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EXPERT CONSENSUS DECISION PATHWAY

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 Task Force on Expert Consensus Decision Pathways

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PREFACE

The American College of Cardiology (ACC) develops a number of policy documents to provide members with guidance on clinical topics. Although clinical practice guidelines remain the primary mechanism for offering evidence-based recommendations, such guidelines may contain gaps in how to make clinical decisions, particularly when equipoise is present. Expert Consensus Documents are intended to provide guidance for clinicians in areas where evidence may be limited or new and evolving, or where insufficient data exist to fully inform clinical decision making. These documents therefore serve to complement clinical practice guidelines, providing practical guidance for transforming guideline recommendations into clinically actionable information.

To re-evaluate the clinical documents published by the ACC, an ACC Presidential Task Force was formed in 2014 to examine the processes of ACC's clinical documents. The main recommendation of the Task Force was a new focus on concise decision pathways and/or key points of care, instead of the traditional longer documents. The Task Force also established criteria for identifying high-value clinical topics to be addressed, as well as an innovative approach to collecting stakeholder input through a roundtable or think tank meeting. To complement the new focus on brief decision pathways and key points, Expert Consensus Documents were rebranded "Expert Consensus Decision Pathways" (ECDPs).

Although ECDPs have a new format, they maintain the same goal of Expert Consensus Documents: to develop policy based on expert opinion in areas where important clinical decisions are not adequately addressed by available data. ECDPs are designed to complement existing or newly published guidelines and bridge the gaps in clinical guidance that remain. In some cases, topics covered by ECDPs will be addressed subsequently by ACC/American Heart Association (AHA) guidelines as the evidence base evolves. The writing groups are charged with developing algorithms that are more actionable and can be implemented into tools or apps to accelerate the use of these documents at point of care. Decision Pathways are intended not to provide a single correct answer, but to encourage clinicians to ask certain questions and consider important factors as they come to their own decision on a treatment plan to be recommended and discussed with their patients. There may be multiple pathways that can be taken for treatment decisions, and the goal is to help clinicians make a more informed decision.

James L. Januzzi, Jr, MD, FACC
Chair, ACC Task Force on Expert Consensus Decision Pathways

ABSTRACT

The 2017 ACC/AHA/Heart Failure Society of America (HFSA) heart failure (HF) guidelines (1) reflect a focused update of the ACC/AHA 2013 HF guidelines (2) and include guidance based on new evidence supporting novel drug therapies, a new treatment algorithm replete with more options for care than before, an updated approach to prevention, and important updates regarding various forms of HF and important comorbidities. The care of patients with HF is more involved than ever. Current care for the patient with HF with reduced ejection fraction (EF)

includes no fewer than 7 evidence-based medications, 3 evidence-based device strategies, and a number of recommend processes of care. The opportunity to change the natural history of HF with reduced EF has never been better, but with more choices comes greater complexity. This necessitates careful guidance to clinicians, emphasis on best principles for initiating and titrating guideline-directed medical therapy for HF with reduced EF, and advice on managing the overall complexity of the condition.

This ACC Expert Consensus Decision Pathway addresses steps to follow when introducing 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 expansive text, the document provides practical tips, tables, and figures to make clear the steps, tools, and provisos needed to successfully and expeditiously treat the patient with HF with reduced EF. Many of the pivotal issues addressed in this document are not the substance of clinical trials; rather, they represent the challenge of clinical practice. Whenever possible, resources are included or hyperlinked. The treatment of HF with reduced EF can feel overwhelming, and many opportunities to improve patient outcomes are being missed; hopefully, this Expert Consensus Decision Pathway may streamline care to realize best possible patient outcomes in HF.

1. INTRODUCTION

The prevalence of HF is escalating rapidly. Compounding this, HF is an illness that consumes significant health care resources, inflicts significant morbidity and mortality, and greatly impacts 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, including readmission reduction programs and ambulatory outpatient disease management for those with more advanced disease.

HF exists in several phenotypes, in part reflected by differences in left ventricular ejection fraction (LVEF). These include heart failure with reduced ejection fraction (HFrEF), HF with preserved EF, as well as HF with improved EF. Although the evidence base for the treatment of HFrEF has expanded substantially, much work remains for the other forms of HF. New therapies for HF with preserved EF are under exploration, and the evidence base addressing HF with improved EF is just emerging.

The purpose of this document is to complement the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACC/AHA Guideline for the Management of Heart Failure (1) by addressing new medical therapies, prevention, and comorbidities relevant to HFrEF for which data are available. Despite new guideline statements, information voids exist, and a practical, consensus approach is needed for areas that have incomplete evidence. To that end, we have identified 10 pivotal issues that remain unresolved in the guidelines. This document attempts to address these issues.

Ten Pivotal Issues in HFrEF

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

2. METHODS

A structured format was created subsequent to the release of the 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: an Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure, addressing new pharmacological therapies (3). Questions were developed to identify evidence gaps. A multidisciplinary panel of stakeholders was configured and a literature review was completed to aggregate relevant evidence addressing contemporary HF care. The references were separately reviewed by the Chair and Vice-Chair, and an agreed-upon compendium was developed. Print copies of the references were provided to each member of the panel prior to a live roundtable meeting held on July 19, 2016, at the ACC Heart House. Participants attending the HF roundtable meeting included cardiologists, internists, emergency physicians, hospitalists, nurses, representatives from patient advocacy groups, pharmacists, fellows-in-training, quality improvement experts, epidemiologists, and biostatisticians.

Structured discussions were held addressing new therapies, unanswered questions, adherence, and implementation strategies. Multidisciplinary panel discussions

were convened and archived for online distribution. (Discussions can be found at http://www.acc.org/tools-and-practice-support/quality-programs/succeed-in-managing-heart-failure-initiative/emerging-strategies-for-heart-failure-roundtable.) A writing group was invited to participate, as representative of all stakeholders. A review of outstanding questions was facilitated by a survey of constituent members of the stakeholder groups, with editing of the questions carried out by the writing panel. Subsequent writing assignments were configured according to areas of expertise. Teleconferences were used to edit contributed content. Conference calls of the writing committee were confidential and were attended only by 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 e-mail-generated ballot was implemented. A simple majority prevailed; in the presence of a tie, chair prerogative reconciled the final decision.

The work of the writing committee was supported exclusively by the ACC without commercial support. Writing committee members volunteered their time to this effort. All members of the writing committee, as well as those selected to serve as peer reviewers of this document, were required to disclose relationships with industry (RWI) and other entities (see Appendixes 1 and 2, respectively). The Chair was without any RWI and is responsible for the content of this document. In keeping with ACC policy, the majority of the writing committee were without relevant relationships with industry. 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.

3. ASSUMPTIONS AND DEFINITIONS

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

General Clinical Assumptions

1. Although many topics are generalizable to all patients with HF, the focus of this effort, including pathway recommendations, only applies to patients with HFrEF.
2. Although some of the recommendations may be relevant to patients hospitalized with acute HF, this document mainly deals with the management of patients with chronic ambulatory HFrEF.
3. The expert consensus writing committee endorses the evidence-based approaches to HF therapy and management enumerated in the 2013 ACC/AHA Guideline for the Management of Heart Failure (2) and the 2016 and 2017 ACC/AHA/HFSA focused updates (1,3).
4. These algorithms assume the clinician will seek input as needed from a pharmacist, cardiologist, HF specialist and/or disease management program, and other relevant medical specialist (e.g., endocrinologist or nephrologist) to guide clinical management, and will consider patient preference in all clinical decision-making.
5. These algorithms are based on best available data; all clinical decisions should be governed by judgment and influenced by discussions with the patient about treatment preferences.
6. At any point in time, these suggestions and algorithms may be superseded by new data.

Definitions

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.

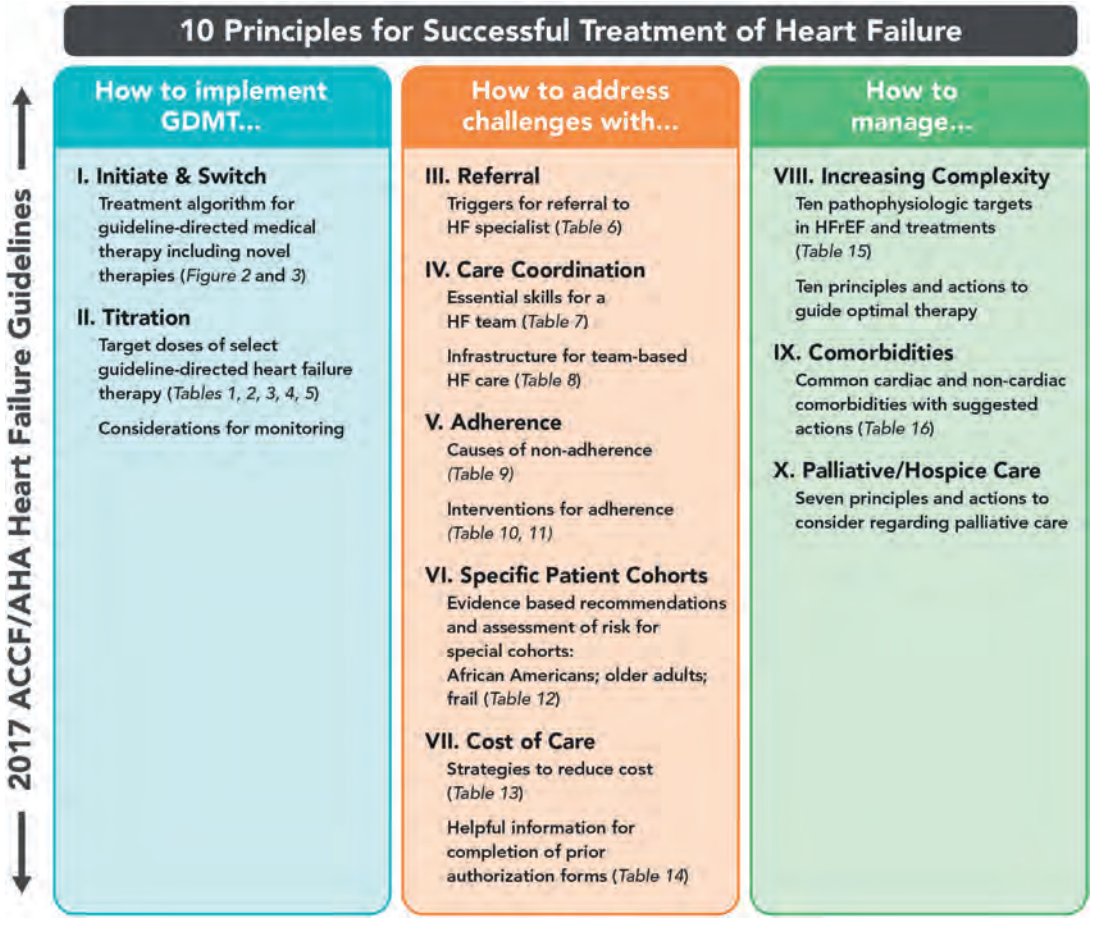
GDMT: Guideline-directed medical therapy.
Optimal therapy: Treatment provided at either the target or the highest-tolerated dose for a given patient.
Target dose: Doses targeted in clinical trials.
ACC/AHA Stages of HF:

- *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.

