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REVIEW

Summary and Comparison of the 2022 ACC/AHA/HFSA and 2021 ESC Heart Failure Guidelines

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ABSTRACT

The guidelines released by the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) in 2022 and those released in 2021 by the European Society of Cardiology (ESC) play a crucial role in offering evidence-based recommendations for the diagnosis and management of heart failure (HF). This comprehensive review aims to provide an overview of these guidelines, incorporating insights from relevant clinical trials. While there is considerable alignment between the two sets of guidelines, certain notable differences arise due to variations in publication timelines, which we will outline. By presenting this summary, our objective is to empower clinicians to make informed decisions regarding HF management in their own practice, and facilitate the development of more harmonized guidelines in the future.

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Abbreviations

A-HeFT	African-American Heart Failure Trial
AVID	Antiarrhythmics versus implantable defibrillators
BBmeta-HF	Beta-blockers in Heart Failure Collaborative Group
BLOCK-HF	Biventricular versus right ventricular pacing in heart failure
CANVAS program	Canagliflozin Cardiovascular Assessment Study
CARE-HF	Cardiac resynchronization heart failure
CASH	Cardiac Arrest Study Hamburg
CHARM	Candesartan in heart failure-assessment reduction in mortality and morbidity
CIDS	Canadian Implantable Defibrillator Study
COMPANION	Comparison of medical therapy, pacing, and defibrillation in heart failure
DANISH	Defibrillator implantation in patients with nonischemic systolic heart failure

DAPA-HF	Dapagliflozin and prevention of adverse outcomes in heart failure
DECLARE-TIMI 58	Dapagliflozin effect on CardiovascuLAR events-thrombolysis in myocardial infarction 58
DEFINITE	Defibrillators in non-ischemic cardiomyopathy treatment evaluation
EMPA-REG	Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients
EMPEROR-Preserved	Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction
EMPEROR-Reduced	EMPagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction
MADIT-II	Multicenter automated defibrillator implantation trial II
MADIT-CRT	Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy
MIRACLE	Multicenter insync randomized clinical evaluation
OUTSMART-HF	Routine versus selective cardiac magnetic resonance for patients with non-ischemic heart failure
PARADIGM-HF	Prospective comparison of ARNI [angiotensin receptor–neprilysin inhibitor] With ACEI [angiotensin-converting enzyme inhibitor] to determine impact on global mortality and morbidity in heart failure
PARAGON-HF	Prospective comparison of ARNi with ARB global outcomes in heart failure with preserved ejection fraction
PIONEER-HF	Comparison of sacubitril/valsartan versus enalapril on effect on NT-pro BNP [N-terminal pro-B type natriuretic peptide] in patients stabilized from an acute HF episode
RAFT	Resynchronization-defibrillation for ambulatory heart failure
REVERSE	Resynchronization reverses remodeling in systolic left ventricular dysfunction
SCD-HEFT	Sudden cardiac death in heart failure trial
SHIFT	Ivabradine and outcomes in chronic heart failure
SPRINT	Systolic blood pressure intervention trial
STOP-HF	The St. Vincent's screening to prevent heart failure
TOPCAT	Treatment of preserved cardiac function heart failure with an aldosterone antagonist
V-HeFT I	Vasodilator heart failure trial
VICTORIA	Vericiguat global study in subjects with heart failure with reduced ejection fraction

Key Summary Points

The key changes in the 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) heart failure (HF) guidelines include updated staging of HF, and recommendations on treatments such as sodium glucose cotransporter-2 inhibitor (SGLT2i), mineralocorticoid receptor antagonists (MRA), and angiotensin receptor-neprilysin inhibitors (ARNIs), especially in HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF).

There are minimal differences between the 2022 ACC/AHA/HFSA HF guideline and the 2021 European Society of Cardiology (ESC) HF guideline, although the key differences in staging and medication recommendation come from the time difference of publication.

