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EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

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

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PREFACE

The American College of Cardiology (ACC) has a long history of developing documents (e.g., decision pathways, health policy statements, appropriate use criteria)

to provide members with guidance on both clinical and nonclinical topics relevant to cardiovascular (CV) care. In most circumstances, these documents have been created to complement clinical practice guidelines and to inform clinicians about areas where evidence may be new and evolving or where sufficient data may be more limited. Despite this, numerous care gaps continue to exist, highlighting the need for more streamlined and efficient processes to implement best practices in service to improved patient care.

Central to the ACC's strategic plan is the generation of "actionable knowledge"—a concept that places emphasis on making clinical information easier to consume, share, integrate, and update. To this end, the ACC has evolved from developing isolated documents to developing integrated "solution sets." Solution sets are groups of closely related activities, policy, mobile applications, decision support, and other tools necessary to transform care and/or improve heart health. Solution sets address key questions facing care teams and attempt to provide practical guidance to be applied at the point of care. They use both established and emerging methods to disseminate information for CV conditions and their related management. The success of the solution sets rests firmly on their ability to have a measurable impact on the delivery of care. Because solution sets reflect current evidence and ongoing gaps in care, the associated content will be refined over time to best match changing evidence and member needs.

Expert consensus decision pathways (ECDPs) represent a key component of solution sets. The methodology for ECDPs is grounded in assembling a group of clinical experts to develop content that addresses key questions facing our members across a range of high-value clinical topics (1). This content is used to inform the development of various tools that accelerate real-time use of clinical policy at the point of care. They are not intended to provide a single correct answer; rather, they encourage clinicians to ask questions and consider important factors as they define treatment plans for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy. In some cases, covered topics will be addressed in subsequent clinical practice guidelines as the evidence base evolves. In other cases, these will serve as stand-alone policy.

Ty J. Gluckman, MD, FACC
Chair, ACC Solution Set Oversight Committee

ABSTRACT

The 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment was created to provide a practical, streamlined resource for clinicians managing patients with heart failure with reduced ejection fraction (HFrEF) (2). The 2017 ECDP was based on the 2013 ACCF/American Heart Association (AHA) Guideline for the Management of Heart Failure and the 2017 ACC/AHA/Heart Failure Society of America (HFSA) Focused Update of the 2013 Guideline (3,4). The 2017 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 successfully and expeditiously treat the patient with HFrEF. 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 the 2017 ECDP, new therapies for HFrEF have emerged that expand the armamentarium for the treatment of patients with HFrEF. In particular, the emergence of angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and percutaneous therapy for mitral regurgitation (MR) represent significant advances in the treatment of HFrEF. As such, a focused update to the 2017 ECDP that incorporates these advances into the recommendations is warranted. This update can serve as interim guidance to clinicians while we await the comprehensive and definitive heart failure (HF) guideline update under development by the ACC. 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.

1. INTRODUCTION

The prevalence of HF is escalating rapidly (5). Compounding this, HF is an illness that consumes substantial healthcare resources, inflicts considerable morbidity and mortality, and greatly affects quality of life. Important breakthroughs have redefined opportunities to change

the natural history of the disease with a broad range of medical therapies, devices, and care strategies.

The purpose of this focused ECDP update is to supplement the 2017 ECDP with data from emerging studies and to continue to provide succinct, practical guidance for managing patients with HFrEF. The format of the 10 Pivotal Issues in the 2017 ECDP was preserved, and their associated treatment algorithms and tables have been updated to accommodate this new, evolving evidence.

Ten Pivotal Issues in HFrEF

1. How to initiate, add, or switch therapies to new evidence-based guideline-directed treatments for HFrEF.
2. How to achieve optimal therapy given multiple drugs for HF including augmented clinical assessment (e.g., imaging data, biomarkers, and filling pressures) that may trigger additional changes in guideline-directed therapy.
3. When to refer to an HF specialist.
4. How to address challenges of care coordination.
5. How to improve medication adherence.
6. What is needed in specific patient cohorts: African Americans, older adults, and the frail.
7. How to manage your patients' costs and 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 into hospice care.

2. METHODS

The original 2017 ACC ECDP was drafted using a structured format that was created subsequent to the release of the 2016 and 2017 ACC/AHA/HFSA focused updates of the 2013 ACCF/AHA HF guideline (2,4,6). The evolution of that ECDP involved developing questions to identify evidence gaps and convening a multidisciplinary panel of stakeholders who carried out a literature review to aggregate relevant evidence addressing contemporary HF care. At that time, the references were separately reviewed by the Chair and Vice Chair of the ECDP, and an agreed-upon compendium was developed. Print copies of the references were provided to each member of the panel before a live roundtable meeting held on July 19, 2016, at the ACC Heart House. Participants attending the HF roundtable included cardiologists, internists, emergency physicians, hospitalists, nurses, representatives from patient advocacy groups, pharmacists, fellows-in-training, quality improvement experts, epidemiologists, and biostatisticians.

Since the publication of the 2017 ECDP, numerous clinical trials have been reported, providing updated knowledge to inform the clinical management of patients with HFrEF. In addition, more knowledge is now available regarding biomarkers and imaging, management of comorbidities, and the mitigation of difficulties encountered in care coordination. Lastly, the considerable impact of the coronavirus disease 2019 (COVID-19) pandemic on outpatient management of chronic disease states such as HFrEF justifies its consideration in this document.

To address these newer data and how they relate to prior logic for clinical management of HFrEF, the ACC convened structured discussions to address new therapies, unanswered questions, adherence, and implementation strategies. The College also convened multidisciplinary panel discussions, which have been archived for online distribution (https://www.acc.org/tools-and-practice-support/quality-programs/succeed-in-managing-heart-failure-initiative/emerging-strategies-for-heart-failure-roundtable). Based on those discussions, a writing committee was formed to provide practical guidance to address gaps in care related to optimal management of HF treatment. For this 2021 update, the writing committee convened in mid-2020 on confidential conference calls attended only by writing committee members and ACC staff. When consensus within the writing committee was deemed necessary by the Chair and Vice Chair, either a roll call vote or an email-generated ballot was implemented. A simple majority prevailed; in the presence of a tie, the Chair's prerogative reconciled the final decision.

The formal peer-review process was completed consistent with ACC policy and included a public comment period to obtain further feedback. Following reconciliation of all comments, this document was approved for publication by the Clinical Policy Approval Committee.

The ACC and the Solution Set Oversight Committee (SSOC) recognize the importance of avoiding real or

perceived relationships with industry (RWI) or other entities that may affect clinical policy. The ACC maintains a database that tracks all relevant relationships for ACC members and persons who participate in ACC activities, including those involved in the development of ECDPs. ECDPs follow ACC RWI Policy in determining what constitutes a relevant relationship, with additional vetting by the SSOC.

ECDP writing groups must be chaired or co-chaired by an individual with no relevant RWI. Although vice chairs and writing group members may have relevant RWI, they must constitute <50% of the writing group. Relevant disclosures for the writing group, external reviewers, and SSOC members can be found in Appendixes 1 and 2. To ensure complete transparency, a full list of disclosure information, including relationships not pertinent to this document, is available in Supplemental Appendix 1. Participants are discouraged from acquiring relevant RWI throughout the writing process.

3. ASSUMPTIONS AND DEFINITIONS

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

3.1. General Clinical Assumptions

1. Although many topics are generalizable to all patients with HF, the focus of this effort, including pathway recommendations, is on patients with HFrEF.
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 mainly focuses on the management of patients with chronic ambulatory HFrEF with LVEF ≤40%.
3. The expert consensus writing committee endorses the evidence-based approaches to HF therapy and management enumerated in the 2013 ACC/AHA HF guideline (3) and the subsequent 2016 and 2017 ACC/AHA/HFSA focused updates (4,6).
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 medical specialists (e.g., endocrinologists or nephrologists) to guide clinical management.
5. In all cases, patient preferences and values, in partnership with 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.

3.2. Definitions

ACC/AHA Stages of HF:

- Stage A: At high risk for HF but without structural heart disease or symptoms of HF.
- Stage B: Structural heart disease but without signs or symptoms of HF.
- Stage C: Structural heart disease with prior or current symptoms of HF.
- Stage D: Refractory HF requiring specialized interventions.

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

HFrEF: Clinical diagnosis of 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.

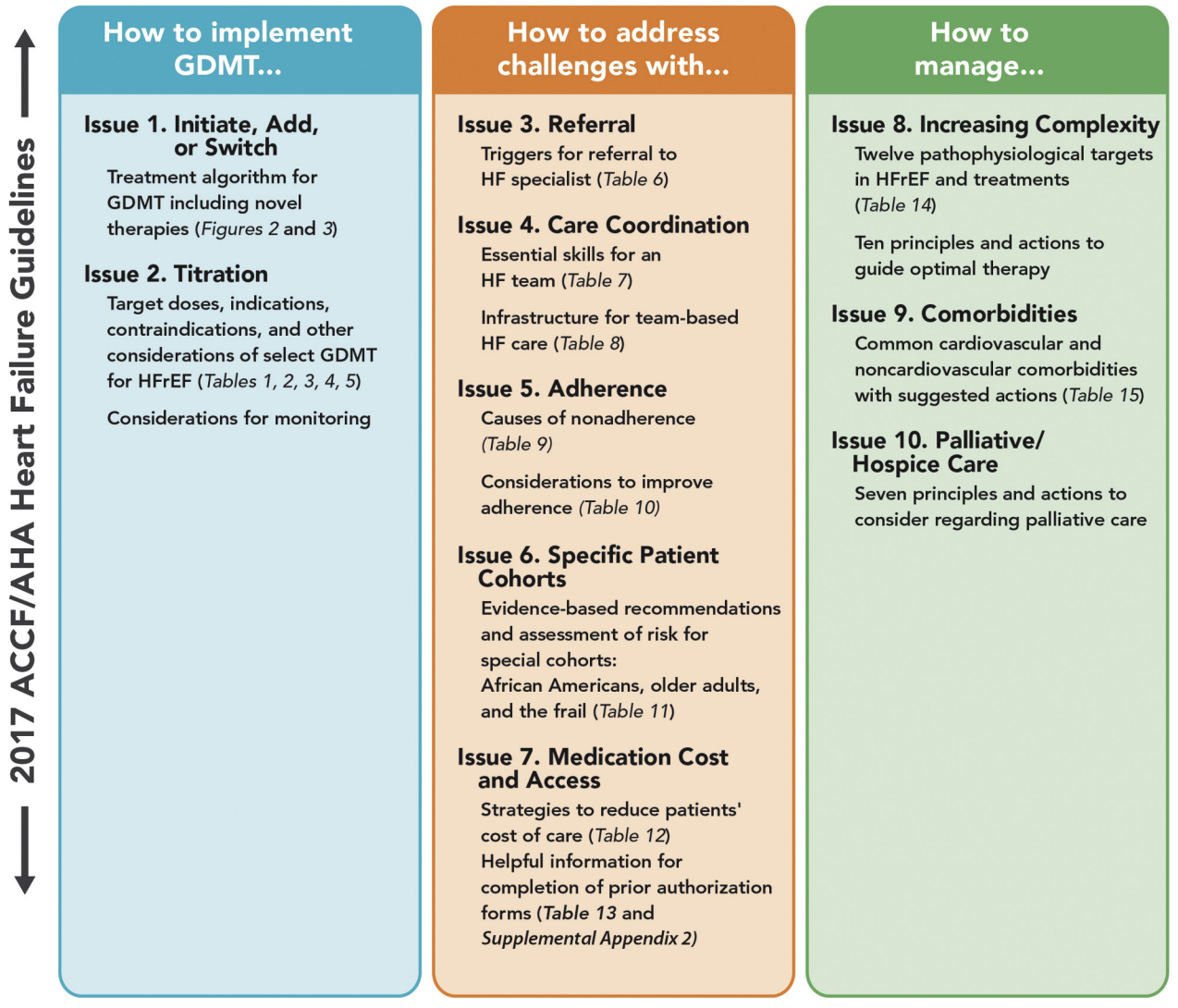
Optimal therapy: Treatment provided at either the target or the highest-tolerated dose for a given patient.