4. PATHWAY SUMMARY GRAPHIC

Figure 1 summarizes 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.

FIGURE 1 Ten Principles for Successful Treatment of Heart Failure



ACCF = American College of Cardiology Foundation; AHA = American Heart Association; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = HF with reduced ejection fraction.

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

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

Established therapies for chronic HFrEF include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers, loop diuretics, aldosterone antagonists, and hydralazine/isosorbide dinitrate (HYD/ISDN); with the exception of loop diuretics, all have been shown in randomized controlled trials to improve symptoms, reduce burden of hospitalization, and/or provide survival benefit (2). Recently, in addition to established GDMT, an angiotensin receptor-neprilysin inhibitor (ARNI) and the hyperpolarization channel blocker ivabradine have been added to the treatment guidelines for HFrEF (3). Understanding when and how to add, switch, and titrate all therapies to maximally tolerated doses and ideally target doses (Figure 1, Table 1) is important.

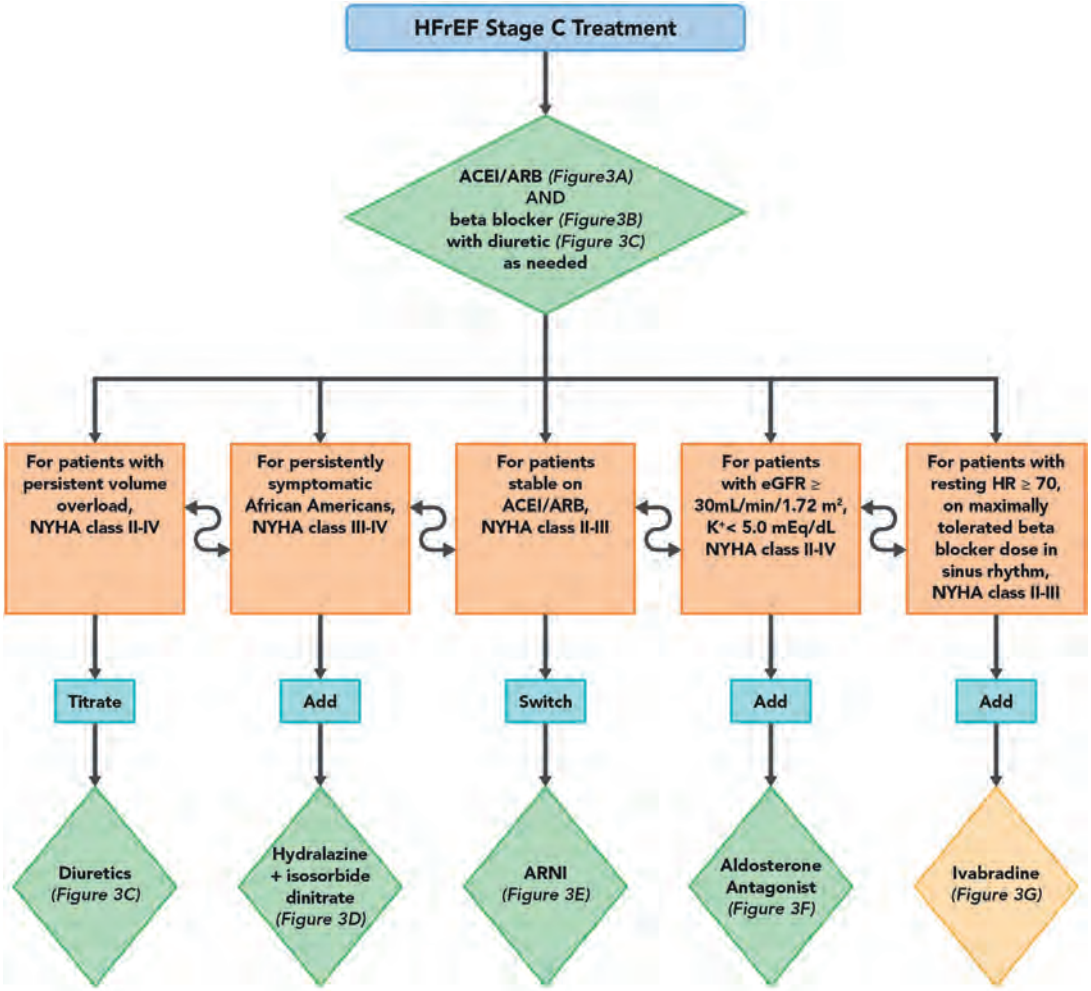
HF is a complex syndrome typically associated with multiple comorbidities; most patients are on multiple medications. No clinical trials have specifically evaluated the potential for greater benefit or excessive risk of indicated therapies among patients with multimorbidity. To assess tolerability of medications and best assess the trajectory of HF, it is often necessary for patients to have more frequent follow-up, especially after initiation or titration of therapy.

Initiating GDMT

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

In a patient with new-onset HFrEF, a common question is whether to initiate a beta blocker or ACEI/ARB first.

FIGURE 2 Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies (2,9)



Green diamonds indicate Class I guideline recommendations, while the yellow diamond indicates a Class II recommendation. ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; NYHA = New York Heart Association.

Data from the randomized CIBIS (Cardiac Insufficiency Bisoprolol) III trial suggest that either is safe (4). Initiation of ACEI or ARB (**Table 1, Figures 2 and 3**) is often better tolerated when the patient is still congested ("wet"; when renin-angiotensin-aldosterone system activation is less), whereas beta blockers are better tolerated when the patient is less congested ("dry") with adequate resting heart rate. Only evidence-based beta blockers should be used in patients with HFrEF (**Table 1, Figures 2 and 3**).

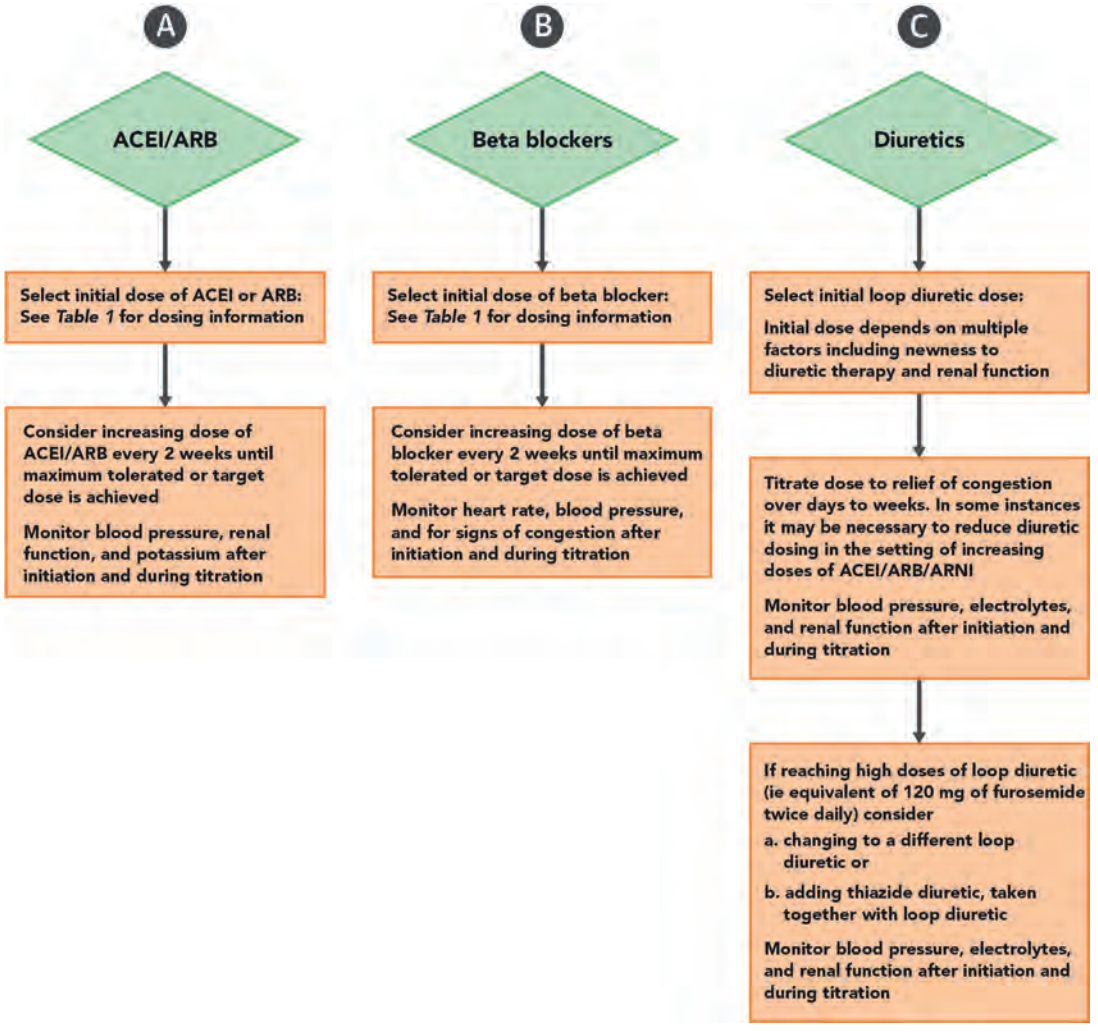
In selected patients with HFrEF, a clinician may choose to start a low dose of a beta blocker *and* an ACEI/ARB; in persistently symptomatic patients who tolerate an ACEI or ARB, switching to an ARNI would be recommended (**Table 1, Figure 2**).

Titration of ACEI/ARB and beta blockers is discussed in Issue 2.

Angiotensin Receptor-Neprilysin Inhibition

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 (5). Because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors raise angiotensin levels, which explains the rationale for coadministration of ARB. Neprilysin inhibitors are not combined with ACEI due to a higher risk of angioedema (6).

