ Treat according to current ACC/AHA/Multisociety Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults[228]
Dyslipidemia	Uncertain	Strong for prevention	■ Treat according to current AHA/ACC/Multisociety Guideline on the Management of Blood Cholesterol[229] and the ACC ECDP on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk[230]
Peripheral vascular disease	Moderate	None	■ Treat according to current AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease[231]
Cerebrovascular disease	Moderate	Weak	■ Treat according to current ASA/AHA Guideline for the Early Management of Patients with Acute Ischemic Stroke[232]
Noncardiovascular			
Diabetes	Strong	Strong	■ Consider consult with endocrinologist ■ Monitor serum creatinine and albuminuria at least yearly ■ Treat with SGLT inhibitor for management of hyperglycemia ■ Treat according to the current ACC ECDP on Novel Therapies for CV Risk Reduction in Patients with T2D[117] and ADA Standards of Medical Care in Diabetes[233]
Chronic kidney disease	Strong	Strong	■ Optimize RAAS inhibitor therapy ■ Use hydralazine/ISDN if an ARNI/ACE inhibitor/ARB cannot be used ■ Treat with SGLT inhibitor if GFR allows ■ Consider nephrology consult
Sleep disordered breathing	Strong	Intermediate; note that in patients with symptomatic HFrEF and central sleep apnea, adaptive servo-ventilation is harmful[234]	■ Refer for sleep study to confirm diagnosis ■ Treat obstructive sleep apnea ■ Consider referral to sleep medicine specialist
Iron deficiency (with or without anemia)	Strong	Intermediate	■ Consider intravenous iron replacement for symptom improvement
Malnutrition	Strong	Intermediate to Strong	■ Poor nutrition may result in worse HF outcomes. In line with the 2019 ACC/AHA Primary Prevention Guidelines, a low salt, plant-forward diet has robust evidence to aid in the management of HFrEF patients, including their common morbidities.[235]
Anemia	Moderate	Weak; note that in patients with HF and anemia, use of erythropoietin-stimulating agents is harmful[236]	■ Evaluate secondary causes ■ Consider transfusion in severe cases
Hyperkalemia	Uncertain; may limit initiation and titration of GDMT	Weak	■ Recommend dietary modifications ■ Consider treating with patiromer or sodium zirconium cyclosilicate
Obesity	Moderate (inverse association)	Weak	■ Data are suggestive of symptomatic benefit from treatment of obesity using glucagon-like peptide receptor agonist-1 in HFpEF[237]; however, additional data needed regarding safety and efficacy of weight-loss agents in HFrEF

Continued on the next page

TABLE 15 Continued

Comorbidity	Association With Heart Failure Outcomes	Clinical Trial Evidence for Modulating Comorbidity	Suggested Action
Chronic lung disease	Strong	Weak	■ Smoking cessation ■ Optimize therapy ■ Consider pulmonary consultation
Thyroid disorder (hypo or hyper)	Strong	Weak	■ Evaluate and initiate treatment ■ Consider referral to endocrinologist
Viral infection (eg, COVID-19, RSV, or influenza)	Strong	Strong	■ Encourage vaccination per the Standards for Adult Immunization Practice[254]

ACC = American College of Cardiology; ACCP = American College of Clinical Pharmacy; ACE = angiotensin-converting enzyme; ADA = American Diabetes Association; AF = atrial fibrillation; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ASA = American Stroke Association; ASCVD = atherosclerotic cardiovascular disease; AV = atrioventricular; COVID-19 = coronavirus disease 2019; CV = cardiovascular; ECDP = Expert Consensus Decision Pathway; GDMT = guideline-directed medical therapy; GFR = glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HRS = Heart Rhythm Society; ISDN = isosorbide dinitrate; LDL = low-density lipoprotein; MR = mitral regurgitation; RAAS = renin-angiotensin-aldosterone system; RSV = respiratory syncytial virus; SGLT = sodium-glucose cotransporter; T2D = type 2 diabetes.

ischemic stroke.[236,257] For this reason, erythropoietin-stimulating agents should not be used to treat anemia in patients with HF.