Target dose: Doses targeted in clinical trials.

4. PATHWAY SUMMARY GRAPHIC

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

FIGURE 1 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction



GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.

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

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

Established therapies for chronic HFrEF include ARNIs, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, loop diuretics, aldosterone antagonists, hydralazine/isosorbide dinitrate (HYD/ISDN), and ivabradine, an I_f channel blocker highly selective for the sinoatrial node pacemaker current. With the exception of loop diuretics, all of these therapies have been shown in randomized controlled trials to improve symptoms, reduce hospitalizations, and/or prolong survival (3). Use of digoxin as a treatment for HFrEF lacks new 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.

Following the publication of the 2017 ECDP focused on optimizing therapy for HFrEF, more data have emerged to support an expanded role for ARNIs in patients with HFrEF. These data include their use as a de novo therapy in some patients naive to ACEIs or ARB therapies (7–10), evidence for rapid improvement in patient-reported outcome measures (e.g., symptoms, physical functioning, and quality of life), and the

TABLE 1 Starting and Target Doses of Select GDMT and Novel Therapies for HF (choice and timing of each therapy and in whom they should be added 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
ARNIs		
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily
ACEIs		
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
Aldosterone antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5–25 mg daily	25–50 mg daily
SGLT2 inhibitors		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 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 (1 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

*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 (3).
†Isosorbide mononitrate is not recommended by the ACC/AHA/HFSA guideline.
‡The ACC/AHA/HFSA guideline 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; ACEI = angiotensin-converting enzyme inhibitor; 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; SGLT2 = sodium-glucose cotransporter-2.

demonstration of a reverse-remodeling effect of ARNIs in chronic HFrEF, independent of background therapy with ACEIs/ARBs (11). It is not yet clear that de novo initiation is best for all patients with HFrEF (such as those with hypotension or very advanced HF), and we do recognize access challenges for some patients with regards to payer coverage and associated costs of ARNIs.

Another important development since the publication of the 2017 ECDP is the Food and Drug Administration's approval of a candidate SGLT2 inhibitor and its addition to the armamentarium of medications available for the treatment of patients with HFrEF. In the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening HF or CV Death in Patients with Chronic HF) trial, dapagliflozin demonstrated a reduction in CV death and HF hospitalization in patients with and without type 2 diabetes (T2D) (12). In addition, the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic HFrEF) trial demonstrated a reduction in HF hospitalization/CV death from empagliflozin treatment in patients with HFrEF with and without diabetes (13). As such, it is clear that SLGT2 inhibitors exhibit a beneficial class effect in patients with HFrEF.

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.

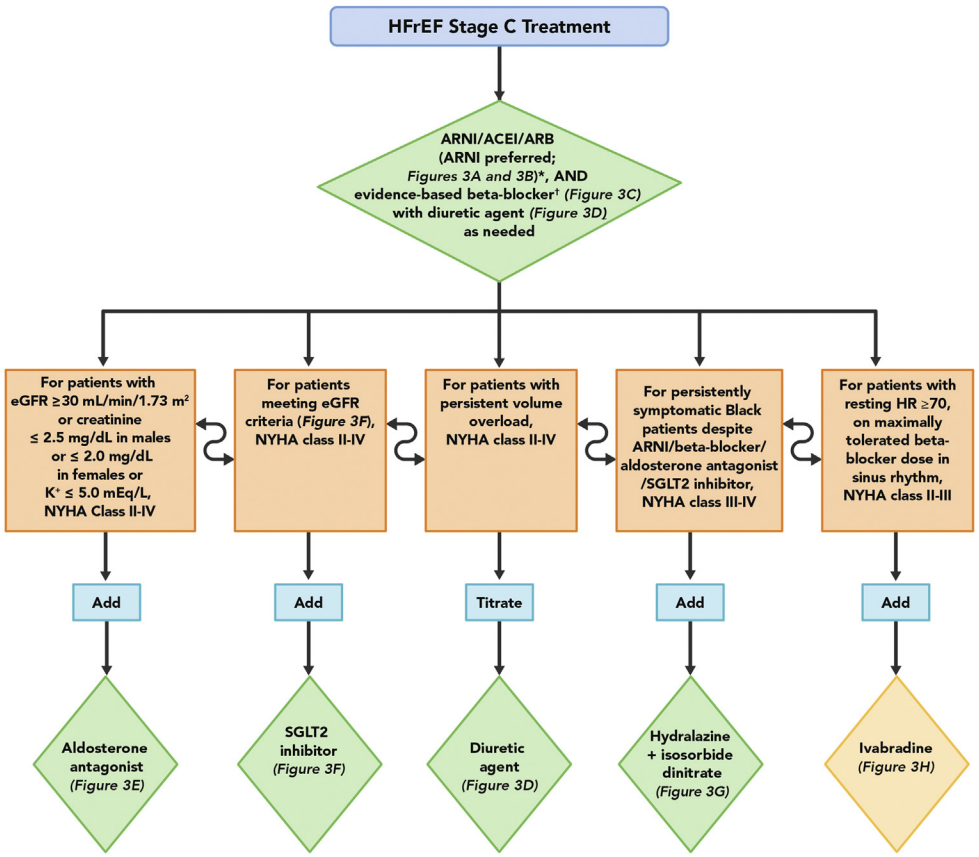
HF is a complex syndrome typically associated with multiple comorbidities; most patients are on multiple medications. No clinical trials have specifically evaluated the potential for greater benefit or excessive risk of indicated therapies among patients with multimorbidity. To assess tolerability of 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.

5.1.1. Initiating GDMT

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

In a patient with new-onset stage C HFrEF, a common question is whether to initiate a beta-blocker or an inhibitor of the renin-angiotensin system (ARNI/ACEI/ARB) first. The writing committee recommends that either an ARNI/ACEI/ARB or beta-blocker should be started. In some cases, an ARNI/ACEI/ARB and a beta-blocker can be started at the same time. Regardless of the initiation sequence, both classes of agent should be up-titrated to the maximum tolerated or target doses in a timely fashion (e.g., every 2 weeks). Initiation of an ARNI/ACEI/ARB (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;

FIGURE 2 Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies



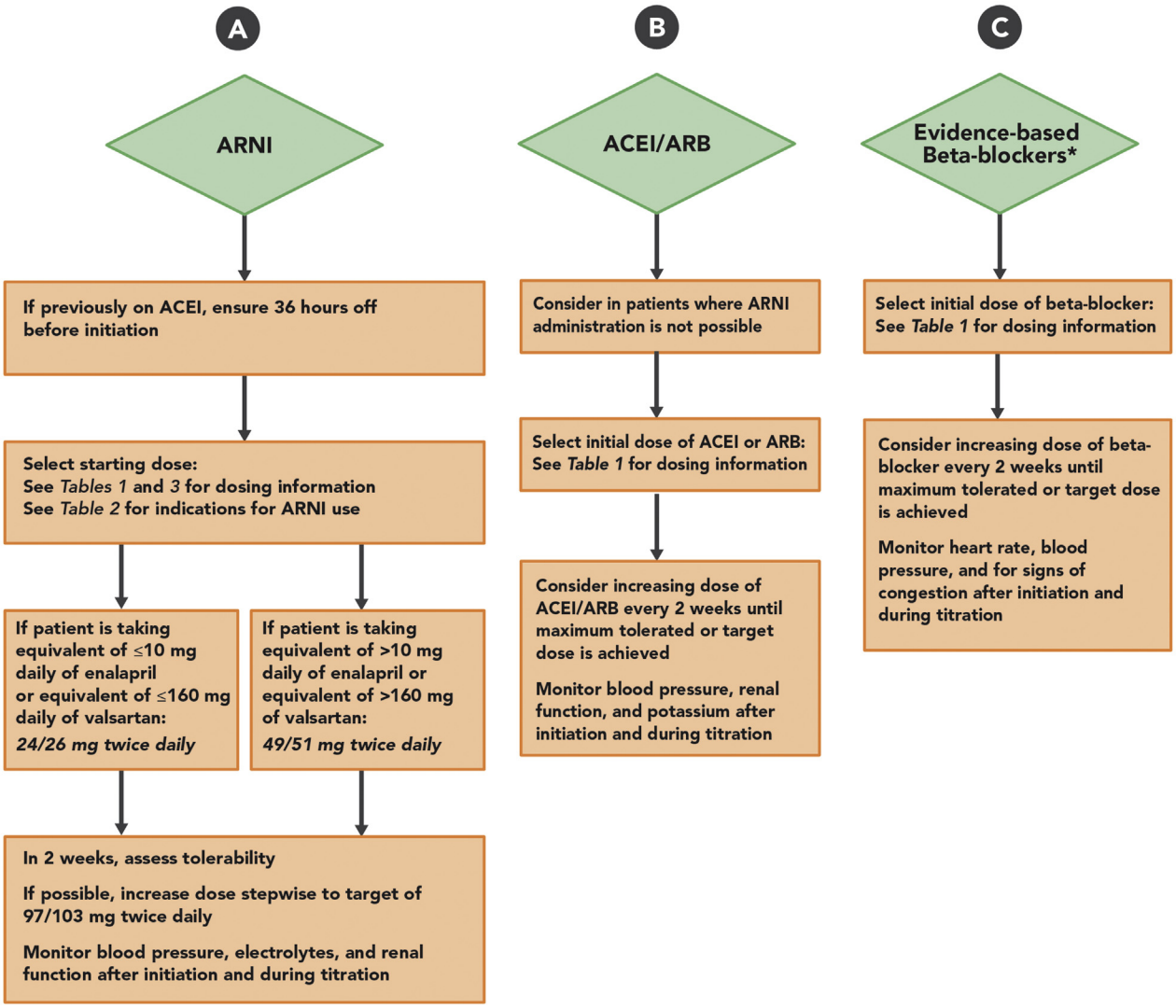
*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.

†Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K^+ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Green color identifies a Class I therapy from clinical practice guidelines, whereas yellow color indicates a Class II therapy.