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



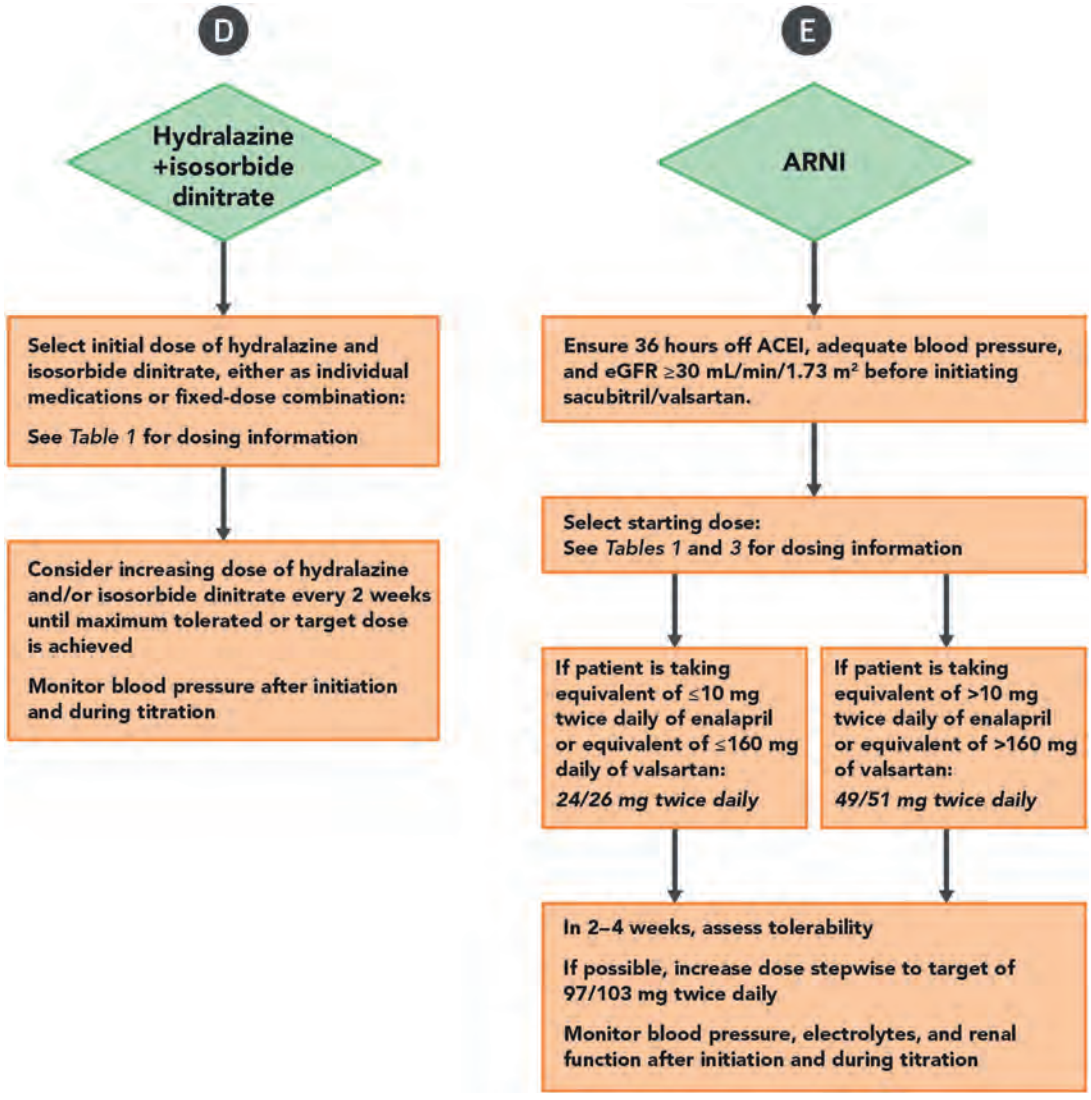
Green diamonds indicate Class I guideline recommendations, while the yellow diamond indicates a Class II recommendation. ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; bpm = beats per minute; eGFR = estimated glomerular filtration rate.

Continued on the next page

Sacubitril/valsartan (7,8) was tested among patients with chronic HFrEF in a randomized controlled trial, PARADIGM HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure). The trial enrolled patients with NYHA class II to IV symptoms with an EF ≤40% (modified to ≤35% 1 year into the trial), stable on doses of ACEI/ARB, 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 current decompensated HF were excluded. The trial began with a sequential run-in period to ensure that every patient randomized could tolerate both sacubitril/valsartan and the comparator enalapril target doses. Of the 10,513 candidates screened, 2,079 were not randomized due to the 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 a 20% reduction in the primary outcome of cardiovascular death or HF hospitalization (hazard ratio: 0.80; 95% confidence interval: 0.73 to 0.87; $p < 0.001$) in patients treated with sacubitril/valsartan. The number needed to treat to prevent 1 primary endpoint over 27 months was 21. These differences in outcomes included a 20% reduction in sudden cardiac death.

FIGURE 3 Continued



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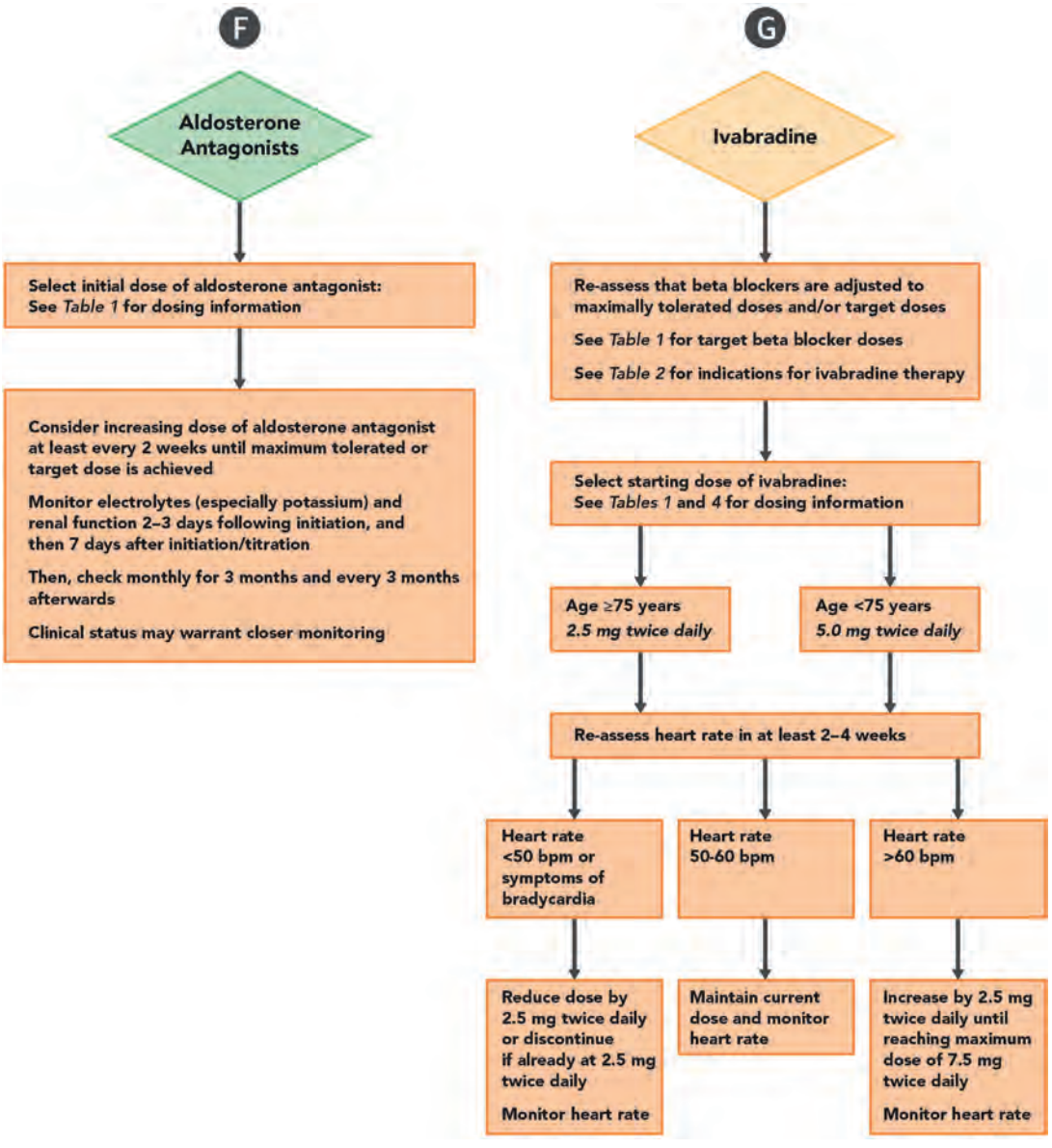
Symptomatic hypotension was more common with sacubitril/valsartan but was not associated with a worsening of renal function. Angioedema was numerically higher but not statistically significantly different from enalapril in the sacubitril/valsartan group. It should be noted that most patients likely to have angioedema were excluded by the requirement to tolerate enalapril.

The most recent clinical HF guidelines (3) recommend 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) (1,2). Use of an aldosterone antagonist, although also recommended to improve outcomes, is not considered mandatory prior to changing a patient to ARNI. Guidance for the transition from an ACEI or ARB to ARNI are detailed in **Figures 2 and 3** and in **Tables 1 to 4**.

When making the transition from an ACEI to 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 ARNI. In a recent study (9), a condensed and conservative approach 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

FIGURE 3 Continued



of the target dose of sacubitril/valsartan in patients previously receiving low doses of ACEI/ARB.

Initiation of an ARNI de novo without prior exposure to ACEI or ARB

It is possible that a patient may be identified who meets all criteria for initiation of ARNI, but the patient has not yet been treated with an ACEI or ARB. The committee is aware that clinicians may occasionally consider initiating ARNI in patients who have not previously been treated with ACEI or ARB. To be explicitly clear, no predicate data supports this approach. For well-informed patients who, within a framework of shared-decision making, accept the uncertainty about effectiveness and safety as well as potentially greater out-of-pocket costs, de novo initiation of ARNI with close follow-up and serial assessments (blood pressure, electrolytes, and renal function) might be considered. Any such usage should consider concerns regarding risk of angioedema or hypotension (**Figures 2 and 3, and Tables 1 to 4**).

Ivabradine

Heart rate independently predicts outcomes in HFrEF. Evidence from beta-blocker trials suggests that heart

TABLE 1 Starting and Target Doses of Select Guideline-Directed Medical Therapy for HF (3,15)

	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/d	200 mg daily
ARNI		
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily
ACEI		
Captopril	6.25 mg 3× daily	50 mg 3x 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
ARB		
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
Vasodilators		
Hydralazine	25 mg 3× daily	75 mg 3× daily
Isosorbide dinitrate*	20 mg 3× daily	40 mg 3× daily
Fixed-dose combination isosorbide dinitrate/ hydralazine†	20 mg/37.5 mg (one tab) 3× daily	2 tabs 3× daily
Ivabradine		
Ivabradine	2.5–5 mg twice daily	Titrate to heart rate 50–60 bpm. 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 (2). *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.

ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; ARB = angiotensin receptor blocker; bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction.

rate lowering is directly related to improved outcomes (10). 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). Prior to initiating any other agent with heart-rate slowing effects, the dose of an evidence-based beta blocker should be optimized. However, some apparently well-compensated patients on optimal beta blocker therapy continue to have a persistent resting heart rate over 70 bpm.

TABLE 2 Guideline-Recommended Indications for ARNI and Ivabradine Use

Indications for Use of an ARNI

- HFrEF (EF ≤40%)
- NYHA class II or III HF

Indications for Use of Ivabradine

- HFrEF (EF ≤35%)
- On maximum tolerated doses of beta blocker
- Sinus rhythm with a resting heart rate ≥70 bpm
- NYHA class II or III HF

ARNI = angiotensin receptor-neprilysin inhibitor; bpm = beats per minute; EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; NYHA = New York Heart Association.

Ivabradine is an adjunctive means to reduce 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) 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 (11). Benefits were noted especially for those patients with: contraindications to beta blockers, beta blocker doses <50% of GDMT targets (12), and resting heart rate ≥77 bpm at study entry (13). It is important to emphasize that ivabradine is indicated only for patients in sinus rhythm, not in those with atrial fibrillation, patients who are 100% atrially paced, or unstable patients. From a safety standpoint, patients treated with ivabradine had more bradycardia and developed more atrial fibrillation as well as transient blurring of vision (11).