Studies have also focused on the treatment of iron deficiency, given its prevalence of nearly 50% in patients with symptomatic HF and association with worse functional capacity and increased mortality.[258,259] Iron deficiency, according to current definitions used in HF clinical trials, is defined as ferritin <100 μg/L or 100 to 300 μg/L with transferrin saturation <20%. In patients with HF meeting these criteria, with or without anemia, intravenous iron repletion improves exercise capacity and quality of life.[260,261] Recent studies have also demonstrated reductions in HF hospitalization and a composite of HF hospitalization and CV death,[262,263] and a meta-analysis of trials of intravenous iron therapy in patients with HF and iron deficiency showed an association between iron repletion and reduction in HF hospitalization but not mortality.[264] The most recent and largest trial of 3,065 patients with HFrEF and iron deficiency did not show a clear benefit of intravenous iron replacement on a hierarchical composite of death, HF hospitalization, or 6-minute walk distance.[265] Further investigation in this regard is needed. Importantly, relevant improvements have not been seen with oral iron supplementation, most likely due to poor absorption and tolerability of oral iron.[266] Therefore, it is recommended that in patients with symptomatic HF and iron deficiency, with or without anemia, intravenous iron replacement be considered for symptom improvement.[18,19,72,267]

Of note, the recent COVID-19 pandemic has illustrated an association between underlying CV disease, including HF, and worse clinical outcomes.[268] It is now known that in patients with HFrEF, renin-angiotensin-aldosterone system inhibition is not associated with risk of infection or severity of disease and should be continued, even in the setting of COVID-19 infection, as long as it is hemodynamically tolerated.[269-273]

4.10. How to Integrate Palliative Care and Transition to Hospice Care

Advances in care have delayed the progression of disease but rarely lead to a cure, such that the palliative care needs of patients, caregivers, and health care systems are as great as ever. Most palliative care is provided by non-palliative care specialists. Accordingly, such clinicians shoulder the primary responsibility for coordinating an end-of-life plan consistent with the values and goals expressed by the patient and family. The following are important points to consider regarding palliative care and transition to hospice.

Principle 1: Palliative care strives to reduce suffering through the relief of pain and other distressing symptoms while integrating psychological and spiritual aspects of care.

Action: Soliciting goals of care and focusing on quality of life are appropriate throughout the clinical course of HF and become increasingly important as the disease progresses.

Principle 2: Good HF management is the cornerstone of symptom palliation.

Action: Meticulous management of HF therapies—particularly diuretic agents—is a critical component of symptom management and should continue through the end of life.

Principle 3: Palliative care consultation and complementary approaches to care may further ameliorate refractory HF symptoms of dyspnea, fatigue, and pain, although study results have been mixed. These approaches also improve patient satisfaction and quality-of-life metrics.

Action: Targeted specialty palliative care consultation can be helpful for especially complex decisions, refractory symptoms, and end of life. Palliative care teams should have expertise in management of both HF-related and non-HF-related symptoms.

Principle 4: Patients with HF often face major treatment decisions over time and should be provided with support when thinking through the benefits and burdens of each treatment option.

Action: Decision support tools (patient decision aids) help frame options, which should then be followed by dynamic and personalized conversations.

Principle 5: Proactive shared decision-making discussions simplify difficult decisions in the future.

Action: Preparedness planning discussions should occur at least annually between patients and clinicians, leading to a review of clinical status and current therapies, estimates of prognosis, clarification of patient values and beliefs, anticipation of treatment decisions, and advanced care directives that identify surrogate decision-makers and health care proxies.[2,7] Resources to assist patients in these difficult discussions may be useful (eg, the Advanced Care Training module from HFSA: hfsa.org/hfsa-patient-education-advance-care-planning). Similar preparedness-planning discussions should occur at the time of major procedural interventions (eg, LV assist device implantation, heart transplantation).

Principle 6: Attention to the clinical trajectory is required to calibrate expectations and guide timely decisions, but prognostic uncertainty is inevitable and should be included in discussions with patients and caregivers.