FIGURE 3 Guideline-Directed Medical Therapy Including Novel Therapies in the Expert Consensus Decision Pathway for Chronic Heart Failure



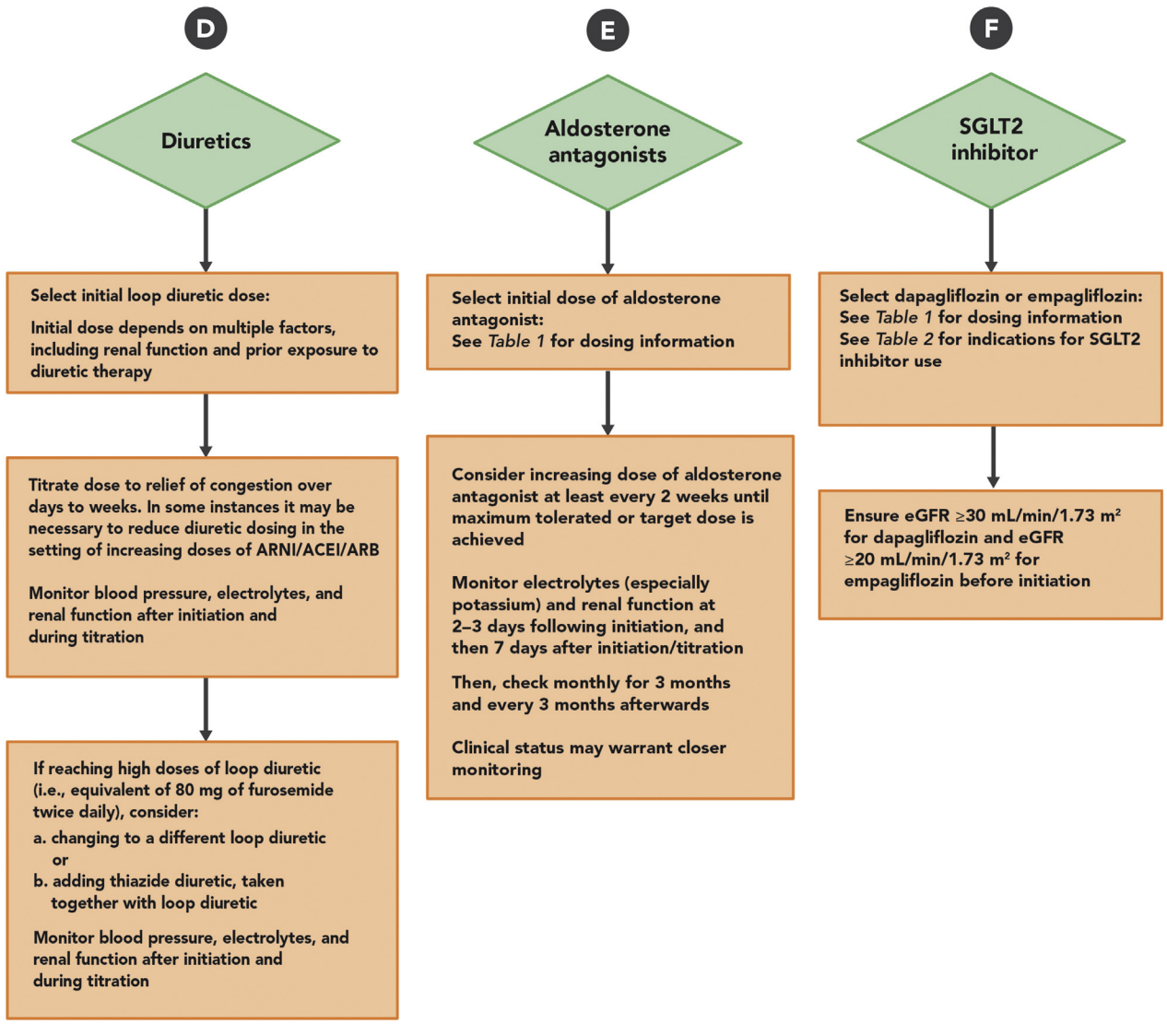
ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate.

*Carvedilol, metoprolol succinate, or bisoprolol.

ARNIs are the preferred agents, but for patients in whom ARNI administration is not possible, an ACEI/ARB is recommended.

beta-blockers should not be initiated in patients with decompensated signs or symptoms. Only evidence-based beta-blockers should be used in patients with HFrEF (**Table 1, Figures 2 and 3**). Titration of ARNIs/ACEIs/ARBs and beta-blockers is discussed in Section 5.2. With recent clinical trial data supporting the use of SGLT2 inhibitors in a reasonably broad spectrum of HFrEF severity, the addition of this class of therapy to the regimens of patients with HFrEF provides improvements in clinical outcomes and in patient-reported outcome measures.

FIGURE 3 Continued



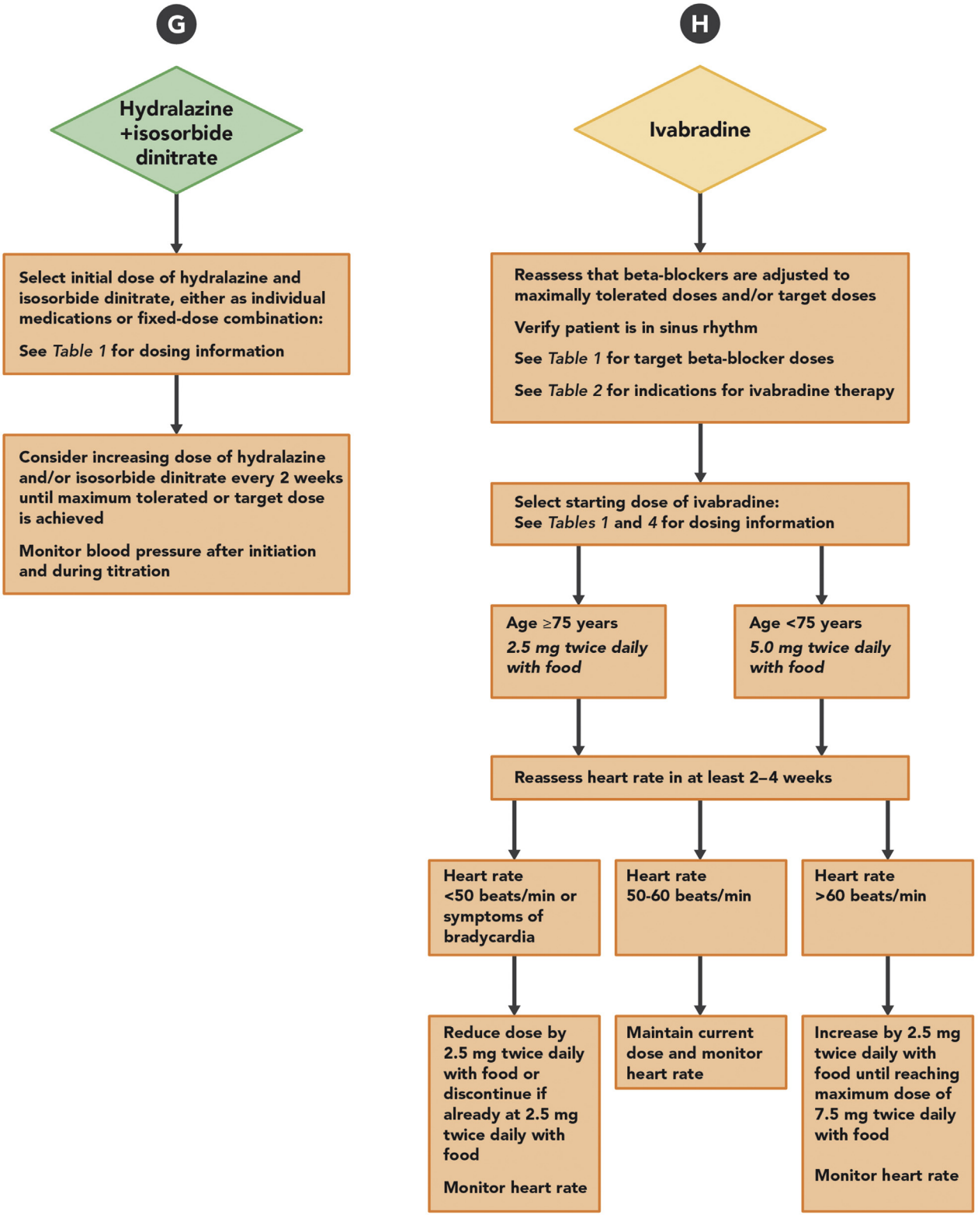
ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; SGLT2 = sodium-glucose cotransporter-2.

5.1.2. Angiotensin Receptor-Neprilysin Inhibitor

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 (14). 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 ACEI due to a higher risk of angioedema (15).

Sacubitril/valsartan (16,17) was tested among patients with chronic HFrEF in a randomized controlled trial,

FIGURE 3 Continued



PARADIGM HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF). The trial enrolled patients with NYHA class II to IV symptoms with an ejection fraction (EF) ≤40% (modified to ≤35% 1 year into the trial), stable on doses of ACEIs/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 class II to III symptoms (<100 patients with NYHA class IV symptoms).

PARADIGM-HF demonstrated an absolute 4.7% reduction in the primary outcome of CV death or HF hospitalization (hazard ratio: 0.80; 95% confidence interval [CI]: 0.73 to 0.87; $p < 0.001$) in patients treated with sacubitril/valsartan versus 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.

Symptomatic hypotension was more common with sacubitril/valsartan (14.% vs. 9.2%; $p < 0.001$) but was not associated with a worsening of renal function. Angioedema was numerically higher but not statistically significantly different from enalapril in the sacubitril/valsartan group. The 2016 update to the HF guidelines (6) recommended an ARNI, ACEI, or ARB to reduce morbidity and mortality in patients with chronic HFrEF and that patients with NYHA class II to III symptoms who can tolerate an ACEI or ARB should transition to an ARNI to further reduce morbidity and mortality (Class I, Level of Evidence: B-R) (3,4,7,8). ARNIs have been associated with improvement in diastolic function, left ventricular (LV) function, quality of life, and burden of ventricular arrhythmias (8,10,11,18,19). 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% to 9.9%]; $p < 0.001$), while the median LV end-diastolic volume index decreased from 86.93 to 74.15 mL/m^2 (difference: −12.25 mL/m^2 [interquartile range: −12.92 to −11.58]; $p < 0.001$) 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]; $p < 0.001$). Indexed left atrial volume by body surface area and the E/e′ ratio also decreased significantly (11). These results were demonstrated in important subgroups not represented in the PARADIGM-HF trial, such as those with de novo HF or naive to ACEIs/ARBs, those with lower enrollment N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations, or those not attaining the target dose in the course of 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 an improvement in echocardiographic parameters of reverse cardiac remodeling as early as 12 weeks with treatment of sacubitril/valsartan compared with enalapril (20).

TABLE 2 Indications for ARNI, Ivabradine, and SGLT2 Inhibitor Use

Indications for Use of an ARNI
■ HFrEF (EF ≤40%)
■ NYHA class II–IV HF
■ Administered in conjunction with a background of GDMT for HF in place of an ACEI or ARB
Indications for Use of Ivabradine
■ HFrEF (EF ≤35%)
■ On maximum tolerated dose of beta-blocker
■ Sinus rhythm with a resting heart rate ≥70 beats/min
■ NYHA class II or III HF
Indications for Use of an SGLT2 Inhibitor
■ HFrEF (EF ≤40%) with or without diabetes
■ NYHA class II–IV HF
■ Administered in conjunction with a background of GDMT for HF

ACEI = angiotensin-converting-enzyme inhibitor; 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; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

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

When making the transition from an ACEI to an ARNI, a 36-hour washout period should be strictly observed to avoid angioedema, a delay that is not required when switching from an ARB to an ARNI. In a recent study (21), a comparison between condensed and conservative approaches to initiation of sacubitril/valsartan was explored. The investigators compared titration to a target dose between 3 and 6 weeks. Both approaches were tolerated similarly, but the gradual titration approach maximized attainment of the target dose of sacubitril/valsartan in patients previously receiving low doses of an ACEI/ARB.