In the 2016 ACC/AHA/HFSA HF guidelines focused update (3), ivabradine was recommended as a Class IIa, Level of Evidence: B-R (1,2) therapy to reduce the risk of HF hospitalization in patients with HFrEF (LVEF ≤35%) already receiving GDMT (including a beta blocker at maximally tolerated dose), and who are in sinus rhythm with a heart rate greater than 70 bpm at rest (**Figures 2 and 3, Tables 1 and 5**). The contraindications to ivabradine are enumerated in **Table 4**.

Consensus Pathway Algorithm for Initiation and Titration of HFrEF Therapies

A strategy for initiating and titrating evidence-based therapies for patients with HFrEF is depicted in **Figures 2 and 3**. As noted in the previous text, after a diagnosis of HF is made, GDMT should be initiated and therapies should be adjusted no more frequently than every 2 weeks to target doses (or maximally tolerated doses). Clinicians should aim to achieve this 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

TABLE 3 Recommended Starting Dose of Sacubitril/Valsartan

Population	Initial Dose
Moderate- or high-dose ACEI *Equivalent of enalapril ≥10 mg twice daily*	**49/51 mg twice daily**
Moderate- or high-dose ARB *Equivalent of valsartan ≥80 mg twice daily*	
Low dose ACEI *Equivalent of <10 mg of enalapril twice daily*	**24/26 mg twice daily**
Low dose ARB *Equivalent of valsartan ≤80 mg twice daily*	
ACEI/ARB naïve*	
Severe renal impairment† (eGFR <30 mL/min/1.73 m^2)	
Moderate hepatic impairment (Child-Pugh Class B)	
Elderly (age ≥75 years)	

*See page 8. †This population was not studied in PARADIGM HF.

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

TABLE 4 Contraindications and Cautions for Sacubitril/Valsartan and Ivabradine

A) Sacubitril/Valsartan

Contraindications	Cautions
■ Within 36 hours of ACEI use ■ Angioedema with an ACEI or ARB previously ■ Pregnancy ■ Lactation (not recommended) ■ Severe hepatic impairment (Child-Pugh C) ■ Concomitant aliskiren use in patients with diabetes ■ Known hypersensitivity to either ARB or ARNI	■ Renal impairment: - Mild-to-moderate (eGFR ≥30 mL/min/1.73 m^2): No starting dose adjustment required - Severe* eGFR <30 mL/min/1.73 m^2): Reduce starting dose to 24 mg/26 mg twice daily; double the dose every 2–4 weeks to target maintenance dose of 97 mg/103 mg twice daily as tolerated ■ Hepatic impairment: - Mild (Child-Pugh A): No starting dose adjustment required - Moderate (Child-Pugh B): Reduce starting dose to 24 mg/26 mg twice daily; double the dose every 2–4 weeks to target maintenance dose of 97 mg/103 mg twice daily as tolerated - Severe (Child-Pugh C): contraindicated ■ Renal artery stenosis ■ Hypotension ■ Volume depletion ■ Hyponatremia ■ Post myocardial infarction

B) Ivabradine

Contraindications	Cautions
■ HFpEF ■ Presence of angina with normal EF ■ Hypersensitivity ■ Severe hepatic impairment ■ 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 bpm ■ Atrial fibrillation or flutter ■ Atrial pacemaker dependence	■ Bradycardia ■ Sinus node disease ■ Cardiac conduction defects ■ Prolonged QT interval

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

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; bpm = beats per minute; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

continue to be up-titrated to achieve maximally tolerated 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. Reassessment of ventricular function should occur after target or maximally tolerated doses of GDMT are achieved for 3 months to determine the need for device therapies such as implantable defibrillators and cardiac resynchronization therapy (2). Structured medication titration plans embedded in disease management programs have been shown to be useful in obtaining target doses of GDMT within 6 months of hospital discharge (14).

Patients in Whom New Therapies May Not be Indicated

Contraindications may preclude the initiation of some agents. Additionally, a well-informed patient may make a personal judgment, in terms of benefits and risks, after being presented with all evidence in favor of these therapies 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 left ventricular (LV) assist device), home inotropes, or hospice, initiation of new drug therapies may not be appropriate, especially given the absence of evidence addressing efficacy in such patients.

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)

Target Doses

To achieve the maximal benefits of GDMT in patients with chronic HFrEF, therapies must be initiated and titrated to maximally tolerated doses (7,16–18). 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.

TABLE 5 Recommended Starting Dose of Ivabradine

Population	Initial Dose
Maximally tolerated beta-blocker dose with persistent resting heart rate ≥70 bpm	**5 mg twice daily**
History of conduction defects	**2.5 mg twice daily**
Age ≥75 years	

bpm = beats per minute.

Strategies for titration are detailed in **Figures 2 and 3**. Achieving target or maximally tolerated doses of GDMT is the goal. Beta-blocker doses should be adjusted every 2 weeks (19) 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, or dizziness.

ACEI and 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. In the absence of hypotension, electrolyte/renal instability, or angioedema on an ACEI or ARB, it is reasonable to change to ARNI. For those taking ARNIs, doses can be increased every 2 to 4 weeks to allow time for adjustment to the vasodilatory effects of the combined angiotensin receptor and neprilysin inhibition while also monitoring renal function, potassium, and especially blood pressure. For optimal titration of ACEI, ARBs, or ARNI, 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 patients with chronic HFrEF already receiving beta blockers and ACEI/ARB/ARNI who do not have contraindications to this therapy (2). It is not necessary to achieve target or maximally tolerated doses of other drugs before adding aldosterone antagonists. The dose of aldosterone antagonists used in clinical trials, which is typically below that which might influence blood pressure, is sufficient for clinical efficacy. Adherence to the guideline recommendations for monitoring of renal function and potassium is required.

For a number of 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 [20]), African-American patients should receive these drugs once target or maximally tolerated doses of beta blocker and ACEI/ARB/ARNI are achieved (2). This is especially important for those patients with NYHA class III to IV symptoms.

Finally, following assiduous titration of beta blockers, in patients whose heart rate remains ≥70 bpm on target or maximally tolerated doses of beta blockers, ivabradine (3) can be added and titrated every 2 weeks to lower heart rate.

Barriers to Medication Titration

In some instances, it may not be possible to titrate GDMT to the target doses achieved in clinical trials. Patients in clinical practice may differ substantially from those enrolled in the trials; such differences may limit the ability to titrate therapies. For example, patients in clinical practice are typically older, may experience more side effects, and are likely to have more comorbidities that will limit titration.

Abnormal renal function and/or hyperkalemia are common barriers to initiation and titration of GDMT. For patients with established renal disease, caution may be necessary when starting GDMT, though ACEI/ARB are generally considered safe in patients with creatinine <3.0 mg/dL. In patients with mild-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 (This population was not studied in PARADIGM HF. The statement is consistent with FDA approved labeling indications) (**Table 4**). 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/dL (**Figure 1**).

Renal function and potassium should be assessed within 1 to 2 weeks of the initiation or dose increase of ACEI/ARB/ARNI. 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 (2). After the initiation or titration of loop diuretics, renal function should be assessed within 2 to 3 days.

During 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 ACEI or ARB do not predict longer-term adverse outcomes (21). In patients with evidence of hypovolemia, the dose of diuretics should be reduced. Doses of ARNI may also need to be reduced in the setting of renal insufficiency or hypotension. Hyperkalemia may also require changes in medical

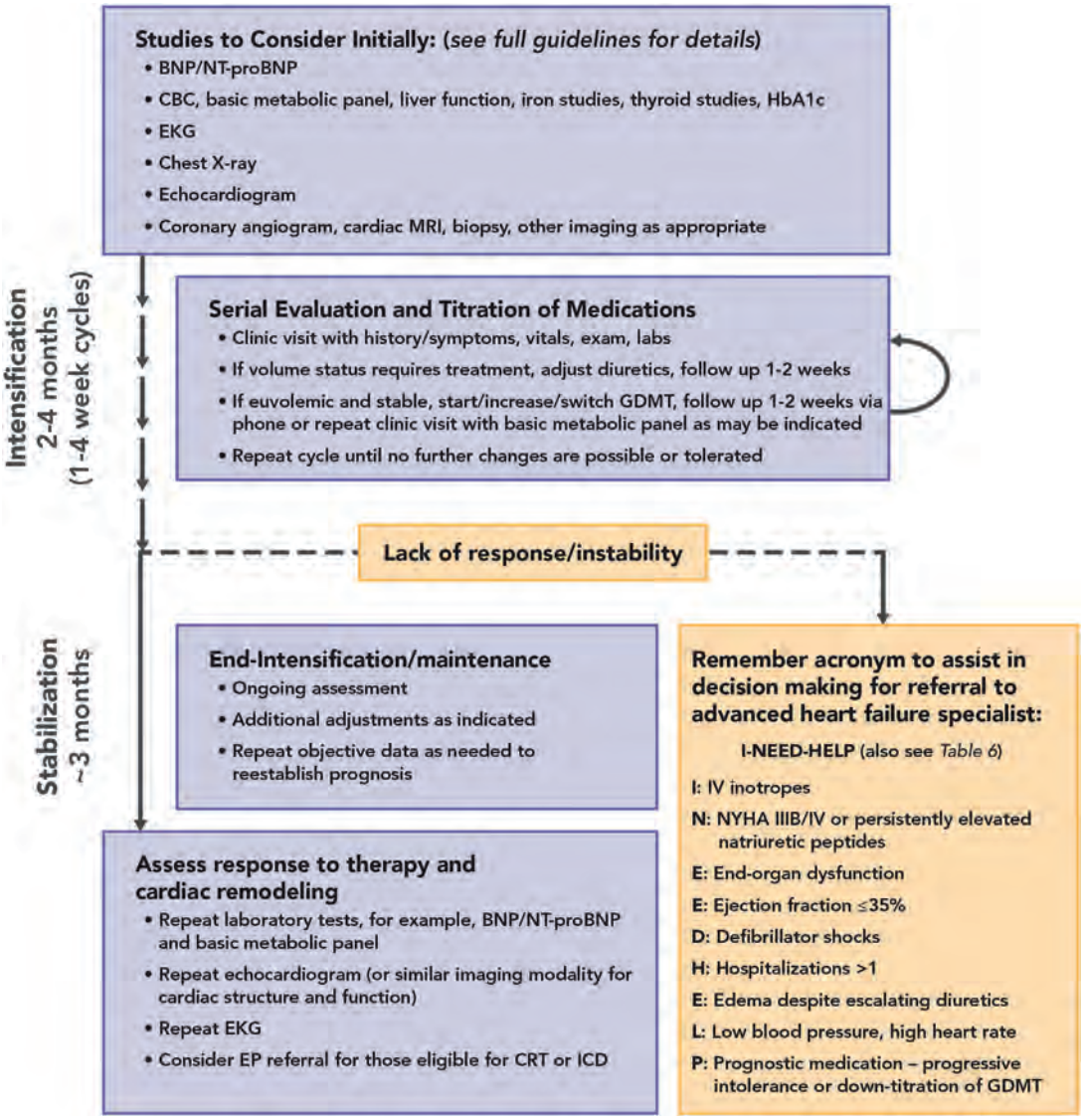
therapy. Clinical assessment and renal stability in each patient dictates whether clinicians may need to monitor certain patients more closely than others.