INTRODUCTION

Guidelines for the diagnosis and management of heart failure (HF) were jointly published by the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA) in 2022 [1]. These replaced the 2013 American College of Cardiology Foundation (ACCF)/AHA guidelines [2] and its subsequent 2017 update [3]. The key changes in the new guidelines that are outlined in the "top 10 take-home messages" include an updated staging of HF, and recommendations on treatments such as sodium glucose cotransporter-2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists (MRA), and angiotensin receptor-neprilysin inhibitors (ARNIs), especially in HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF) [1]. The following review will outline these changes, as well as highlight key differences between the ACC/AHA/HFSA 2022 guidelines and the 2021 European Society of Cardiology (ESC) HF guideline [4]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EVALUATION AND DIAGNOSIS OF HF

The ACC/AHA/AFSA and ESC have similar recommendations for the diagnosis of HF (see Table 1 for comparison). Both ACC/AHA/AFSA and ESC guidelines highlight the importance of history and examination in the diagnosis of HF and its etiology, as well as in the setting of decompensation to identify a cause of clinical deterioration [1, 4]. All patients with a new diagnosis of HF should have a three-generation pedigree analysis to assess family history of cardiomyopathy. The ACC/AHA/HFSA guidelines highlight the findings from the PARADIGM-HF trial showing changes in markers of clinical congestion are associated with quality of life and prognostic information independent of natriuretic peptides or the Meta-Analysis Global

Table 1 Summary of recommendation class for investigations of HF

Recommendation	ACC/AHA/HFSA	ESC
Initial investigations		
For patients who are diagnosed with HF, laboratory evaluation should include full blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose and HbA1c, lipid profile, liver function tests, iron studies, and thyroid-stimulating hormone to optimize management	1	1
For all patients with HF, a 12-lead ECG should be performed	1	1
BNP or NT-proBNP		
Patients presenting with dyspnea	1	
In patients with chronic HF for risk stratification	1	1
In patients hospitalized with HF to establish prognosis	1	
In patients at risk of developing HF, BNP can be used as a screening tool followed by team-based care to prevent development of LV dysfunction or new-onset HF	2a	
A pre-discharge BNP can be useful to inform the trajectory of the patient and establish a postdiagnosis prognosis	2a	
Genetic testing		
In first-degree relatives of selected patients with genetic or inherited cardiomyopathies for early detection and prompt management	1	
In patients with nonischemic cardiomyopathy	2a	

Table 1 continued

Recommendation	ACC/AHA/HFSA	ESC
Chest X-ray		
Suspected or new-onset HF, or those presenting with acute decompensated HF	1	1
TTE		
During initial evaluation of suspected or newly diagnosed HF	1	1
In patients with HF who have significant clinical change, or who have received GDMT and are being considered for invasive procedures or device therapy	1	
If TTE is inadequate, alternative imaging (e.g., CMR, cardiac CT, radionucleotide imaging) is recommended for the assessment of LVEF	1	1
CMR		
In patients with HF or cardiomyopathy, CMR can be useful for diagnosis and management	2a	
For the characterization of myocardial tissue in suspected infiltrative disease, Fabry disease, inflammatory disease, LV non-compaction, amyloid, sarcoidosis, iron overload		1
Cardiopulmonary exercise testing		
In selected ambulatory patients to determine appropriateness of advanced treatments (e.g., LV assist device, heart transplant)	1	1
In ambulatory patients to assess functional capacity	2a	
In ambulatory patients to assess cause of dyspnea	2a	2a
Invasive evaluation		
Endomyocardial biopsy may be useful when specific diagnosis is suspected that would influence therapy	2a	2a
Right heart catheterization in selected patients with HF with persistent or worsening symptoms, signs, diagnostic parameters, and in whom hemodynamics are uncertain	2a	
Right heart catheterization in patients with severe HF being evaluated for heart transplant or mechanical circulatory support		1
Other imaging		
In patients with HF, an evaluation for possible ischemic heart disease can be useful to identify the cause and guide management	2a	
In patients with HF and CAD who are candidates for coronary revascularization, non-invasive stress imaging may be considered for detection of myocardial ischemia to help guide coronary revascularization	2b	2b
No imaging		

Table 1 continued

Recommendation	ACC/AHA/HFSA	ESC
In patients with HF in the absence of: (1) clinical status change, (2) treatment interventions that might have a significant effect on cardiac function, or (3) candidacy for invasive procedures or device therapy, routine repeat assessment of LV function is not indicated	3	

BNP brain natriuretic peptide, *CAD* coronary artery disease, *CMR* cardiac magnetic resonance, *CT* computed tomography, *ECG* electrocardiography, *HbA1c* hemoglobin A1c, *GDMT* guideline-directed medical therapy, *HF* heart failure, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *NT-Pro-BNP* N-terminal-Pro-BNP, *TTE* transthoracic echocardiography

Group in Chronic Heart Failure (MAGGIC) risk score [5].