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

Population	Initial Dose
High-dose ACEI *> Enalapril 10-mg total daily dose or therapeutically equivalent dose of another ACEI*	**49/51 mg twice daily**
High-dose ARB *> Valsartan 160-mg total daily dose or therapeutically equivalent dose of another ARB*	
De novo initiation of ARNI *Low- or medium-dose ACEI* *≤ Enalapril 10-mg total daily dose or therapeutically equivalent dose of another ACEI*	**24/26 mg twice daily**
Low- or medium-dose ARB *≤ Valsartan 160-mg total daily dose or therapeutically equivalent dose of another ARB*	
ACEI/ARB naive	
*Severe renal impairment** *(eGFR <30 mL/min/1.73 m²)*	
Moderate hepatic impairment (Child-Pugh Class B)	
Elderly (age ≥75 years)	

*This population was not studied in the PARADIGM-HF trial. The statement is consistent with FDA-approved labeling indications.

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

An ideal time to consider therapy 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 (22). Although discussion of hospital-based initiation of sacubitril/valsartan is outside of the scope of this document, it is important to prioritize ongoing 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 (23) after the patient has been hemodynamically stabilized; in PIONEER-HF, up to 25% of patients developed hypotension when treated with sacubitril/valsartan. Therefore, ensuring 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 the patients could achieve the target dose within 10 weeks after in-hospital initiation or soon after discharge (24). Accordingly, following the patient's discharge from the hospital, ongoing efforts toward GDMT optimization (including titration to target doses whenever possible) should continue.

Clinicians should be advised that sacubitril/valsartan may exert a more noteworthy effect on blood pressure when compared with ACEIs/ARBs. Therefore, in patients with borderline blood pressure (e.g., systolic blood pressure ≤100 mm Hg), careful administration and follow-up are advised. In noncongested patients with otherwise stable clinical profiles, empiric modest lowering of loop diuretic agents has been found to mitigate the hypotensive effects of sacubitril/valsartan. Lastly, although the number of patients in studies of ARNI with chronic HFrEF and NYHA class IV symptoms is limited, sacubitril/valsartan remains indicated in this higher-risk population; the role of sacubitril/valsartan in more advanced forms of HFrEF continues to be explored (25).

5.1.3. Initiation of an ARNI De Novo Without Prior Exposure to an ACEI or ARB

It is possible that a patient may be identified who meets all criteria for initiation of an ARNI but has not yet been treated with an ACEI or ARB. Recent data from clinical studies (7–9), along with aggregate clinical experience, suggest that directly initiating an ARNI, rather than a pretreatment period ACEI or ARB, is a safe and effective strategy. In a prospective study comparing the tolerability of different initiation strategies of sacubitril/valsartan (21), patients with de novo HFrEF or those who were naive to ACEIs/ARBs demonstrated no unexpected adverse effects compared with those already taking an ACEI/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 ACEIs/ARBs, in whom an average 12% increase in LVEF by 1 year was noted. These results are also supported by data from studies of acute HFrEF that indicate efficacy and tolerability for those not previously treated with an ACEI/ARB (9,26). 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 (23); such improvement in early clinical outcomes would be lost in a scenario of ACEI/ARB pre-treatment.

Because of this totality of data, a direct-to-ARNI approach is now recommended. When de novo initiation of ARNI is performed, close follow-up and serial assessments (blood pressure, electrolytes, and renal function) should be considered, and any such usage should consider concerns regarding the risk of angioedema or hypotension (**Figures 2 and 3, Tables 1 to 4**).

When making a recommendation to initiate an ARNI (either as a switch or as de novo treatment), the Writing Committee recommends the decision occurs within a

TABLE 4 Contraindications and Cautions for Sacubitril/Valsartan, Ivabradine, and SGLT2 inhibitors

A) Sacubitril/Valsartan

Contraindications	Cautions
■ Within 36 hours of ACEI use ■ History of angioedema with or without an ACEI or ARB ■ Pregnancy ■ Lactation (no data) ■ Severe hepatic impairment (Child-Pugh C) ■ Concomitant aliskiren use in patients with diabetes ■ Known hypersensitivity to either ARBs or ARNIs	■ Renal 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 24/26 mg twice daily; double the dose every 2-4 weeks to target maintenance dose of 97/103 mg twice daily, as tolerated ■ Hepatic impairment: – Mild (Child-Pugh A): no starting dose adjustment required – Moderate (Child-Pugh 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) Ivabradine

Contraindications	Cautions
■ HFpEF ■ Presence of angina with normal EF ■ Hypersensitivity ■ Severe hepatic impairment (Child-Pugh C) ■ Acute decompensated HF ■ Blood pressure <90/50 mm Hg ■ Sick sinus syndrome without a pacemaker ■ Sinoatrial node block ■ 2nd or 3rd degree block without a pacemaker ■ Resting heart rate <60 beats/min ■ Persistent AF or flutter ■ Atrial pacemaker dependence	■ Sinus node disease ■ Cardiac conduction defects ■ Prolonged QT interval

C) SGLT2 Inhibitors

Contraindications	Cautions
■ Not approved for use in patients with type I diabetes due to increased risk of diabetic ketoacidosis ■ Known hypersensitivity to drug ■ Lactation (no data) ■ On dialysis	■ For HF care, dapagliflozin, eGFR <30 mL/min/1.73 m^2 ■ For HF care, empagliflozin, eGFR <20 mL/min/1.73 m^2 ■ Pregnancy ■ Increased risk of mycotic genital infections ■ May contribute to volume depletion. Consider altering diuretic dose if applicable ■ Ketoacidosis in patients with diabetes: ■ Temporary discontinuation 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 renal 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's 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

*This population was not studied in PARADIGM-HF. The statement is consistent with FDA-approved labeling indications.

ACEI = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FDA = Food and Drug Administration; 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; SGLT2 = sodium-glucose cotransporter-2.

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 challenges with payer coverage and unaffordable copays. Although an ARNI is the preferred renin-angiotensin antagonist in HFrEF, an ACEI/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.

5.1.4. Ivabradine

Heart rate independently predicts outcomes in HFrEF. A meta-analysis of beta-blocker trials suggests that heart rate lowering is directly related to improved outcomes (27). A dose-response relationship for evidence-based beta-blockers used in HFrEF has been demonstrated (i.e., the higher the dose, the better the outcome) (27). Before initiating ivabradine, the dose of an evidence-based beta-blocker should be optimized and increased to the target dose as long as excessive bradycardia is not an issue. Some apparently well-compensated patients on optimal beta-blocker therapy continue to have a persistent resting heart rate over 70 beats/min, and some patients do not tolerate up-titration of beta-blockade to the target dose and have an elevated heart r ate. In patients on low-dose beta-blockers who may have heart rates below 70 beats/min, a beta-blocker should continue to be

up-titrated to the maximum tolerated or target dose as long as the patients remain asymptomatic.

Ivabradine is an adjunctive means to reduce the heart rate in patients with chronic HFrEF who are in sinus rhythm. Ivabradine is a specific inhibitor of 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 class II and III HFrEF, ivabradine therapy, when added to GDMT, resulted in a significant reduction in HF hospitalizations (28). Benefits were noted especially for those patients with contraindications to beta-blockers, on beta-blocker doses ≤50% of GDMT targets (29), and with resting heart rate ≥77 beats/min at study entry (30). 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 unstable patients. 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 (28).

In the 2016 ACC/AHA/HFSA HF guideline update (6), ivabradine was recommended as a Class IIa, Level of Evidence: B-R (3,4) therapy 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 greater than 70 beats/min at rest (**Figures 2 and 3, Tables 1, 2, and 5**). The contraindications to ivabradine are enumerated in **Table 4**.

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 years	2.5 mg twice daily with meals

5.1.5. Sodium-Glucose Cotransporter-2 Inhibitors

The use of SGLT2 inhibitors for general CV risk reduction was recently covered in the ACC's 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes (31). This document, however, was not specifically focused on the emerging role of SGLT2 inhibitors for HFrEF care.

Among patients with prevalent HFrEF, data support an SGLT2 inhibitor as valuable therapy, with evidence showing a reduced risk for major events (such as hospitalization or death) regardless of the presence of diabetes. Although the mechanism of benefit from these agents in HFrEF remains uncertain, treatment with SGLT2 inhibitors leads to osmotic diuresis and natriuresis, decreases in arterial pressure and stiffness, and a shift to ketone-based myocardial metabolism (32). Further benefits may be due to reduction of preload and afterload blunting of cardiac stress/injury with less hypertrophy and fibrosis, which would have favorable effects on myocardial remodeling.

The first study to demonstrate a benefit of SGLT2 inhibitors for HFrEF care examined the role of dapagliflozin in patients with HFrEF. The DAPA-HF 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 T2D (16.3% in the dapagliflozin group versus 21.2% in the placebo group; hazard ratio: 0.74; 95% CI: 0.65 to 0.85). 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 (12). The DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients with HF) study demonstrated that dapagliflozin increased the proportion of patients experiencing clinically meaningful improvements in HF-related health status or natriuretic peptide concentrations in patients with HFrEF, regardless of the presence of diabetes (33). In the EMPEROR-Reduced trial in which 3,730 patients with chronic HFrEF were randomized to empagliflozin versus placebo, empagliflozin was found to significantly reduce the composite endpoint of CV death or HF hospitalization in adults with and without diabetes (19.4% in the empagliflozin group versus 24.7% in the placebo group; hazard ratio: 0.75; 95% CI: 0.65 to 0.86). The trial also showed that treatment with empagliflozin slowed the decline in the eGFR over time (13). 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 renal outcomes in patients (34).

The dosing for SGLT2 inhibitors is detailed in **Table 1**, whereas cautions and contraindications for SGLT2 inhibitors are enumerated in **Table 4**. The DAPA-HF trial did not enroll patients with an eGFR <30 mL/min/1.73 m^2, yet dapagliflozin is approved for HFrEF care in patients with worse renal function. The lower limit of eGFR for inclusion in the EMPEROR-Reduced trial was 20 mL/min/1.73 m^2. The writing committee recognizes that glucosuric effects of SGLT2 inhibitors may be

attenuated in those with eGFRs below these thresholds; benefits of SGLT2 inhibitors for HFrEF management in those with more advanced renal dysfunction than the patients in these recent studies remains less clear. Caution is advised when using SGLT2 inhibitors in patients with eGFRs below the inclusion criteria from pivotal studies, particularly as SGLT2 inhibitors have been associated with mild worsening of renal function during the first year of use.

5.1.6. 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 in the previous text, after a diagnosis of HF is made, adjustment of therapies should occur every 2 weeks, and some patients may tolerate more rapid titration of GDMT. Clinicians should aim to achieve optimal GDMT within 3 to 6 months of an initial diagnosis of HF (however, this rapid timeline may not be logistically feasible for some patients). GDMT should continue to be up-titrated to achieve maximally tolerated or targeted doses of these therapies. During follow-up, frequent reassessment of the clinical status of the patient, blood pressure, and kidney function (and electrolytes) should be performed. Structured medication titration plans embedded in disease management programs that articulate a strategy for drug initiation and strategies for follow-up have been shown to be useful in obtaining target doses of GDMT within 6 months of hospital discharge (35).

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 implantable cardioverter-defibrillators and cardiac resynchronization therapy. For those at higher risk for sudden death (e.g., with ischemic cardiomyopathy, LVEF <30%, evidence for ventricular ectopy), the time to follow-up imaging might be shorter (e.g., 3 months), whereas in those at lower risk, time to follow-up might be longer (e.g., 6 months) (3). In patients who already have such devices, reimaging might be deferred even further.

5.1.7. Severe Mitral Regurgitation and the Use of Transcatheter Mitral Valve Repair

Surgical treatment is recommended in cases of severe primary chronic MR resulting in HFrEF (36). The treatment for severe chronic functional MR is somewhat controversial; initial steps should incorporate optimization of GDMT and participation in team management decisions before the use of percutaneous transcatheter repair.

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 (37,38).