Social or economic barriers to care may also undermine ability to achieve GDMT. 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. Cost may also pose a substantial barrier to care, particularly for ARNI and ivabradine therapy. In such cases, if all solutions are exhausted, optimizing care with the most financially manageable program is recommended (see answer to Issue 7).

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

FIGURE 4 Testing and Medication Titration Following Diagnosis of HFrEF



BNP = B-type natriuretic peptide; CBC = complete blood count; CRT = cardiac resynchronization therapy; EKG = electrocardiogram; EP = electrophysiology; GDMT = guideline-directed medical therapy; HbA1c = hemoglobin A1c; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; IV = intravenous; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

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 beneficial and remains underutilized.

High-risk features (conveniently summarized in the acronym "I NEED HELP" in **Figure 4 and Table 6**) should trigger consideration for referral for advanced HF consultation (22); features triggering referral to advanced HF care are also discussed in the answers to Issue 3 and **Table 6**.

Imaging—When to Order an Echocardiogram

An echocardiogram is recommended in the evaluation of the patient with incident HF to assess LVEF, diastolic function, chamber size, ventricular wall thickness, valvular abnormalities, strain imaging when available, 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 and/or cardiac resynchronization therapy) or referral for advanced therapies (ventricular assist device or transplant). Repeat imaging may also be considered at the time of clinically important changes in clinical status (2). Routine surveillance echocardiograms (e.g., annually) in the absence of change in clinical status or some other signal of risk are unwarranted. If echocardiography does not provide an assessment of LVEF, guidelines recommend other modalities including radionuclide ventriculography or magnetic resonance imaging (2).

When recovery of LVEF to >40% is noted in the setting of prior HFrEF, it is likely that outcomes may improve as well. However, there are no data to guide what adjustment (if any) should be made with GDMT in most cases, and in the absence of a defined, reversible cause for HFrEF (e.g., tachycardia-mediated cardiomyopathy), current therapies should be continued.

Biomarkers—When to Order Natriuretic Peptides

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (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 informs high risk, particularly when the concentrations are rising. Current clinical practice guidelines give a Class I recommendation to measure NT-proBNP or BNP to support a clinical diagnosis of HF, to assess disease severity, or to establish prognosis (2).

More recently, biomarkers have been examined for their role as a marker of clinical responsiveness to GDMT. This is, in part, due to the fact that a wide range of GDMT 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 (23). Therefore, measurement of BNP or NT-proBNP is useful to monitor risk, to assist in decision making regarding the ordering of imaging studies to evaluate LV remodeling, to support clinical

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

1. New onset HF (regardless of EF) for evaluation of etiology, guideline-directed evaluation and management of recommended therapies, and assistance in disease management.
2. Chronic HF with high-risk features, such as development of 1 or more of the following risk factors: ■ Need for chronic IV 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 or ventricular arrhythmias or repetitive ICD shocks ■ Two or more emergency department visits or hospitalizations for worsening HF in 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 validated risk model for further assessment and consideration of advanced therapies (http://www.onlinejacc.org/content/62/16/e147/T10)
3. To assist with management of GDMT, including replacement of ACEI or ARB therapy with ARNI for eligible patients, or to address comorbid conditions such as chronic renal disease or hyperkalemia, which may complicate treatment.
4. Persistently reduced LVEF ≤35% despite GDMT for ≥3 months for consideration of device therapy in those patients without prior placement of ICD or CRT, unless device therapy contraindicated.
5. Second opinion regarding etiology of HF; for example: ■ Evaluation for potential ischemic etiology ■ Suspected myocarditis ■ Established or suspected specific cardiomyopathies, e.g., hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, Chagas disease, restrictive cardiomyopathy, cardiac sarcoidosis, amyloid, aortic stenosis. ■ Valvular heart disease with or without HF symptoms
6. Annual review 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.
7. Assess the possibility of 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.

judgment with respect to prescription of GDMT, and to provide helpful objective data regarding decision-making for referral to advanced HF therapies (See **Figure 4 and 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 (24), the reassessment of BNP or NT-proBNP may be informative. However, serial assessment of BNP or NT-proBNP to guide aggressive titration of GDMT is not indicated and not warranted (25). Severe renal dysfunction may interfere with the interpretation of natriuretic peptide concentrations.

While rising natriuretic peptide concentrations are correlated with adverse outcomes, this relationship can be confounded with the use of sacubitril/valsartan. Due to neprilysin inhibition, concentrations of BNP rise in patients treated with sacubitril/valsartan and tend not to return to baseline despite chronic therapy. In contrast, NT-proBNP concentrations typically decrease, as NT-proBNP is not a substrate for neprilysin (26). Therefore, clinicians should interpret natriuretic peptides in the context of GDMT; BNP concentrations will increase (while NT-proBNP will most often fall) with ARNI therapy, and thus it may be more prudent to check only NT-proBNP in patients on ARNI. Also, transient increases in natriuretic peptide levels have been documented in the initial phases of beta-blocker initiation; such changes should not preclude up-titration of beta-blocker therapy, which should be guided by patient tolerance instead of asymptomatic change in natriuretic peptide levels.

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 diuretics, those who develop worsening renal function with attempts to increase doses of diuretic, 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 Heart Failure Patients) study, patients with NYHA class III HF symptoms were randomly assigned to receive a wireless implantable pulmonary artery pressure monitor versus usual care (27). Patients managed with data from implantable pulmonary artery pressure monitoring had more changes in GDMT and diuretic doses (28). Those managed with implantable pulmonary artery pressure monitoring had a 37% relative reduction in HF hospitalization ($p<0.001$). 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. A team-based approach may be necessary to best deploy this monitoring strategy (see answers to Issue 8).

Patients on optimal GDMT who have either high-risk features (see Issue 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.

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 (**Table 6**) to optimize therapies and evaluate advanced HF care options (2).

Referrals are 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 (2,29–34). 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 (22,35–38).

4. How to Address Challenges of Care Coordination

Delivering optimal 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 and monitoring. 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. This complexity 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 HF Medicare patients have 4 or more noncardiovascular comorbidities and more than 25% have 6 or more (39). 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, rehabiliatation facilities, and ambulatory clinics). This raises the risks

TABLE 7 Essential Skills for a Heart Failure Team

Heart failure diagnosis and monitoring for progression
Treatment prescription, titration, and monitoring
Patient and caregiver education on disease and treatments
Lifestyle (e.g., diet, exercise) prescription, 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

of inefficiencies in care delivery, miscommunication, potential drug-drug interactions and drug-disease interactions, and missed opportunities to achieve optimal HF outcomes.

Team-based care may be the most effective approach to complex HF care (40). By definition, team-based care is the delivery of health services to individuals, families, and/or their communities by at least 2 healthcare providers who work collaboratively with patients and their caregivers, in concordance with patient preference, to achieve shared goals within and across settings (41). Randomized trials have demonstrated the superiority of the team-based approach over usual care in patients with HF (42-45) with respect to the risks of death, hospitalization, lengths of stay, and quality of life (46-49). 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 (50,51). Team-based HF care is thus recommended in the most recent HF guidelines (2).

Necessary skills for care teams include proficiency in monitoring for HF progression and exacerbation, care coordination, treatment prescription and monitoring, and education for patients and their caregivers (Table 7). Effective team-based HF care may be possible with small teams as long as the requisite skills are available. Recent innovations in patient and clinician education, such as group visits, remote specialist video consultation, and telemonitoring programs, may also be useful (52-57).

The necessary 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 (27), wearable activity monitors (58), and smartphone applications (59), have potential to improve monitoring and patient engagement. However, these innovations are largely unproven, so the focus should remain on the effectiveness and evidence, rather than the form of these tools. "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 objective data. Patient and caregiver educational tools also support team-based HF care. Recent advances in optimizing health literacy and empowering patient engagement and self-management in HF care are promising in this respect (60,61). Ongoing monitoring of team-based care implementation, outcomes, and safety through periodic data collection, analysis, benchmarking, and—as needed—process improvements is an essential aspect of optimal team-based HF care.

5. How to Improve Adherence

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 prescribing (62). Estimates of significant nonadherence are as high as 50% (63,64); such nonadherence is associated with worse outcomes in HF (65). Reasons for nonadherence are complex, and vary for

TABLE 8 Infrastructure to Support Team-Based HF Care

Modality	Challenges	Potential Benefits
Electronic health records	Ease of access, interoperability with other electronic data repositories, data accuracy	Reduction in errors; decision support; accurate medication reconciliation to facilitate guideline adherence; if available, an effective patient portal to facilitate patient/caregiver engagement
Patient monitoring devices: e.g., scales, implanted devices, bioimpedance devices	Accuracy; false alerts; 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	Need for more useful apps	Activity tracking, diet records, weight management, communication with HF team, prompts for medication adherence

AF = atrial fibrillation; HF = heart failure.

TABLE 9 Reasons for Nonadherence (World Health Organization)

Patient	Perceived lack of effect Poor health literacy Physical impairment (vision, cognition) Depression and social isolation Cognitive impairment
Medical condition	High HF regimen complexity Polypharmacy due to multiple comorbidities
Therapy	Frequency of dosing Polypharmacy Side effects
Socioeconomic	Out-of-pocket cost Difficult access to pharmacy Lack of support
Health system	Poor communication Silos of care No automatic refills

HF = heart failure.

different medications in different illnesses (66,67). Unintentional nonadherence is thought to be more common than intentional nonadherence (62,68). The ability of patients to follow treatment plans in an optimal manner is frequently compromised by more than 1 barrier (**Table 9**) (69,70).

Patients with HF are prescribed an average of 6 different medications, totaling more than 10 daily doses (71), with multiple new medications required to achieve GDMT (72). Consequently, interventions that target adherence in HF must be multidisciplinary, multifactorial, and tailored to the particular demands experienced by the patient.

General Approaches to Improving Adherence

The past decade has seen a transition from a hierarchical approach to a shared approach around medications, with greater focus on systems solutions (**Tables 10 and 11**). Appropriately, the language has shifted from patient "*compliance*" to "*adherence*" and now to "*activation,*" "*engagement,*" and "*empowerment*" (73). Patients need support; blame is counterproductive. Shared decision making, personal responsibility, and behavioral theories underlie many of the evolving approaches to enhancing medication adherence (74,75). 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.

Specific Patient Interventions

A number of adherence interventions have been developed and tested, some specifically for patients with HF (**Table 10**) (76). Formal assessments generally show benefit from a variety of adherence strategies. In a systematic review of 57 studies (77), interventions to enhance adherence for patients with HF included medication education, disease education, improved integration of care, self-management teaching, self-monitoring, and other strategic combinations. Interventions were associated with lower mortality (relative risk: 0.89; 95% confidence interval: 0.81 to 0.99) and hospital readmission (odds ratio: 0.79; 95% confidence interval: 0.71 to 0.89). A systematic review of 27 studies of mobile health interventions for cardiovascular diseases including HF (78) found that mobile health improved adherence to medical therapy (odds ratio: 4.51; $p<0.00001$), including both to pharmacological and nonpharmacological therapy (odds ratio: 3.86; $p<0.00001$).