Action: Worsening disease and "milestone events" (eg, recurrent hospitalization or progressive intolerance of medications due to hypotension and kidney dysfunction) should trigger heightened preparation with patients and families, but without specific estimates of how much time remains due to high levels of unpredictability in the clinical course of HF.

Principle 7: The transition from "do everything" to "comfort only/hospice" is often bridged through a phase of "quality survival," during which time patients increasingly weigh the benefits, risks, and burdens of initiating or continuing life-sustaining treatments.

Action: Revising the medical regimen for symptom relief and quality of life may involve discontinuation of some recommended therapies (eg, reducing neurohormonal antagonists in the setting of symptomatic hypotension, deactivation of defibrillator therapy) and the addition of therapies not usually recommended (eg, opioids for refractory dyspnea). These decisions should be individualized and made in partnership with the patient, their caregivers, and their care team.

5. DISCUSSIONS AND IMPLICATIONS OF PATHWAY

The primary objective of this updated ECDP is to provide a framework for the many decisions required in the management of patients with HFrEF. Most importantly, the checklists and algorithms provided in this ECDP should be applied only in the context of the most recent update to the AHA/ACC/HFSA guideline for management of adults with chronic HF and, in this case, patients with HFrEF. No guideline, pathway, or algorithm should ever supersede clinical judgment.

Management of HFrEF often involves multidisciplinary care, may require complex decision-making, and benefits from a solid foundation of knowledge to manage these often fragile patients. HF is a major public health concern, one in which broader clinician experience in GDMT would be expected to significantly benefit affected patients. With recent changes in available diagnostics and therapeutic agents for HFrEF, along with the evolution in recommended management strategies for affected patients, many questions have emerged regarding optimal deployment of these newer approaches to patient care. Additionally, clinical practice guidelines continue to evolve. In this context, we have highlighted important literature citations explaining the rationale for this changing picture in HFrEF care, candidate best practices, and, where evidence or best practices are lacking, templates for clinical decision-making to manage patients rationally. As more evidence emerges, many more topics will be clarified.

PRESIDENT AND STAFF

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KEY WORDS ACC Expert Consensus Decision Pathway, ARNI, heart failure, HFrEF, SGLT inhibitor

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2024 ACC EXPERT CONSENSUS DECISION PATHWAY FOR TREATMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION

To avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing committee, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all current health care-related relationships, including those existing 12 months before initiation of the writing effort. The ACC Solution Set Oversight Committee reviews these disclosures to determine what companies make products (on market or in development) that pertain to the document under development. Based on this information, a writing committee is formed to include a majority of members with no *relevant* relationships with industry (RWI), led by a chair with no *relevant* RWI. RWI is reviewed on all conference calls and updated as changes occur. Author RWI pertinent to this document is disclosed in the table below, and peer reviewer RWI is disclosed in Appendix 2. Additionally, to ensure complete transparency, authors' *comprehensive disclosure information*—including RWI not pertinent to this document—is available online in a Supplemental Appendix. The ACC RWI Policy for the Development of Clinical Documents is available online. http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy.

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Quentin R. Youmans	Northwestern University Feinberg School of Medicine—Assistant Professor, Division of Cardiology, Department of Medicine	None	None	None	None	None	None

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AANP = American Association of Nurse Practitioners; ACC = American College of Cardiology; DSMB = Data Safety Monitoring Board; CTEPH = chronic thromboembolic pulmonary hypertension; TTUSHC = Texas Tech University Health Sciences Center; UCLA = University of California, Los Angeles.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)