Substantial differences exist between MITRA-FR and COAPT, but a primary difference relates to the requirement in COAPT for optimized GDMT before the use of percutaneous mitral valve edge-to-edge reapposition; in COAPT, 90% of study participants received a beta-blocker, 70% received an ARNI/ACEI/ARB, and 50% received an aldosterone antagonist before the procedure. Optimal GDMT leads to reversal of cardiac remodeling, reduction of LV volumes (7), and a concomitant reduction in functional MR (39); thus, 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 of optimal GDMT together with edge-to-edge repair.

5.1.8. Patients in Whom New Therapies May Not Be Indicated

Contraindications may preclude the initiation of some agents among 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.

In a patient whose life expectancy is short (<1 year) due to other comorbidities, some therapies (such as implantable devices) may not be appropriate. Similarly, in patients with NYHA class IV and Stage D HF being considered for advanced therapies (i.e., transplant or LV assist device), home inotropes, hospice, or initiation of new drug therapies may not be appropriate, especially given the absence of evidence addressing their efficacy in such patients.

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

5.2.1. Target Doses

To achieve the maximal benefits of GDMT in patients with chronic HFrEF, therapies must be initiated and titrated to maximally tolerated doses (16,40–42). 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**. Achieving target or maximally tolerated doses of GDMT is the goal of titration. Beta-blocker doses should be adjusted every 2 weeks (43) 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 hemodynamics, whereas more rapid titration may be reasonable in clinically stable patients without hypotension. 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/renal instability, or prior angioedema on an ACEI or ARB. If administration of an ARNI is not possible, then an ACEI or ARB should be used, barring contraindication. An ARNI/ACEI/ARB may be titrated similarly to beta-blockers with monitoring of renal 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 2 weeks to allow time for adjustment to the vasodilatory effects of the combined inhibition of the angiotensin receptor and neprilysin while also monitoring renal function, potassium, and especially blood pressure. For optimal titration of an ARNI/ACEI/ARB, lower loop diuretic doses may be necessary to permit titration; in this circumstance, careful attention to potassium concentrations is needed, as the kaliuretic effects of loop diuretics may no longer be present, and restriction of supplemental and/or dietary potassium may be necessary.

Aldosterone antagonists are added in as part of the therapy for patients with symptomatic chronic HFrEF who are already receiving beta-blockers and an ARNI/ACEI/ARB and who do not have contraindications to this therapy (3). It is not necessary to achieve target or maximally tolerated doses of other drugs before adding aldosterone antagonists. The doses of aldosterone 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 renal function and potassium is required (4).

SGLT2 inhibitors are added in as part of the therapy for patients with chronic HFrEF who are already receiving beta-blockers, an ARNI/ACEI/ARB, and aldosterone antagonists, if not contraindicated. There is little data addressing the combination of an ARNI and an SGLT2 inhibitor. However, in both DAPA-HF and EMPEROR-Reduced, the benefit of SGLT2 inhibition was consistent in patients already treated with an ARNI, and a meta-analysis of the 2 trials affirms this finding (12,34,44). In the DAPA-HF trial, among the small number of patients receiving an ARNI, additive benefit was seen across each timepoint from the addition of dapagliflozin (45). Achieving target or maximally tolerated doses of other drugs is not necessary before adding SGLT2 inhibitors. The loop diuretic dose may need to be adjusted based on close monitoring of weight and symptoms (46). In patients using insulin or insulin-secretagogues (such as sulfonylureas), coordinating care through the inclusion of endocrinologists and primary care providers may be helpful in order 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. 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 (47), African-American patients should receive these drugs once target or maximally tolerated doses of beta-blocker, ARNI/ACEI/ARB, and aldosterone antagonists are achieved (3). This combination of drugs is especially important for those patients with NYHA class III to IV symptoms.

Finally, in patients whose heart rate remains ≥70 beats/min on target or maximally tolerated doses of beta-blockers, ivabradine (6) can be added and titrated at 2 weeks to lower the heart rate.

5.2.2. Barriers to Medication Titration

In some instances, it may not be possible to 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.

Abnormal renal 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. In addition, newer potassium binders (patiromer and sodium zirconium cyclosilicate) are now approved by the Food and Drug Administration and may be considered; however, more data are needed regarding use of such agents in patients with HFrEF, as their use has not been shown to increase GDMT use or have an impact on outcomes in patients. Additionally, these agents raise concerns in terms of cost/access and their contribution to polypharmacy. A trial examining whether a strategy of potassium binding will potentiate GDMT prescription and improve HFrEF

outcomes is ongoing, and more data may be available in the future.

For patients with established renal disease, caution may be necessary when starting GDMT. In patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 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 renal 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 4**). ACEIs/ARBs are generally considered safe in patients with severe renal impairment, although definitive data are lacking. Aldosterone antagonists are contraindicated in patients with severe renal 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**).

Renal function and potassium should be assessed within 1 to 2 weeks after initiation or dose increase of an ARNI/ACEI/ARB. In patients with preserved renal function or mild to moderate renal impairment, renal function and potassium after initiation and titration of aldosterone antagonists should be assessed within 2 to 3 days and again at 7 days. The schedule for subsequent monitoring should be dictated by the clinical stability of renal function and volume status but should occur at least monthly for the first 3 months and every 3 months thereafter (3).

During the initiation and titration of agents that affect renal function, a decrease in eGFR of >30% or the development of hyperkalemia should alert the clinician that a reduction in doses may be necessary, even though short-term changes in eGFR during intense diuretic therapy or with the initiation of an ACEI or ARB do not predict longer-term adverse outcomes (48), and initial mild worsening of renal function after SGLT2 inhibitor initiation may also occur before longer-term renal function preservation (13). 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 renal insufficiency or hypotension. Hyperkalemia may also require changes in medical therapy. Among SGLT2 inhibitors for patients with chronic HFrEF, clinical trial experience with dapagliflozin is lacking in those with an eGFR <30 mL/min/1.73 m^2, whereas for empagliflozin, there is a similar lack of clinical trial data for those with an eGFR <20 mL/min/1.73 m^2. Volume status should be closely monitored, as intravascular volume contraction may necessitate a reduction in loop diuretic dosing. Clinical assessment and renal stability in each patient dictates whether clinicians may need to monitor certain patients more closely than others.

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 an ARNI, SGLT2 inhibitor, and ivabradine (see the discussion on costs of care in Section 5.7). In such cases, if all solutions are exhausted, optimizing care with the most financially manageable program is recommended. 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 renal 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 (49). Virtual care in particular may be a more viable strategy, with the recent increases in its use due to the COVID-19 pandemic. Useful guidance exists regarding the use of virtual visits to allow for medical access, monitoring of symptoms/signs, and adjustments of GDMT (50).

5.2.3. Clinical Assessment

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

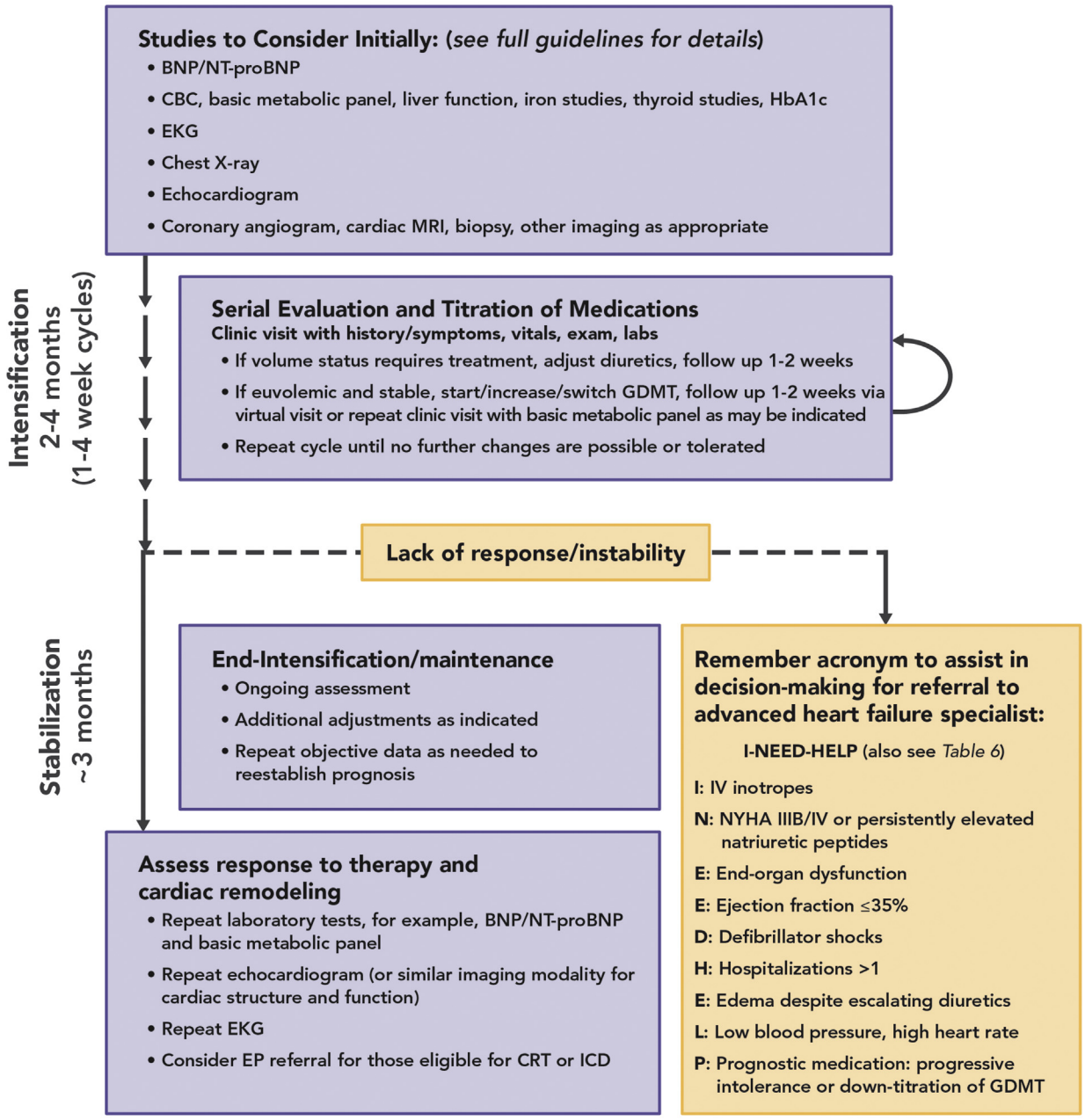
After GDMT is initiated and titrated with the goal of achieving clinical trial doses or maximally tolerated doses, patients with chronic HFrEF should be evaluated on a regularly scheduled basis. For most patients, a reasonable interval is every 3 to 6 months, although many may require more frequent follow-up 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 (51). During the COVID-19 pandemic, virtual care to allow for outpatient GDMT titration has been useful in certain patients (52) and will likely take on a larger role in HFrEF care post-pandemic.

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 (53). Features triggering referral to advanced HF care are also discussed in Section 5.3 and **Table 6**.

5.2.4. Imaging—When to Order an Echocardiogram

An echocardiogram, with strain imaging when available, 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 (implantable cardioverter defibrillator, cardiac resynchronization therapy, or transcatheter mitral valve repair) or referral for advanced therapies (ventricular assist device

FIGURE 4 Testing and Medication Titration Following Diagnosis of HFrEF



BNP = B-type natriuretic peptide; CBC = complete blood count; CRT = cardiac resynchronization therapy; ECG= electrocardiogram; EP = electrophysiologist; GDMT = guideline-directed medical therapy; HbA1c = hemoglobin A1c; 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.