System and Policy Solutions

Individual patients and clinicians must be supported by systems that promote adherence (79). Value-based insurance designs that tailor cost sharing to value are promising. The CMS Innovation Center aims to support patient adherence through the Beneficiary Engagement and Incentives models (https://innovation.cms.gov/initiatives/Beneficiary-Engagement/). 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. Automated screening and assessment tools can identify and target

TABLE 10 Interventions to Improve Adherence

Example	Scenario	Intervention
Medication education	Patient confusion about polypharmacy	Pharmacist and other clinician-based education
Disease education	Misunderstanding about HF and its management	Support groups, one-on-one disease teaching
Improved integration of care	Fragmented care due to multiple comorbidities	Team-based care (see answers to Issues 4 and 8), involvement of a case manager. Effective use of electronic health record and patient portal access
Self-management teaching	Challenges in salt avoidance or fluid restriction	Clinic and home-based nursing program.
Self-monitoring	Difficulties in achieving optimal fluid and weight monitoring.	Home-based monitoring programs for select patients, biomarker and/or (for those with implantable devices) impedance monitoring in the office, in select patients implantable pulmonary artery pressure monitoring.

TABLE 11 Ten Considerations to Improve Adherence

1. Capitalize on opportunities when patients are most disposed 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
   - Use decision aids when available
   - Ask patient how they learn best and provide education accordingly
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 caregiver a week at a time
   - Alarms for each time of the day medications are due
   - Smartphone M-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 problems
10. Monitor adherence and target patients at risk
   - Ask 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 databases (e.g., https://www.colorado.gov/pacific/dora/PDMP) 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

BNP = B-type natriuretic peptide; INR = international normalized ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

patients who are at the greatest risk for nonadherence (e.g., those with dementia, depression, homelessness, or drug use) (80). Health information technologies increasingly have the ability to assess rates of filling and refilling of prescriptions as well as to share these data across care providers and care settings.

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

Randomized clinical trials typically enroll highly selected patients, which results in uncertainty about the benefits and risks of patients not resembling those studied (Table 12). In the latter group of patients, only approximations of risks and benefits must guide therapy (81).

African Americans. Sacubitril/valsartan and ivabradine were tested in populations with few African Americans receiving HYD/ISDN. Thus, for this population, there are no data for the efficacy or safety of ARNI in patients with an indication for HYD/ISDN. Moreover, both HYD/ISDN and ARNI purportedly act via up-regulation of cGMP pathways, which may increase the risk of hypotension. Additionally, the risk of angioedema with ACEI and ARNI is particularly high in African-American patients (0.5% with ACEI and 2.4% with ARNI) (82); this risk, however, should not preclude initiation of these agents absent a documented history of angioedema.

Two options exist:

A. *Establish GDMT with ACEI/ARB, beta blocker, and an aldosterone antagonist, then switch to ARNI (akin to patients studied in PARADIGM); if stable, follow with HYD/ISDN if patient has persistent class III to IV symptoms with careful blood pressure monitoring.*

OR

B. *Establish GDMT with ACEI/ARB, beta blocker, and an aldosterone antagonist and then proceed with HYD/ISDN if persistent class III to IV symptoms (akin to patients studied in A-HeFT [20]); if stable, follow with ARNI substitution for ACEI/ARB with careful blood pressure monitoring.*

In the absence of randomized controlled data, it is reasonable to treat an African-American patient using either approach. However, the risk for hypotension with either strategy is uncertain. The treatment decision should be determined after an informed shared decision-making discussion with the patient, indicating the uncertainty of benefit.

HYD/ISDN are available as a fixed-dose combination or as individual medications. The ACC/AHA/HFSA guideline considers either as acceptable in this context.

Older adults, especially the very elderly, represent yet another conundrum. The upper range for inclusion in HF clinical trials has typically been age 75 ± 5 years; there are essentially no randomized data for drugs or devices in patients older than age 80 years. However, observational data support similar treatment benefits in older patients, but also suggest higher risks of adverse events (81). The pharmacokinetic profile for all GDMT as a function of age is not known. Optimal doses for older patients may be lower than those studied in trials or tolerated in younger patients. Nevertheless, targeting clinical trial recommended doses with close surveillance for adverse drug reactions is recommended.

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

TABLE 12 Specific Patient Cohorts in HF Care

Patient Cohorts	Description	Evidence-Based Recommendations	Risks	Uncertainties
African Americans	Self-identified	GDMT	ACEI, ARB, and ARNI: higher risk of angioedema compared with Caucasian patients Uncertain risk of hypotension when combining new drugs with HYD/ISDN	Expected outcomes of ARNI and/or ivabradine in those treated with HYD/ISDN
Older adults	≥75 years	Attempt to establish GDMT; however, doses utilized might need to be lower. Device therapy should be carefully considered due to possibly higher risk for complications in older patients	Falls, worsening of renal function, polypharmacy, costs, comorbidity	Efficacy of lower-dose GDMT on outcomes
Frail	Meets established frailty criteria (83)	GDMT as tolerated	Uncertain response to GDMT, increase risk for adverse drug reactions	Ability to impact 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.

present, exaggerates both morbidity and mortality. Standard assessments of frailty are available (83). We do not yet have evidence that any current therapies should be withheld or dose modified in the setting of frailty.

7. How to Manage Your Patients' Cost of Care for HF

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, while total costs (including indirect outlay) are estimated to increase from $31 billion to $70 billion (84). After hospital costs, the cost of cardiovascular medications is the second most important for patients with HF, accounting for 15.6% of direct costs (85).

Strategies to Reduce Costs. Several potential strategies to reduce the cost of HF have been identified (Table 13) (84). Implementing new therapies for the treatment of HF as well as improving utilization of existing therapies provide opportunities to reduce costs by slowing the progression of disease, thus reducing hospitalizations and death (86). Unfortunately, GDMT is still underutilized. Therefore, one significant challenge is how to effectively disseminate information that supports evidence-based therapies to healthcare professionals. Programs, such as accountable care organizations, alternative payment models, quality improvement initiatives as championed by the AHA Get With The Guidelines, and practice improvement as exemplified by the ACC Practice Innovation and Clinical Excellence (PINNACLE) and the AHA/ACC accreditation programs, are designed to identify candidates for evidence-based care, provide practitioners with useful reminders based on the guidelines, and continuously assess success achieved in providing GDMT (84). Care, including labs and imaging, should be coordinated among clinicians, preferably within 1 healthcare system.

Cost and Access to Medications. As mentioned previously, the cost and number of medications (polypharmacy) prescribed for HF continues to grow and presents a barrier to many patients. This barrier is compounded as most patients also have several comorbidities requiring additional medications. For example, diabetes is present in over 40% of all patients with HF, and the polypharmacy for diabetes treatment is also growing rapidly (87).

Whenever possible, generic equivalents for GDMT should be considered, although this is not feasible for some therapies such as ARNI or ivabradine. Costs can still be prohibitive even after following these cost-reduction measures. Pricing for common generic HF drugs (digoxin, carvedilol, and lisinopril) varies widely, even in a limited geographic area (88). This issue could have potential negative implications on adherence while increasing time and travel costs, and encourages patients to "shop around" for the best price, leading to obtaining drugs at multiple pharmacies. Use of multiple pharmacies negates having a single pharmacist who can oversee all of a patient's medications, identify potential drug interactions, perform medication synchronization and assess adherence, as well as provide disease management programs and ensure that vaccinations are current. Patients and clinicians should be encouraged to work with pharmacists to help identify copay assistance programs and request "price matching" when possible, should medication be found at a lower cost at another pharmacy.

TABLE 13 Tactics for Managing Costs of HF

■ Coordinate care (including laboratory results and imaging) among clinicians
■ Consider limitations of medication coverage (insurance, Medicaid, and so on) when prescribing
■ Use generic equivalents for GDMT whenever possible
■ Split tablets (without reducing dose) when appropriate
■ Work with a pharmacist 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; HF = heart failure.

TABLE 14 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 agent requested or additional testing required with indications supported by evidence and/or guideline statements where applicable; especially for testing requests, clinical judgment is an appropriate rationale
Address previous therapies used and rationale for switching or addition of treatment requested
Address known contraindications to use, adverse effects, and steps intended to minimize risk of drugs or procedures
Document when appropriate that delay or interruption 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 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; EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

TABLE 15 Important Pathophysiologic Targets in HFrEF and Treatments

Target	Therapy
Renin-angiotensin-aldosterone system	ACEI, ARBs, ARNI, aldosterone antagonists
Sympathetic nervous system	Beta blockers
Natriuretic and other vasodilator peptides	ARNI
Elevated heart rate (in sinus rhythm, on optimal beta-blocker dose)	Ivabradine, beta blocker
Balanced vasodilation and oxidative stress modulation in African Americans	HYD/ISDN
Arrhythmic sudden death	Implantable cardioverter-defibrillators
Ventricular dyssynchrony due to conduction abnormalities	Cardiac resynchronization therapy
Congestion	Diuretics (with chronic ambulatory pulmonary artery pressure monitoring in select patients)
Reduced aerobic capacity	Exercise training/cardiac rehabilitation

ACEI = angiotensin converting enzyme inhibitors; ARB =angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; HYD/ISDN = hydralazine/isosorbide dinitrate.

Having access to newer proven therapies can be even more daunting, as these drugs are typically associated with higher monthly costs and copays and frequently require more time and effort to obtain them; obtaining prior authorization from payers is a central aspect of this process. Recently, 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) (89).

Managing approvals for medications may be time consuming; tips for managing such processes are outlined in Table 14. 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 cardiovascular therapies when they were first adopted or approved (90–92). Pharmacists can help navigate insurance coverage and patient assistance programs to make sure that patients have access to the appropriate medications. Supplementary Tables 1 and 2 provide product-specific information for assistance in payment for newer HF therapies and appropriate use criteria to assist in the prior authorization process.

8. How to Manage the Increasing Complexity of HF

Ten Pathways and Principles to Guide Optimal Therapy

Therapeutic advances for the management of HFrEF have led to both improvements in outcomes for patients as well as increasing decision-making complexity for clinicians. As detailed in Table 15, modulation of 9 pathophysiological targets has been shown to improve symptoms and/or outcomes for patients with HFrEF.

These targets are related to direct treatments for HF and do not include management of comorbidities, which are discussed separately.

Several guiding principles can improve decision making and adherence with GDMT, which in turn, is likely to improve patient outcomes. For the purpose of this section, the term *target dose* is used to denote doses targeted in clinical trials and *optimal therapy* is used to denote treatment provided at the highest dose tolerated by a given patient up to the target dose. These principles apply for medication use in the absence of absolute contraindications.

Principle 1: Target doses are associated with best outcomes

Action: Attempt to achieve target doses of all recommended therapies, in the absence of contraindications and intolerance. Titration should occur even if the patient appears "stable"; change of ACEI or ARB to ARNI should not be reserved for onset of clinical decompensation.

Principle 2: When facing clinical scenarios that limit the ability to use target doses of all relevant therapies, a top priority should be to address the factor(s) limiting GDMT.