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Nicole Martin Bhave	Official Reviewer—Solution Set Oversight Committee	University of Michigan—Clinical Associate Professor	■ ACCF: clinical adjudication committee for vaccine-associated myocarditis	None	None	■ Rednvia, Inc.	None	None
Lauren Eyadiel	Official Reviewer—ACC CV Team Section Council	Wake Forest University School of Medicine—Assistant Professor	None	None	None	None	None	None
Lee R. Goldberg	Content Reviewer—ACC Expert	University of Pennsylvania—Vice Chair of Medicine	■ Abbott Laboratories ■ Respircardia/Zoll* ■ Viscardia†	None	None	■ NIH† ■ Respircardia/ Zoll†	None	None
Vicki L Groo	Official Reviewer—ACC CV Team Section Council	University of Illinois Chicago—Clinical Associate Professor	■ Cytokinetics	None	None	None	None	None
Benjamin A Hocutt	Official Reviewer—ACC CV Team Section Council	Multicare Tacoma General Hospital, Pulse Heart Institute— Nurse Practitioner	None	■ Merck & Co.	None	None	■ HFSA†	None
Steven M. Hollenberg	Content Reviewer—ACC Expert	Emory University—Director, Cardiac Intensive Care	None	None	None	None	None	None
Michelle Maya Kittleson	Content Reviewer—ACC Expert	Cedars-Sinai—Cardiologist	None	■ Encore Medical Education	None	■ ATG Study, Sanofi (Genzyme Corporation)‡ ■ Eidos AG10-301, Eidos Therapeutics Inc‡ ■ SOPRANO Study, Actelion‡ ■ TDE-PH-311, United Therapeutics‡ ■ Tocilizumab study, NIH‡ ■ Trojan-C (Hep-C Study), Gilead/One Legacy/Baylor‡	None	None
Gurusher S. Panjrath	Official Reviewer—Solution Set Oversight Committee	George Washington University Medical Faculty Associates—Director, Heart Failure and Mechanical Support Program	■ American Regeant* ■ CVRx*	■ Pfizer Inc*	None	■ Guide HF, Abbott Laboratories‡ ■ TTRTransfrom, IONIS‡	■ Franklin & Prokopik, P.C*	■ 2022, Heart failure related to eye injury*
Lynne Warner Stevenson	Content Reviewer—ACC Expert	Vanderbilt University—Director of Cardiomyopathy	■ American Board of Internal Medicine ■ Novartis- EP	None	None	■ NHLBI* ■ ProACTIV III, Endotronic‡ ■ LivaNova (DSMB)	■ Abbott† ■ Abbott Medical ■ Biotronik ■ Boston Scientific ■ Bristol Myers Squibb† ■ Endotronic† ■ Johnson and Johnson ■ NHLBI	None

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Justin Marinus Vader	Content Reviewer—ACC Expert	Washington University—Associate Professor	None	None	None	■ NIH* ■ APOLLO Trial, Medtronic‡ ■ CORCINCH-HF, Ancora Heart, Inc‡ ■ Donor-Derived Cell-free DNA–Outcomes AlloMap Registry, CareDx, Inc.‡ ■ Eli Lilly Protocol J2L-MC-EZBB, Eli Lilly‡ ■ TAVR Unload, Cardiovascular Research Foundation (CRF)‡ ■ VICTOR, Merck & Co., Inc.‡	None	■ 2023, LVAD candidate selection

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‡Relationship with this company is limited to enrolling patients in clinical trials. This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the ACC/AHA Disclosure Policy for Writing Committees.

ACC = American College of Cardiology; AHA = American Heart Association; DSMB = Data Safety Monitoring Board; HFSA = Heart Failure Society of America.

APPENDIX 3. ABBREVIATIONS

ACC = American College of Cardiology
ACE = angiotensin-converting enzyme
AF = atrial fibrillation
AHA = American Heart Association
ARB = angiotensin receptor blocker
ARNI = angiotensin receptor/neprilysin inhibitor
BNP = B-type natriuretic peptide
CI = confidence interval
COVID-19 = coronavirus disease of 2019
CV = cardiovascular
ECDP = expert consensus decision pathway
EF = ejection fraction
eGFR = estimated glomerular filtration rate
GDMT = guideline-directed medical therapy
HF = heart failure
HFrEF = heart failure with reduced ejection fraction
HFSA = Heart Failure Society of America
HYD/ISDN = hydralazine/isosorbide dinitrate
LV = left ventricular
LVEF = left ventricular ejection fraction
MR = mitral regurgitation
NT-proBNP = N-terminal pro-B-type natriuretic peptide
NYHA = New York Heart Association
RWI = relationships with industry
SGLT = sodium-glucose cotransporter
T2D = type 2 diabetes