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 (11). Repeat imaging may also be considered at the time of important changes in clinical status (3). Routine surveillance echocardiograms (e.g., annually) in the absence of

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 one 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 ■ Two or more emergency department visits or hospitalizations for worsening HF in the prior 12 months ■ Inability to tolerate optimally dosed beta-blockers and/or ACEI/ARB/ARNI and/or aldosterone antagonists ■ Clinical deterioration, as indicated by worsening edema, rising biomarkers (BNP, NT-proBNP, others), worsened exercise testing, decompensated hemodynamics, or evidence of progressive remodeling on imaging ■ High mortality risk using a validated risk model for further assessment and consideration of advanced therapies, such as the Seattle Heart Failure Model
	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 (e.g., 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

ACEI = angiotensin converting enzyme inhibitors; 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; SGLT2 = sodium-glucose cotransporter-2.

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 (3).

When recovery of LVEF to >40% is noted in the setting of prior HFrEF, outcomes improve (54). Clinicians are often faced with the question of whether to continue GDMT or reduce/eliminate it in patients with complete LVEF recovery. The recent 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 an HF event within 6 months (55). Therefore, in the absence of a defined, reversible cause for HFrEF (e.g., tachycardia-mediated cardiomyopathy), current GDMT should be continued (56).

5.2.5. Biomarkers—When to Order Natriuretic Peptides

B-type natriuretic peptide (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 (3).

More recently, biomarkers have been examined for their role as markers of clinical responsiveness to GDMT. This is due, in part, to the fact that a wide range of GDMTs may reduce BNP and NT-proBNP concentrations in parallel with the benefits of these therapies. Patients whose natriuretic peptide concentrations do not fall with GDMT ("nonresponders") have a worse prognosis and more deleterious LV remodeling (7,57,58). 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 (59). 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 (7,54). 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 advanced HF therapies (**Figure 4, Table 6**). Concentrations of BNP or NT-proBNP are supported with a Class I guideline recommendation to determine prognosis. In the setting of worsening

symptoms (60), the reassessment of BNP or NT-proBNP may be informative. Severe renal dysfunction may interfere with the interpretation of natriuretic peptide concentrations. Importantly, current evidence does not suggest targeting treatment to specific BNP or NT-proBNP levels.

Although rising natriuretic peptide concentrations are correlated with adverse outcomes, this relationship can be confounded by the use of sacubitril/valsartan. Due to neprilysin inhibition, concentrations of BNP sometimes modestly rise in patients treated with sacubitril/valsartan and tend not to rapidly return to baseline despite chronic therapy. In contrast, NT-proBNP concentrations typically decrease much more consistently than do BNP concentrations, as NT-proBNP is not a substrate for neprilysin (61). 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. However, during treatment, either biomarker predicts the risk of major adverse outcomes in patients treated with sacubitril/valsartan (8).

5.2.6. 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 renal 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. 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. In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients) study, patients with NYHA class III HF symptoms were randomly assigned to receive a wireless implantable pulmonary artery pressure monitor versus usual care (62). Patients who were managed with data from implantable pulmonary artery pressure monitoring experienced more changes in GDMT and diuretic doses (63). In addition, those managed with implantable pulmonary artery pressure monitoring had a 28% relative reduction in HF hospitalization (0.49 events/patient/year in the treatment arm versus 0.69 events/patient/year in the control arm; $p < 0.001$). Such improvement was seen in patients with both HFrEF and HF with preserved EF. This suggests that in well-selected patients with recurrent congestion, this highly specialized monitoring strategy may guide therapeutic decision-making. The impact on mortality is unknown but is being evaluated in an ongoing randomized clinical trial, GUIDE-HF (Hemodynamic-Guided Management of HF). A team-based approach may be necessary to best deploy this monitoring strategy (see Section 5.8).

Patients on optimal GDMT who have either high-risk features (Section 5.3 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.

5.3. When to Refer to an HF Specialist

Appropriate and timely referral to an HF specialist and/or HF program is essential in selected patients to optimize therapies and evaluate advanced HF care options (**Table 6**) (3,64). Referrals should be made for consultation and, if indicated, for comanagement as well as consideration of advanced therapies (heart transplantation or mechanical circulatory support), recognition and management of specific or unusual cardiomyopathies, or annual review (3,65–71). Clinical triggers for referral (**Table 6**) include persistent or worsening symptoms, adverse clinical events, or other features suggesting that the patient is at high risk for disease progression or death (53,72–75).

5.4. How to Address Challenges of 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 implantable cardioverter-defibrillator or cardiac resynchronization therapy devices. As outlined in Section 5.9, the complexity of HF care is further exacerbated by the frequent coexistence of both cardiac and noncardiac comorbidities found 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 (76). 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 (e.g., 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 new glucose modifying therapies (SGLT2 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 (31). In a team approach, an interprofessional multidisciplinary group of clinicians (e.g., primary care, endocrinologists, cardiologists, pharmacists, nurses, advanced practice professionals, and dieticians) consider novel therapies collectively (31). Regardless, all approaches to HFrEF management need to be patient-centered, use shared decision-making, and involve communication across disciplines (31).

Randomized trials have demonstrated the superiority of the team-based approach over usual care in patients with HF (77-80) with respect to the risks of death, hospitalization, lengths of stay, and quality of life (81-84). 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 (85,86). Team-based HF care is thus recommended in the most recent HF guidelines (3).

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**).

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 (e.g., diet, exercise), education, and monitoring
■ Psychological and social support assessment, treatment, and monitoring
■ Palliative and end-of-life counseling and care
■ Coordination of care for concomitant comorbidities

HF = heart failure.

Effective team-based HF care may be possible with small teams as long as 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 post-discharge care, and follow-up outcome reporting. Each program will define the roles and responsibilities of various care team members in an effort to effectively communicate and obtain optimal patient outcomes (87). In addition, recent innovations in HF care delivery, such as group visits, remote specialist video consultation, and telemonitoring programs, may also be useful (88-93). As previously noted, the COVID-19 pandemic has accelerated the uptake and reimbursement of virtual care, including telephone and video visits. In addition, remote patient monitoring programs to monitor patients with HF for early signs of clinical decompensation have also been accelerated by the pandemic, given their ability to assess patients without unnecessarily exposing them to COVID-19. These advances may ultimately have an impact on HF care well after the pandemic subsides. For example, communication may be enhanced with telehealth by leveraging remote symptom monitoring captured between visits, which can be used to inform clinical decisions through patient engagement in self-care (94). It will be important to rigorously study the ability of telehealth to effectively manage patients with HFrEF. In the interim, virtual visits serve as one avenue to avoid delays in care, including titration of GDMT remotely, if needed, while taking appropriate precautions to keep patients and caregivers safe during the COVID-19 pandemic.

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. 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 pulmonary arterial pressure monitoring devices (62), wearable activity monitors (95), and smartphone and other mobile applications (96), have the potential to improve monitoring and patient engagement (96). These advances have been accompanied by new billing codes for remote monitoring activities. However, as previously noted, these innovations are largely unproven, so the focus should remain on the 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

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

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

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

promising in this respect (97,98). 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.

5.5. How to Improve Adherence

5.5.1. 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 (99). Estimates of significant nonadherence in patients with HFrEF vary from 20% to 50% (100-103), with some difference by drug (104). Such nonadherence is associated with worse outcomes in HF (105,106). In addition to nonadherence, a large proportion of patients with HFrEF do not receive target doses of medical therapies (107), even in the absence of documented intolerance.

Reasons for nonadherence are complex (108,109), as outlined in **Table 9**. Unintentional nonadherence is thought to be more common than intentional nonadherence (99,110). As **Table 9** shows, the ability of patients to follow treatment plans in an optimal manner is frequently compromised by more than 1 barrier (111,112).

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 (113,114). Consequently, interventions that target adherence in HF must be multidisciplinary, multifactorial, and personalized to the particular demands experienced by the patient.

5.5.2. 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

TABLE 9 Reasons for Nonadherence (World Health Organization)

Patient	■ Perceived lack of effect ■ Poor health literacy ■ Physical impairment (vision, cognition) ■ Mental health conditions (depression, anxiety) ■ Social isolation ■ Cognitive impairment (dementia)
Medical condition	■ High HF regimen complexity ■ Impact of comorbidities (e.g., depression) ■ Polypharmacy due to multiple comorbidities
Therapy	■ Frequency of dosing ■ Polypharmacy ■ Side effects
Socioeconomic	■ Out-of-pocket cost ■ Difficult access to pharmacy ■ Lack of social support ■ Homelessness
Health system	■ Poor communication ■ Silos of care ■ No automatic refills ■ Difficulty navigating patient assistance programs

HF = heart failure.

TABLE 10 Ten Considerations to Improve Adherence

1. Capitalize on opportunities when patients are most predisposed to adherence
■ In-hospital/pre-discharge 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 relevant patient education materials
3. Simplify medication regimens whenever possible
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
■ 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
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
8. Consider behavioral supports
■ Motivational interviewing
■ Participate in engaged benefit designs
9. Anticipate problems
■ Communicate common side effects
■ Provide instructions on when to call for refills or report problems
■ Remind patients using pharmacy assistance programs that refills/reorders are not automatic
10. Monitor adherence and target patients at risk
■ Inquire patients directly (e.g., "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
■ Assess remaining dosage units (i.e., count excess remaining tablets)
■ Monitor pharmacy fills, using available clinical databases or automated alerts for failed fills and refills
■ Review available drug levels (e.g., 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.

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" (115). Within this new paradigm, patients are seen as needing support, whereas blame is counterproductive. 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 (116,117). 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 (102). A systematic review and meta-analysis of 771 intervention trials on medication adherence

TABLE 11 Specific Patient Cohorts in HF Care

Patient Cohorts	Description	Evidence-based recommendations	Risks	Uncertainties
African-American patients	Self-identified	GDMT	■ ARNIs, ACEIs, and ARBs: possibly higher risk of angioedema compared with Caucasian patients ■ Uncertain risk of hypotension when combining new drugs with HYD/ISDN	Expected outcomes of ARNI, SGLT2 inhibitors, and/or ivabradine in those treated with HYD/ISDN
Older adults	≥75 years of age	■ GDMT, but recognize that this population is excluded from many trials supporting GDMT ■ Consider starting with lower doses of GDMT	■ Potential falls ■ Worsening of renal function ■ Polypharmacy ■ Comorbidity	Efficacy of lower-dose GDMT on outcomes
Frail patients	Meets established frailty criteria (134)	GDMT as tolerated	■ Uncertain response to GDMT ■ Possibly increased risk for adverse drug reactions	Ability to have an impact on natural history in the frail with HF

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

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 (118). In a systematic review of 57 studies (119), interventions to enhance adherence for patients with HF were associated with lower mortality (relative risk: 0.89; 95% CI: 0.81 to 0.99) and hospital readmission (odds ratio: 0.79; 95% CI: 0.71 to 0.89). A systematic review of 27 studies of mobile health interventions for CV diseases including HF (120,121) found that mobile health significantly improved adherence to medical therapy (odds ratio: 4.51; $p < 0.00001$).

5.5.3. 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 (122). Automated screening and assessment tools can identify and target patients who are at the greatest risk for nonadherence (e.g., those with dementia, depression, homelessness, or drug use) (123). Health information technologies increasingly have the ability to collect pooled data on prescription fills as well as to 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 (124-126).