Scenario 1: *Worsening renal function or hyperkalemia.*

Action: Use less than target doses of ACEI/ARB/ARNI and discontinue aldosterone antagonist if estimated creatinine clearance <30 cc/min or serum K^+ >5.5 mEq/dL. Available data support a survival benefit even with low-dose ACEI, which may be the default choice in the setting of renal insufficiency and marginal blood pressure.

Scenario 2: *Symptomatic hypotension.*

Hypotensive symptoms may be due to overdiuresis, other vasoactive medication, autonomic dysfunction, or taking multiple medications together. All of these should be addressed prior to deciding to lower doses of evidence-based therapies.

Action: 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.

Principle 3: Optimal SNS modulation with target doses of beta blocker appears to have the best effect on HFrEF outcomes (cardiovascular mortality, pump failure mortality, and sudden cardiac death).

Scenario: *Patient is able to tolerate target doses of one and less than target doses of the other therapeutic agent.*

Action: Use target doses of beta blocker and, as necessary and if needed, lower doses of RAAS blockade.

Principle 4: Although high heart rate is associated with worse outcomes, not all medications that lower heart rate impact outcomes equally.

Scenario: *Patients in sinus rhythm with a heart rate >70 bpm.*

Action: Optimize beta-blocker doses, then consider ivabradine.

Important caveat: Persistent tachycardia may be a manifestation of severe cardiac dysfunction or non-cardiovascular disease, such as thyroid dysfunction.

Principle 5: African-American patients experience further benefit from the use of HYD/ISDN therapy.

Scenario: *African-American patients on optimal doses of all other therapies with persistent NYHA class III symptoms.*

Action: Add HYD/ISDN therapy.

Principle 6: Primary prevention device therapy and cardiac resynchronization therapy should only be considered after consistent use of optimal doses of all medications for 3 to 6 months.

Scenario: *Persistent low EF after at least 3 to 6 months of optimal doses of all medications.*

Action: Evaluate or refer for candidacy for implantable cardioverter-defibrillator and/or cardiac resynchronization therapy.

Principle 7: Symptomatic congestion should be treated with diuretics irrespective of other therapies.

Action: Use adequate (but avoid excessive) diuretic therapy to relieve congestion. In select patients with a volume status that is challenging to assess based on bedside clinical parameters, pulmonary artery catheterization and/or implanted pulmonary artery monitoring may be useful. Continuous hemodynamic monitoring with implantable devices may improve outcomes, but the infrastructure to support use and the optimal patient population for implantation must be addressed prior to widespread deployment.

Principle 8: Optimize team-based care.

Action: Employ multidisciplinary teams that include advanced practice nurses, clinical nurses, and pharmacists to help titrate GDMT. Team management also facilitates serial assessment and longitudinal care, including management of comorbidities.

Principle 9: Tolerability and side effects in part depend on how and when the therapy is prescribed.

Action: Start at low doses and up-titrate based on tolerability. Patient education and frequent contact will shorten the time to achieve optimal therapy.

Important caveat: Frequent visits may include telephone contact or virtual visits.

Principle 10: Focus on both the patients' symptoms and functional capacity as well as improving cardiac function.

Action: Reassess functional status and health state and refer appropriate patients when stable after recent hospitalization for HF for a formal supervised cardiac rehabilitation program.

Optimizing therapy not only involves addressing each of these 10 principles, but also involves dose titration, monitoring of response, interactions (e.g., hypotension, renal function), and side effects. This occurs over a minimum of months. Furthermore, multiple clinicians are often required (e.g., HF and electrophysiology experts, physicians, nurses, pharmacists, and other clinicians).

TABLE 16 Common Cardiac and Noncardiac 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 current ACC/AHA/HRS Guideline for the Management of Patients with Atrial Fibrillation (94)
Mitral Regurgitation	Strong	Intermediate	Refer to structural heart disease expert & treat according to current AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease (95)
Aortic Stenosis	Strong	Strong	Refer to structural heart disease expert & treat according to current AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease (95)
Hypertension	Uncertain	Strong for prevention	Treat according to current ACC/AHA hypertension guidelines
Dyslipidemia	Uncertain	Strong for prevention	Treat according to ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (96). Also see the nonstatin treatment of dyslipidemia clinical pathways (97)
Peripheral Vascular Disease	Moderate	None	Treat according to current AHA/ACC vascular guidelines (98)
Cerebrovascular Disease	Moderate	Weak	Treat according to current AHA stroke guidelines (99)
		Noncardiovascular	
Obesity	Moderate (inverse association)	Weak	Further data needed
Chronic Lung Disease	Strong	Weak	Optimize therapy, consider pulmonary consultation
Diabetes Mellitus	Strong	Intermediate	Optimize therapy, consider SGLT2 inhibitors, consider endocrine consult and follow current American Diabetes Association Standards of Medical Care in Diabetes (100)
Chronic Renal Disease	Strong	Weak	Optimize RAASi therapy, consider nephrology consult
Anemia	Moderate	Weak	Evaluate secondary causes, consider transfusing in severe cases
Iron Deficiency	Strong	Intermediate	Consider intravenous iron replacement for symptom improvement
Thyroid Disorder—hypo or hyper	Strong	Weak	Consider referral to endocrinologist and/or treatment
Sleep Disordered Breathing	Strong	Intermediate	Consider sleep study and treat severe obstructive sleep apnea to improve sleep quality, consider referring to sleep specialist

ACC = American College of Cardiology; AHA = American Heart Association; HRS = Heart Rhythm Society; RAASi = renin-angiotensin-aldosterone system inhibitor; SGLT2 = sodium-glucose co-transporter 2.

A team-based approach is an ideal strategy to attain optimal therapy for HF.

9. How to Manage Common Comorbidities

There is a bidirectional relationship between HF and comorbidities whereby,

1. The presence of one increases the risk of incident development of the other,

   AND

2. Prognosis for the patient is worse if both are present simultaneously.

Targeting comorbidities does not uniformly improve HF outcomes, although encouraging data are emerging with the new antidiabetic class of sodium-glucose cotransporter-2 inhibitors (93). Nevertheless, comorbidities should be evaluated and treated to improve overall patient outcomes, as these are the cause of a large proportion of hospitalizations in patients with HF and are associated with worsening symptoms and progression. Being on high alert for and appropriately evaluating these comorbidities is necessary, as their symptoms may overlap with those of HF. Appropriate referral to clinicians with relevant experience treating the various comorbidities is an important aspect of management. Table 16 classifies comorbidities into cardiac and noncardiac comorbidities, and provides guidance on appropriate management options.

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 nonpalliative 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 disease progresses.

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

Action: Meticulous management of HF therapies—particularly diuretics—is a critical component of symptom management and should continue through 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.

Action: Targeted specialty palliative care consultation can be helpful for especially complex decisions, refractory symptoms, and end of life.

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 (healthcare proxies) (2). Resources to assist patients in these difficult discussions may be useful (e.g., the Advanced Care Training module from HFSA: http://www.hfsa.org/module-9/). 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 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).

6. DISCUSSION AND IMPLICATION OF PATHWAY

The primary objective of this document 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 Decision Pathway should be applied only in the context of the most recent update to the AHA/ACC guideline for management of adults with chronic HF, and in this case, patients with HFrEF. No guideline, pathway, or algorithm should ever supersede clinical judgment.

Management of HFrEF often involves multidisciplinary care, may require complex decision making, and benefits from a solid foundation of knowledge to

manage these 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 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 rationally manage patients. As more evidence emerges, many topics will be clarified.

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70:776–803.

2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147–239.

3. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016;68:1476–88.

4. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005;112:2426–35.

5. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. J Am Coll Cardiol HF. 2014;2:663–70.

6. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002;106:920–6.

7. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.

8. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327:685–91.

9. Senni M, McMurray JJV, Wachter R, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. Eur J Heart Fail. 2016;18:1193–202.

10. McAlister F, Wiebe N, Ezekowitz J, et al. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med. 2009;150:784–94.

11. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875–85.

12. Swedberg K, Komajda M, Bohm M, et al. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose? Findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. J Am Coll Cardiol. 2012;59:1938–45.

13. Bohm M, Borer J, Ford I, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clin Res Cardiol. 2013;102:11–22.

14. Hickey A, Suna J, Marquart L, et al. Improving medication titration in heart failure by embedding a structured medication titration plan. Int J Cardiol. 2016;224:99–106.

15. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787–847.

16. Merit-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001–7.

17. CIBIS-II Investigators Committee. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13.

18. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med. 1996;334:1349–55.

19. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation. 1996;94:2807–16.

20. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049–57.

21. Testani JM, Stevens SR, Brisco MA, et al. Influence of diuretic dose and route of administration on loop diuretic efficiency: insights from the Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE-AHF) trial. J Card Fail. 2014;20:S40.

22. Baumwol J. "I Need Help"—a mnemonic to aid timely referral in advanced heart failure. J Heart Lung Transplant. 2017;36:593–4.

23. Karlström P, Alehagen U, Boman K, et al. Brain natriuretic peptide-guided treatment does not improve morbidity and mortality in extensively treated patients with chronic heart failure: responders to treatment have a significantly better outcome. Eur J Heart Fail. 2011;13:1096–103.

24. Weiner RB, Baggish AL, Chen-Tournoux A, et al. Improvement in structural and functional echocardiographic parameters during chronic heart failure therapy guided by natriuretic peptides: mechanistic insights from the ProBNP Outpatient Tailored Chronic Heart Failure (PROTECT) study. Eur J Heart Fail. 2013;15:342–51.

25. Fang JC, Ewald GA, Allen LA, et al. Advanced (stage D) heart failure: a statement from the Heart Failure Society of America Guidelines Committee. J Card Fail. 2015;21:519–34.

26. Langenickel TH, Dole WP. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure. Drug Discov Today: Ther Strateg. 2012;9:e131–9.

27. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011;377:658–66.

28. Costanzo MR, Stevenson LW, Adamson PB, et al. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. J Am Coll Cardiol HF. 2016;4:333–44.

29. Allen LA, Stevenson LW, Grady KL, et al. Decision making in advanced heart failure: a scientific statement from the American Heart Association. Circulation. 2012;125:1928–52.

30. Ehrmann Feldman D, Xiao Y, Bernatsky S, et al. Consultation with cardiologists for persons with new-onset chronic heart failure: a population-based study. Can J Cardiol. 2009;25:690–4.

31. Fanaroff AC, DeVore AD, Mentz RJ, et al. Patient selection for advanced heart failure therapy referral. Crit Pathw Cardiol. 2014;13:1–5.

32. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant. 2013;32:157–87.

33. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. J Heart Lung Transplant. 2006;25:1024–42.

34. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant. 2016;35:1–23.

35. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113:1424–33.

36. Chyu J, Fonarow GC, Tseng CH, et al. Four-variable risk model in men and women with heart failure. Circ Heart Fail. 2014;7:88–95.

37. Thorvaldsen T, Benson L, Stahlberg M, et al. Triage of patients with moderate to severe heart failure: who should be referred to a heart failure center? J Am Coll Cardiol. 2014;63:661–71.

38. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2017;318:713–20.

39. Vader JM, Rich MW. Team-based care for managing noncardiac conditions in patients with heart failure. Heart Fail Clin. 2015;11:419–29.