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 (127-131).
2. Limiting copays has been associated with small increases in patient prescription fills (101,132). 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. Monetary incentives or other rewards for adherence to medications may be cost-saving for highly efficacious and inexpensive drugs, such as beta-blockers, in HFrEF.

5.6. What Is Needed in Specific Patient Cohorts: African Americans, Older Adults, and the Frail

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**) (133).

Examples of populations that have been relatively understudied in HFrEF trials include African Americans, older adults (≥75 years), and frail patients.

African Americans. ARNIs, SGLT2 inhibitors, and ivabradine were tested in clinical trial populations with few or no African Americans. In fact, the landmark ivabradine study SHIFT included almost no African Americans (12,28,135). Nonetheless, no significant differences in the efficacy of ARNIs or SGLT2 inhibitors have been observed by race. Ivabradine is now actively being studied in African Americans with HF. Given the established benefits in the general public, we recommend that African Americans receive these newer medications as part of their HF GDMT.

A key therapy among African Americans with HFrEF is HYD/ISDN. However, the combined benefit of HYD/ISDN with an ARNI, SGLT2 inhibitor, and/or ivabradine is less clear—nevertheless, this lack of clarity should not prevent prescription of these new medications. African Americans are underprescribed HYD/ISDN, a treatment with survival benefits isolated to those of self-defined African-American race; it should be a priority to initiate evidence-based medications in all applicable populations. We recommend consideration of both HYD/ISDN and ARNI prescriptions for African-American patients, with the acknowledgment that both purportedly act via upregulation of cyclic guanosine monophosphate (cGMP) pathways and could increase the risk of hypotension. Additionally, the risk of angioedema with both ACEIs and ARNIs is higher in African-American patients (136).

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

a. *Establish GDMT with an ARNI/ACEI/ARB (ARNI preferred, if possible), a beta-blocker, and an aldosterone 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 class III to IV symptoms, titration should proceed with careful blood pressure monitoring and close monitoring of other side effects (e.g., headache, dizziness). (Note: HYD/ISDN are available as a fixed-dose combination or as individual medications. The ACC/AHA/HFSA guideline considers either form acceptable in this context.)*
b. *Avoid ARNIs in settings of known or hereditary angioedema with ACEIs or ARBs.*
c. *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.*
d. *Use of an SGLT2 inhibitor should also be considered as concomitant treatment for HFrEF in African Americans. Importantly, given the risk of HF in African Americans, use of an SGLT2 inhibitor is especially important in the pre-HF stage to reduce the onset of the disease in those with known diabetes.*
e. *Social barriers to GDMT and optimal HFrEF management should be assessed and, where present, addressed to avoid health inequities in HFrEF outcomes* (137).
f. *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 no randomized data for drugs or devices in patients older than 80 years of age. And although data from DAPA-HF can inform the use of a SGLT2 inhibitor in persons over the age of 75 years, for other evidence-based therapies in HFrEF, observational data represent the only lines of evidence supporting similar treatment benefits in older patients. Nevertheless, 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 (133) have been described in older populations. Accordingly, 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, is an appropriate action (138).

Frailty. Frailty is a specific pathophysiological entity affecting at least 20% of those over the age of 80 years and amplifies cachexia, muscle wasting, and neurological decline. Frailty 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 (139,140). Standard assessments of frailty are available (134).

5.7. How to Manage Your 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. Between 2012 and 2030, total direct medical costs for HF are projected to increase from $21 billion to $53 billion (141), while total costs (including indirect outlay) are estimated to increase from $30.7 billion to $69.8 billion (5). 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 (142). This creates 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 (143).

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

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

GDMT = guideline-directed medical therapy.

widely, even within a limited geographic area (144). 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, and assessing adherence, as well as 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 (e.g., GoodRx) can be used to assist patients in locating the retailers with the lowest cost medications.

Medication Access Measures: Newer HFrEF therapies are often expensive, with higher monthly costs and copays, and frequently more time and effort are 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.aacap.org/App_Themes/AACAP/docs/homepage/2017/PA_Reform_Principles.pdf) (145).

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

It is important to consider the cost-effectiveness of any new therapy to justify out-of-pocket costs. Cost-effectiveness analyses of sacubitril/valsartan and ivabradine showed an incremental cost-effectiveness ratio that compares favorably to other accepted CV therapies when they were first adopted or approved (146-148). Pharmacists can help navigate insurance coverage and patient

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. 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.

assistance programs to make sure that patients have access to the appropriate medications. 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 (149). Many pharmaceutical companies accept signed letters from clinicians indicating that the patient has no known income. This can be used in place of official income documentation, although this option is not clearly apparent on many of the patient assistance program websites. Likewise, patients and clinicians need to be cognizant of reordering procedures, which becomes especially important if doses are changed—refills/reorders are not always sent and, unfortunately, refills/reorders cannot be requested before the 60-day post-approval date. Supplemental Appendix 2 provides product-specific information on assistance in payment for newer HF therapies and appropriate use criteria to assist in the prior authorization process.

5.8. How to Manage the Increasing Complexity of HF Management

The 2017 HF ECDP was motivated by an increasingly complex HFrEF management environment and the need to assist clinicians in navigating it (2). In the 3 years since its publication, GDMT for HFrEF now has additional medications that improve patient outcomes, thus further increasing the complexity of achieving target GDMT in all

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

Target	Therapy
Renin-angiotensin-aldosterone system	ARNIs/ACEIs/ARBs, aldosterone antagonists
Sympathetic nervous system	Beta-blockers
Natriuretic and other vasodilator peptides	Neprilysin inhibitor (ARNI)
Sodium-glucose cotransporter-2	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

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; HYD/ISDN = hydralazine/isosorbide dinitrate; SGLT2 = sodium-glucose cotransporter-2.

patients with HFrEF. 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.

These targets include not only those modulated by the recommended treatments in this document, but also emerging treatments. For example, vericiguat, a soluble guanylyl cyclase stimulator, has demonstrated benefit for the combined outcome of death from CV causes or first hospitalization for HF (150). 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, ARNIs, evidence-based beta-blockers, aldosterone antagonists, and SGLT2 inhibitors are first-line medications for all populations. HYD/ISDN is also a first-line medication for self-identified African Americans. Ivabradine is a second-line medication for select populations.

Principle 2: Target doses are associated with best outcomes. Attempt to 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.

Principle 3: Start GDMT immediately. Delayed initiation of GDMT is associated with never initiating GDMT (151).

Principle 4: Attention to the clinical, social, and financial barriers to achieving GDMT should be prioritized. Multidisciplinary care should be targeted to the individual patient's barriers. 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 pulmonary artery pressure 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 renal function or hyperkalemia.

Use less than target doses of an ARNI/ACEI/ARB and discontinue aldosterone antagonist if estimated creatinine clearance <30 ml/min or serum potassium >5.0 mEq/L. Available data support a survival benefit even with a low-dose ACEI, which may be the default choice in the setting of renal insufficiency and marginal blood pressure.

Scenario: Symptomatic hypotension.

Hypotensive symptoms may be due to over-diuresis, use of non-CV drugs with hemodynamic effects (e.g., 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.

Principle 7: Primary prevention implantable cardioverter-defibrillator and cardiac resynchronization therapy 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 among symptomatic patients with chronic moderate-severe to severe mitral regurgitation 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 (e.g., 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 healthcare 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.

Employ 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.

5.9. How to Manage Common Comorbidities

In many cases, there is a bidirectional relationship between HF and certain comorbidities whereby the presence of one may increase the risk of the other, and the prognosis for the patient may be worse if both are present simultaneously.

Patients with HF, particularly older patients, frequently have other CV and non-CV comorbidities that affect their prognosis. 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. Furthermore, these comorbid conditions can greatly affect the treatment of HF and the ability to optimize therapies. To optimally manage these patients and improve clinical outcomes, clinicians must increasingly consider diagnosis and treatment of relevant comorbidities alongside the use of evidence-based HF therapies. Appropriate referral to clinicians with experience treating the various comorbidities is another important aspect of management and lays the foundation for effective team-based care.

Diabetes is a common comorbidity that deserves careful attention (152,153). Diabetes is strongly associated with the risk of both incident HF and adverse clinical outcomes and 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 SGLT2 inhibitors improves glycemic control but also significantly reduces HF events in patients with established CV disease or CV risk factors (154–156). Among patients with chronic kidney disease, SGLT2 inhibitors also decrease the risk of renal disease progression in a manner additive to renin-angiotensin-aldosterone system inhibitors (145).

As already indicated, the recent DAPA-HF and EMPEROR-Reduced trials demonstrated that SGLT2 inhibitor therapy reduced the risk of the composite of CV death or worsening HF in patients with HFrEF, regardless of whether they had T2D (12,44). Dapagliflozin is now approved for this indication, and the role of empagliflozin is under review by the Food and Drug Administration. SGLT2 inhibitors must now be included among the established, evidence-based therapies available to clinicians managing patients with HFrEF. Dapagliflozin has also demonstrated efficacy among patients with chronic kidney disease in reducing the composite of disease progression, end-stage kidney disease, or death from renal or CV causes. This effect was independent of the presence of diabetes (157). In a similar manner, empagliflozin slowed the decline of kidney function among patients treated in the EMPEROR-Reduced study (13). **Table 15** classifies comorbidities into CV and non-CV processes and provides guidance on appropriate management options.

Finally, the recent COVID-19 pandemic has illustrated an association between underlying CV disease, including HF, and worse clinical outcomes (171). 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 hemodynamically tolerated (172–176). As approaches to management continue to evolve, readers are encouraged to follow the scientific literature for updated evidence and recommendations for optimal management of these patients.

5.10. 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 healthcare 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 values and goals expressed by 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.

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	■ Evaluate and revascularize in appropriate patients
Atrial fibrillation/ flutter	Strong	Intermediate	■ Treat according to the current AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation (158,159)
Mitral regurgitation	Strong	Intermediate	■ Refer to a structural heart disease expert ■ Treat according to the current AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease (160,161) and ACC ECDP on the Management of MR (162) ■ Consider transcatheter intervention in carefully selected patients with symptomatic HF and secondary MR (163)
Aortic stenosis	Strong	Strong	■ Refer to a structural heart disease expert ■ Treat according to current AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease (160,161)
Hypertension	Uncertain	Strong for prevention	■ Treat according to current ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (164)
Dyslipidemia	Uncertain	Strong for prevention	■ Treat according to current AHA/ACC Guidelines on the Management of Blood Cholesterol (165) and the ACC ECDP on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk (166)
Peripheral vascular disease	Moderate	None	■ Treat according to current AHA/ACC Guidelines on the Management of Patients With Lower Extremity Peripheral Artery Disease (167)
Cerebrovascular disease	Moderate	Weak	■ Treat according to current ASA/AHA Guidelines for the Early Management of Patients with Acute Ischemic Stroke (168)
Noncardiovascular			
Obesity	Moderate (inverse association)	Weak	■ Further data needed
Chronic lung disease	Strong	Weak	■ Smoking cessation ■ Optimize therapy ■ Consider pulmonary consultation
Diabetes	Strong	Strong	■ Optimize therapy ■ Administer SGLT2 inhibitor ■ Consider consult with endocrinologist ■ Treat according to the ACC ECDP on Novel Therapies for CV Risk Reduction in Patients with T2D (31) and ADA Standards of Medical Care in Diabetes (169)
Chronic kidney disease	Strong	Strong	■ Optimize RAAS inhibitor therapy ■ Use hydralazine/ISDN if an ARNI/ACEI/ARB cannot be used ■ Administer SGLT2 inhibitor ■ Consider nephrology consult
Anemia	Moderate	Weak	■ Evaluate secondary causes ■ Consider transfusion in severe cases
Iron deficiency	Strong	Intermediate	■ Consider intravenous iron replacement for symptom improvement
Thyroid disorder (hypo or hyper)	Strong	Weak	■ Evaluate and initiate treatment ■ Consider referral to endocrinologist
Sleep disordered breathing	Strong	Intermediate; note that in patients with symptomatic HFrEF and central sleep apnea, adaptive servo-ventilation is harmful (170)	■ Refer for sleep study ■ Treat severe obstructive sleep apnea ■ Consider referral to sleep medicine specialist
Hyperkalemia	Uncertain; may limit initiation and titration of GDMT	Weak	■ Recommend dietary modifications ■ Consider treating with patiromer (note: data regarding clinical outcomes are pending [NCT03888066]) or sodium zirconium cyclosilicate

ACC = American College of Cardiology; ACEI = angiotensin-converting enzyme inhibitors; ADA = American Diabetes Association; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; ECDP = Expert Consensus Decision Pathway; GDMT = guideline-directed medical therapy; 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; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes.

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- 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 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 healthcare proxies (3). Resources to assist patients in these difficult discussions may be useful (e.g., the Advanced Care Training module from HFSA: hfsa.org). Similar preparedness-planning discussions should occur at the time of major procedural interventions (e.g., 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" (e.g., 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 (e.g., reducing neurohormonal antagonists in the setting of symptomatic hypotension, deactivation of defibrillator therapy) and the addition of therapies not usually recommended (e.g., opioids for refractory dyspnea). These decisions should be individualized and made in partnership with the patient, their caregivers, and their care team.

6. 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 guidelines 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 occasionally 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 therapeutics 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.

ACC PRESIDENT AND STAFF

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KEY WORDS ACC Expert Consensus Decision Pathway, ARNI, heart failure, HFrEF, SGLT2 inhibitor

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2021 UPDATE TO THE ACC EXPERT CONSENSUS DECISION PATHWAY ON OPTIMIZATION OF HEART FAILURE TREATMENT: ANSWERS TO 10 PIVOTAL QUESTIONS ABOUT 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 healthcare-related relationships, including those existing 12 months before initiation of the writing effort. The ACC Task Force on Expert Consensus Decision Pathways 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 in a Supplemental Appendix 1. Disclosure information for the ACC Task Force on Expert Consensus Decision Pathways is also available online at http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces, as well as the ACC disclosure policy for document development at http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy.

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Thomas M. Maddox (Chair)	BJC HealthCare and Washington University School of Medicine–Executive Director, Healthcare Innovation Lab; Professor of Medicine	None	None	None	None	None	None
James L. Januzzi Jr. (Vice Chair)	Harvard Medical School–Hutter Family Professor of Medicine; Director, Dennis and Marilyn Barry Fellowship in Cardiology Research; Senior Cardiometabolic Faculty, Baim Institute for Clinical Research	■ Abbott ■ Roche Diagnostics*	None	None	■ Abbott* ■ Amgen (DSMB)* ■ Boehringer Ingelheim (DSMB)* ■ Janssen Pharmaceuticals (DSMB)* ■ Novartis*	None	None
Larry A. Allen	University of Colorado School of Medicine—Associate Professor of Medicine	■ Abbott ■ Amgen ■ Boston Scientific ■ Novartis	None	None	None	■ Janssen	None
Khadijah Breathett	University of Arizona College of Medicine–Assistant Professor of Medicine, Division of Cardiology, Advanced Heart Failure and Transplant	None	None	None	None	None	None
Javed Butler	University of Mississippi Medical Center—Patrick H. Lehan Professor; Chairman, Department of Medicine	■ Abbott ■ AstraZeneca ■ Boehringer Ingelheim* ■ Eli Lilly* ■ Janssen* ■ Medtronic ■ Novartis* ■ Relypsa* ■ Roche Diagnostics	■ Janssen* ■ Novartis*	None	■ Amgen (DSMB) ■ Bristol-Myers Squibb (DSMB)	None	None
Leslie L. Davis	University of North Carolina at Chapel Hill–Associate Professor of Nursing	None	None	None	None	■ AANP	None
Gregg C. Fonarow	David Geffen School of Medicine, UCLA Division of Cardiology—Professor of Medicine	■ Abbott* ■ Amgen ■ AstraZeneca ■ CHF Solutions Lifesciences* ■ Janssen ■ Medtronic ■ Novartis*	None	None	None	■ Boston Scientific	None

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APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Nasrien E. Ibrahim	Massachusetts General Hospital—Assistant Professor of Medicine, Harvard Medical School; Associate Director, Resynchronization and Advanced Cardiac Therapeutics Program, Massachusetts General Hospital	■ Roche Diagnostics	None	None	■ Boehringer Ingelheim† ■ Novartis	None	None
JoAnn Lindenfeld	Vanderbilt University—Director, Heart Failure and Transplantation Program	■ Abbott ■ AstraZeneca ■ Boehringer Ingelheim ■ Edwards Lifesciences ■ Novartis	None	None	■ AstraZeneca†	None	None
Frederick A. Masoudi	University of Colorado Anschutz Medical Campus—Professor of Medicine	None	None	None	None	None	None
Shweta R. Motiwala	Beth Israel Deaconess Medical Center, Harvard Medical School—Instructor in Medicine	■ Eli Lilly	None	None	■ Relypsa†	None	None
Estefania Oliveros	Temple University Hospital-Pulmonary Hypertension, Right Heart Failure and CTEPH Program	None	None	None	None	None	None
J. Herbert Patterson	University of North Carolina Eshelman School of Pharmacy—Professor of Pharmacy and Research Professor of Medicine	■ Novartis*	None	None	■ Amgen† ■ Boehringer Ingelheim† ■ Novartis†	None	None
Mary Norine Walsh	St. Vincent Heart Center of Indiana—Medical Director, Heart Failure and Cardiac Transplantation	None	None	None	None	None	None
Alan Wasserman	The George Washington University School of Medicine and Health Sciences—Eugene Meyer Professor of Medicine; Chairman, Department of Medicine	None	None	None	None	None	None
Clyde W. Yancy	Northwestern University, Feinberg School of Medicine—Vice Dean, Diversity and Inclusion; Magerstadt Professor of Medicine; Chief, Division of Cardiology	None	None	None	None	None	None
Quentin R. Youmans	Northwestern University Feinberg School of Medicine—Fellow, Division of Cardiology, Department of Medicine	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. According to the ACC, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document;* b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document* or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household* has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the *document*.
*Significant relationship
†No financial benefit.

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

APPENDIX 2. PEER REVIEWER INFORMATION—2021 UPDATE TO THE 2017 ACC EXPERT CONSENSUS DECISION PATHWAY FOR OPTIMIZATION OF HEART FAILURE TREATMENT: ANSWERS TO 10 PIVOTAL ISSUES ABOUT HEART FAILURE WITH REDUCED EJECTION FRACTION

This table represents the individuals, organizations, and groups that peer-reviewed this document. A list of corresponding comprehensive healthcare-related disclosures for each reviewer is available in a Supplemental Appendix 3.

Reviewer	Representation	Employment
Frank V. Aguirre	Official Reviewer—Board of Governors	Prairie Cardiovascular Consultants—Interventional Cardiologist
Nancy M. Albert	Content Reviewer—ACC Expert	Cleveland Clinic—Associate Chief Nursing Officer, Research and Innovation
Nicole Martin Bhave	Content Reviewer—Solution Set Oversight Committee	University of Michigan—Associate Professor of Cardiovascular Medicine
Donald E. Casey Jr.	Content Reviewer—2017 Heart Failure Guideline Writing Committee	IPO 4 Health—Principal
Chad Darling	Content Reviewer	University of Massachusetts Medical School—Associate Professor, Department of Emergency Medicine
Gregory J. Dehmer	Content Reviewer—Solution Set Oversight Committee	Virginia Tech Carilion School of Medicine; Carilion Clinic, Cardiology and Carilion Cardiovascular Institute—Medical Director, Quality and Outcomes
James C. Fang	Content Reviewer—ACC Heart Failure Council	University of Utah School of Medicine—Chief of Cardiovascular Medicine; University of Utah Health Care—Director, Cardiovascular Service Line
Barbara Fletcher	Content Reviewer	University of North Florida—Associate Professor of Medicine
Olivia N. Gilbert	Official Reviewer—Solution Set Oversight Committee	Wake Forest School of Medicine—Assistant Professor, Advanced Heart Failure and Transplant Cardiology
Tyler J. Gluckman	Content Reviewer—Solution Set Oversight Committee, Chair	Providence Heart Institute, Providence St. Joseph Health—Medical Director, Center for Cardiovascular Analytics, Research and Data Science (CARDS); Johns Hopkins Hospital—Adjunct Faculty, Ciccarone Center for the Prevention of Heart Disease
Lee R. Goldberg	Content Reviewer—ACC Expert	Hospital of the University of Pennsylvania—Vice Chair of Medicine
Steven M. Hollenberg	Content Reviewer—2019 Heart Failure Expert Consensus Decision Pathway Writing Committee	Hackensack Meridian University Hospital—Professor of Medicine
Mariell Jessup	Content Reviewer—2017 Heart Failure Guideline Writing Committee	American Heart Association—Chief Scientific Officer
James N. Kirkpatrick	Content Reviewer—2019 Heart Failure Expert Consensus Decision Pathway Writing Committee	University of Washington Medical Center—Associate Professor of Medicine, Division of Cardiology; Director, Echocardiography
Michelle Maya Kittleson	Content Reviewer—2020 Heart Failure Guideline Writing Committee	Cedars-Sinai—Director, Heart Failure Research; Director, Post-Graduate Education in Heart Failure and Transplantation; Professor of Medicine, Smidt Heart Institute
Chayakrit Krittanawong	Content Reviewer—Solution Set Oversight Committee	Baylor College of Medicine and The Michael E. DeBakey VA Medical Center—Physician
Phillip David Levy	Content Reviewer	Wayne State University—Assistant Vice President; Associate Professor of Emergency Medicine; Associate Director of Clinical Research, Department of Emergency Medicine
Judith A. Mackall	Content Reviewer—Heart Rhythm Society	University Hospital of Cleveland, Division of Cardiology—Director, Device Clinic; Case Western Reserve University School of Medicine—Associate Professor of Medicine
Gurusher S. Panjrath	Content Reviewer—ACC Heart Failure Council	George Washington University—Director, Heart Failure and Mechanical Support Program
Sita S. Price	Content Reviewer	Elite Cardiac Care, LLC—Administrator/Director of Nursing
Lynne Warner Stevenson	Content Reviewer—2019 Heart Failure Expert Consensus Decision Pathway Writing Committee	Vanderbilt University—Director, Cardiomyopathy and Heart Failure Program
David E. Winchester	Content Reviewer—Solution Set Oversight Committee	University of Florida College of Medicine—Associate Professor of Medicine; Malcom Randall VAMC—Staff Cardiologist; Assistant Cardiology Fellowship Program Director, Quality and Research; Co-Director, Advanced Fellowship for Cardiovascular Imaging; Co-Director, University of Florida Health Cardiac Imaging Group

ACC = American College of Cardiology; VA = Veterans Administration; VAMC = Veterans Administration Medical Center.

APPENDIX 3. ABBREVIATIONS

ACC = American College of Cardiology
ACEI = angiotensin-converting enzyme inhibitor
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 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
SSOC = Solution Set Oversight Committee
SGLT2 = sodium-glucose cotransporter-2
T2D = type 2 diabetes