40. Cooper LB, Hernandez AF. Assessing the quality and comparative effectiveness of team-based care for heart failure: who, what, where, when, and how. Heart Fail Clin. 2015;11:499–506.

41. Institute of Medicine. Team-Based Care and the Learning Culture. In: Olsen LA, Saunders RS, et al., editors. Patients Charting the Course: Citizen Engagement and the Learning Health System: Workshop Summary. Washington, DC: National Academies Press (US), 2011:187–212.

42. Wever-Pinzon O, Drakos SG, Fang JC. Team-based care for advanced heart failure. Heart Fail Clin. 2015;11:467–77.

43. Rich MW, Beckham V, Wittenberg C, et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med. 1995;333:1190–5.

44. Phillips CO, Wright SM, Kern DE, et al. Comprehensive discharge planning with postdischarge support for older patients with congestive heart failure: a meta-analysis. JAMA. 2004;291:1358–67.

45. Koelling TM, Johnson ML, Cody RJ, et al. Discharge education improves clinical outcomes in patients with chronic heart failure. Circulation. 2005;111:179–85.

46. Kasper EK, Gerstenblith G, Hefter G, et al. A randomized trial of the efficacy of multidisciplinary care in heart failure outpatients at high risk of hospital readmission. J Am Coll Cardiol. 2002;39:471–80.

47. White SM, Hill A. A heart failure initiative to reduce the length of stay and readmission rates. Prof Case Manag. 2014;19:276–84.

48. Feltner C, Jones CD, Cene CW, et al. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. Ann Intern Med. 2014;160:774–84.

49. McAlister FA, Stewart S, Ferrua S, et al. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. J Am Coll Cardiol. 2004;44:810–9.

50. Rich MW, Gray DB, Beckham V, et al. Effect of a multidisciplinary intervention on medication compliance in elderly patients with congestive heart failure. Am J Med. 1996;101:270–6.

51. McDonald K, Ledwidge M, Cahill J, et al. Elimination of early rehospitalization in a randomized, controlled trial of multidisciplinary care in a high-risk, elderly heart failure population: the potential contributions of specialist care, clinical stability and optimal angiotensin-converting enzyme inhibitor dose at discharge. Eur J Heart Fail. 2001;3:209–15.

52. Slyer JT, Ferrara LR. The effectiveness of group visits for patients with heart failure on knowledge, quality of life, self-care, and readmissions: a systematic review protocol. JBI Libr Syst Rev. 2012;10:4647–58.

53. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med. 2011;364:2199–207.

54. Inglis SC, Clark RA, McAlister FA, et al. Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: Abridged Cochrane Review. Eur J Heart Fail. 2011;13:1028–40.

55. Chaudhry SI, Mattera JA, Curtis JP, et al. Telemonitoring in patients with heart failure. N Engl J Med. 2010;363:2301–9.

56. Koehler F, Winkler S, Schieber M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. Circulation. 2011;123:1873–80.

57. Hindricks G, Taborsky M, Glikson M, et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. Lancet. 2014;384:583–90.

58. Anand IS, Tang WH, Greenberg BH, et al. Design and performance of a multisensor heart failure monitoring algorithm: results from the multisensor monitoring in congestive heart failure (MUSIC) study. J Card Fail. 2012;18:289–95.

59. Masterson Creber RM, Maurer MS, Reading M, et al. Review and analysis of existing mobile phone apps to support heart failure symptom monitoring and self-care management using the Mobile Application Rating Scale (MARS). JMIR mHealth uHealth. 2016;4:e74.

60. Gardetto NJ. Self-management in heart failure: where have we been and where should we go? J Multidiscip Healthc. 2011;4:39–51.

61. Peterson PN, Shetterly SM, Clarke CL, et al. Health literacy and outcomes among patients with heart failure. JAMA. 2011;305:1695–701.

62. Riegel B, Dickson VV. A qualitative secondary data analysis of intentional and unintentional medication nonadherence in adults with chronic heart failure. Heart Lung. 2016;45:468–74.

63. Zhang Y, Baik SH. Race/ethnicity, disability, and medication adherence among Medicare beneficiaries with heart failure. J Gen Intern Med. 2014;29:602–7.

64. Choudhry NK, Avorn J, Glynn RJ, et al. Full coverage for preventive medications after myocardial infarction. N Engl J Med. 2011;365:2088–97.

65. Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. J Card Fail. 2011;17:664–9.

66. Garavalia L, Garavalia B, Spertus JA, et al. Exploring patients' reasons for discontinuance of heart medications. J Cardiovasc Nurs. 2009;24:371–9.

67. Dolansky MA, Hawkins MA, Schaefer JT, et al. Association between poorer cognitive function and reduced objectively monitored medication adherence in patients with heart failure. Circ Heart Fail. 2016;9:e002475.

68. Unni EJ, Farris KB. Unintentional non-adherence and belief in medicines in older adults. Patient Educ Couns. 2011;83:265–8.

69. World Health Organization. Adherence to long-term therapies: evidence for action. Available at: http://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed September 1, 2017.

70. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009;119:3028–35.

71. Masoudi FA, Baillie CA, Wang Y, et al. The complexity and cost of drug regimens of older patients hospitalized with heart failure in the United States, 1998-2001. Arch Intern Med. 2005;165:2069–76.

72. Allen LA, Fonarow GC, Liang L, et al. Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures. Circulation. 2015;132:1347–53.

73. Fumagalli LP, Radaelli G, Lettieri E, et al. Patient empowerment and its neighbours: clarifying the boundaries and their mutual relationships. Health Policy. 2015;119:384–94.

74. Rosenstock IM, Strecher VJ, Becker MH. Social learning theory and the Health Belief Model. Health Educ Q. 1988;15:175–83.

75. Bandura A. Human agency in social cognitive theory. Am Psychol. 1989;44:1175–84.

76. Yoon J, Ettner SL. Cost-sharing and adherence to antihypertensives for low and high adherers. Am J Manag Care. 2009;15:833–40.

77. Ruppar TM, Cooper PS, Mehr DR, et al. Medication adherence interventions improve heart failure mortality and readmission rates: systematic review and meta-analysis of controlled trials. J Am Heart Assoc. 2016;5:e002606.

78. Gandhi S, Chen S, Hong L, et al. Effect of mobile health interventions on the secondary prevention of cardiovascular disease: systematic review and meta-analysis. Can J Cardiol. 2017;33:219–31.

79. Cutler DM, Everett W. Thinking outside the pillbox—medication adherence as a priority for health care reform. N Engl J Med. 2010;362:1553–5.

80. MacLaughlin EJ, Raehl CL, Treadway AK, et al. Assessing medication adherence in the elderly: which tools to use in clinical practice? Drugs Aging. 2005;22:231–55.

81. Colvin M, Sweitzer NK, Albert NM, et al. Heart failure in non-Caucasians, women, and older adults: a white paper on special populations from the Heart Failure Society of America Guideline Committee. J Card Fail. 2015;21:674–93.

82. Kaplan A, Streefkerk H, Thorburn C, et al. Comparison of angioedema in heart failure patients treated with Sacubitril/Valsartan or Enalapril in the PARADIGM-HF Study. J Cardiac Fail. 2016;22:S66–7.

83. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol. 2014;63:747–62.

84. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6:606–19.

85. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics–2016 update: a report From the American Heart Association. Circulation. 2016;133:e38–360.

86. Voigt J, Sasha John M, Taylor A, et al. A reevaluation of the costs of heart failure and its implications for allocation of health resources in the United States. Clin Cardiol. 2014;37:312–21.

87. Echouffo-Tcheugui JB, Xu H, DeVore AD, et al. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure: findings from Get With The Guidelines–Heart Failure registry. Am Heart J. 2016;182:9–20.

88. Hauptman PJ, Goff ZD, Vidic A, et al. Variability in retail pricing of generic drugs for heart failure. JAMA Intern Med. 2017;177:126–8.

89. American Academy of Child & Adolescent Psychiatry. Prior authorization and utilization management reform principles. Available at: https://www.aacap.org/App_Themes/AACAP/docs/homepage/2017/PA_Reform_Principles.pdf. Accessed February 12, 2017.

90. Gaziano TA, Fonarow GC, Claggett B, et al. Cost-effectiveness analysis of Sacubitril/Valsartan vs Enalapril in patients with heart failure and reduced ejection fraction. JAMA Cardiol. 2016;1:666–72.

91. Ollendorf DA, Sandhu AT, Pearson SD. Sacubitril-valsartan for the treatment of heart failure: effectiveness and value. JAMA Intern Med. 2016;176:249–50.

92. Kansal AR, Cowie MR, Kielhorn A, et al. Cost-effectiveness of ivabradine for heart failure in the United States. J Am Heart Assoc. 2016;5:e003221.

93. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J. 2016;37:1526–34.

94. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014;130:2071–104.

95. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70:252–89.

96. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889–934.

97. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70:1785–822.

98. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;69:e71–126.

99. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160–236.

100. American Diabetes Association. Standards of medical care in diabetes-2017. Available at: https://professional.diabetes.org/sites/professional.diabetes.org/files/media/dc_40_s1_final.pdf. Accessed September 1, 2017.

KEY WORDS Expert Consensus Decision Pathway, angiotensin receptor–neprilysin inhibitor, beta blockers, Expert Consensus Decision Pathway, heart failure, ivabradine

APPENDIX 1: AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2017 ACC EXPERT CONSENSUS DECISION PATHWAY FOR OPTIMIZATION OF HEART FAILURE TREATMENT

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 Clinical 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 following table, and peer reviewer information is disclosed in Appendix B. Additionally, to ensure complete transparency, authors' comprehensive disclosure information—including RWI not pertinent to this document—is available online (See Online Appendix). Disclosure information for the ACC Task Force on Clinical Expert Consensus Decision Pathways is also available Online, as is the ACC disclosure policy for document development.

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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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.

CEC = Clinical Events Committee; DSMB = Data Safety Monitoring Board; JACC = *Journal of the American College of Cardiology*.

APPENDIX 2: PEER REVIEWER INFORMATION—2017 ACC EXPERT CONSENSUS DECISION PATHWAY FOR OPTIMIZATION OF HEART FAILURE TREATMENT

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 as Online Appendix 2.

Reviewer	Representation	Employment
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APPENDIX 2. CONTINUED

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AAHFN = American Association of Heart Failure Nurses; ABC = Association of Black Cardiologists; ACC = American College of Cardiology; ACEP = American College of Emergency Physicians; AHA = American Heart Association; APhA = American Pharmacists Association; ASE = American Society of Echocardiography; BOG = Board of Governors; LVAD = left ventricular assist device; PCNA = Preventive Cardiovascular Nurses Association; SAEM = Society for Academic Emergency Medicine.

APPENDIX 3: ABBREVIATIONS

ACC = American College of Cardiology
ACEI = angiotensin-converting enzyme inhibitor
AHA = American Heart Association
ARB = angiotensin receptor blocker
ARNI = angiotensin receptor-neprilysin inhibitor
BNP = B-type natriuretic peptide
EF = ejection fraction
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
NT-proBNP = N-terminal pro-B-type natriuretic peptide
NYHA = New York Heart Association