In addition to history and examination, both guidelines concur on the need for several investigations, including:

- Electrocardiogram (ECG)
- Blood tests: Natriuretic peptides, serum urea and electrolytes, creatinine, full blood count, lipid profile, iron studies, liver and thyroid function tests are recommended to differentiate HF from other conditions, provide prognostic information, and guide potential therapy.
- Transthoracic echocardiography (TTE): This aids in determining the left ventricular ejection fraction (LVEF) and identifying the underlying etiology of HF.
- Chest X-ray: This provides supportive evidence of HF and aids in ruling out alternative causes of breathlessness.

Cardiac Magnetic Resonance (CMR)

Cardiac magnetic resonance (CMR) imaging is recommended by both guidelines in the assessment of myocardial structure and function in patients where TTE image quality is inadequate. The ESC guidelines recommend CMR for characterization of myocardial tissue in suspected infiltrative disease, Fabry disease, inflammatory disease (e.g., myocarditis), left ventricular (LV) non-compaction, amyloid, sarcoidosis, and haemochromatosis (class of recommendation [CoR]: 1) [4]. The ACC/AHA/HFSA guidelines find that CMR is reasonable in patients with non-ischemic cardiomyopathy if the diagnosis is uncertain based on the recent OUTSMART-HF trial, although with a lower strength of recommendation than the ESC guidelines (CoR: 2a) [6]. ESC recommends that CMR may be useful for assessment of myocardial ischemia in patients with dilated cardiomyopathy who would be suitable for coronary revascularization (CoR: 2b). In comparison, the ACC/AHA/HFSA guidelines recommend the same may be reasonable (CoR:2b).

Investigating for Underlying Coronary Artery Disease

The ESC and ACC/AHA/HFSA guidelines both suggest non-invasive stress imaging (such as CMR, stress echocardiography, single-photon emission computed tomography [SPECT]) to assess inducible ischemia and viability for patients with coronary artery disease (CAD) who are suitable for coronary revascularization.

For patients with a low to intermediate pre-test probability of CAD or those with inconclusive non-invasive stress tests, computed tomography coronary angiography (CTCA) may be considered to rule out a diagnosis of CAD. Invasive coronary angiography is recommended for patients with persistent angina despite pharmacological therapy and those with an intermediate to high pre-test probability of CAD and heart failure with reduced ejection fraction (HFrEF) who are deemed suitable for coronary revascularization.

Endomyocardial Biopsy

Both sets of guidelines align on the recommendation that endomyocardial biopsy should only be performed when a specific diagnosis is sought, and when that diagnosis would significantly impact management, particularly in cases of rapidly progressive HF or worsening ventricular function despite treatment. This approach ensures that the risks of the procedure are justified by the potential impact on guiding the appropriate management decisions.

Table 2 Stages of HF

Stage	Definition
A	Patients at risk for HF but without current or previous symptoms/signs of HF and without structural/functional heart disease or abnormal biomarkers. This includes patients with hypertension, cardiovascular disease, diabetes, obesity, exposure to cardiotoxic agents, genetic variant cardiomyopathy, or a family history of cardiomyopathy
B	Patients without current signs or previous symptoms/signs of HF but evidence of one of the following: Structural heart disease Evidence of increased filling pressures Risk factors and Increased natriuretic peptide levels or Persistently elevated cardiac troponin
C	Patients with current or previous symptoms/signs of HF
D	Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT

HF heart failure, *GDMT* guideline-directed medical therapy

DEFINITION/STAGING

The 2022 ACC/AHA/HFSA guidelines defined for the first time the "Stages of Heart Failure" based on the Universal Definition of HF [7] (see Table 2). The Universal Definition of HF was developed in 2020 by a writing committee which comprised of members of the HFSA, the Heart Failure Association of the European Society of Cardiology (HFA/ESC), and the Japanese Heart Failure Society (JHFS), and released in 2021, following the release of the 2021 ESC guidelines. Four stages of HF (A, B, C, and D) were defined, with stages A and B occurring in asymptomatic individuals. Stage A is defined as patients at risk of HF without suggestive symptoms or signs, and without structural or functional heart disease or abnormal biomarkers such as natriuretic peptides. This includes patients with hypertension, cardiovascular (CV) disease, obesity, exposure to cardiotoxic agents, genetic variant cardiomyopathy, or family history of cardiomyopathy. The goal of treatment for these patients is to modify risk factors to prevent progression of heart disease. Stage B, pre-HF, is defined as patients who have never had symptoms or signs of HF but do have evidence of one or more of the following: structural heart disease; increased left atrial (LA) or LV filling pressures; increased natriuretic peptide levels or persistently elevated troponin levels. Patients with pre-HF are managed by treating risk factors and structural heart disease to prevent development of symptomatic HF. Stage C, symptomatic HF, and stage D, advanced HF, are treated based on their classification of HF by LVEF with the aim of reducing symptoms, morbidity, and mortality.

ESC and ACC/AHA/HFSA guidelines use the same classification of HF by LVEF as shown in Table 3, however the ACC/AHA/HFSA guideline introduces a newly defined condition, HF with improved ejection fraction (HFimpEF). HFimpEF is defined as HF with previous LVEF $< 40\%$ and a follow up measure of LVEF $> 40\%$. It was previously known as HF with preserved ejection fraction-improved. HFimpEF is more appropriate terminology, since improvement does not

Table 3 Classification of HF by LVEF

Type of HF according to LVEF	ACC/AHA/HFSA 2022 criteria	ESC 2021 criteria
HFrEF	LVEF $\leq$ 40%	LVEF $\leq$ 40%
HFimpEF	Previous LVEF $\leq$ 40% and a follow-up LVEF > 40%	N/A
HFmrEF	LVEF 41–49% Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)	LVEF 41–49%
HFpEF	LVEF $\geq$ 50% Evidence of spontaneous or provokable increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)	LVEF $\geq$ 50% Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides

HF heart failure, *HFimpEF* heart failure with improved ejection fraction, *HFmrEF* heart failure with mildly reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *GDMT* guideline-directed medical therapy, *LV* left ventricular, *LVEF* left ventricular ejection fraction

necessarily represent normalization of LV function or resolution of the cardiomyopathic process and highlights the importance of continuing treatment as per HFrEF recommendations to prevent deterioration in symptomatic status or LVEF [8].

The diagnosis of HFpEF is often challenging, requiring evidence of spontaneous or provokable increased LA or LV filling pressures as evidenced by elevated levels of natriuretic peptides (brain natriuretic peptide [BNP] or N-terminal-Pro-BNP [NT-Pro-BNP]), or a combination of echocardiographic parameters such as an elevation in the ratio of mitral inflow velocity to mitral annular excursion ($E/e' \geq 15$), or a reduction in the latter, as well as increased LA volume or pulmonary hypertension. The H_2FPEF score [9], described in the ACC/AHA/HFSA guideline, and HFA-PEFF score [10], described in the ESC guideline, have been proposed to aid diagnosis, although the ESC suggests a simplified diagnostic approach that is yet to be critically assessed or compared to the score-based algorithms [4].

STAGE A: PATIENTS AT RISK FOR HF

Diet, Exercise, and Blood Pressure Recommendations

The ACC/AHA/HFSA guidelines provide detailed recommendations on management for patients at risk for HF (stage A). While not strictly categorized as a stage of HF, the ESC guidelines do also provide a guide to prevention of HF for those with risk factors. Patients at risk of HF (presence of hypertension, diabetes, or vascular disease) should have a screening BNP with intervention if levels are > 50 pg/ml, as it was found to reduce the composite endpoint of asymptomatic LV dysfunction in the STOP-HF trial [11]. Non-pharmacological strategies have been associated with a lower lifetime risk of developing HF. The guidelines suggest regular physical activity of at least 30 min of walking 5 days/week, or 2.5 h/week of moderate intensity exercise in addition to 75 min of vigorous activity per week [12]. Diets such as the Mediterranean, whole grain, plant-based diet,

and the DASH (Dietary Approaches to Stop Hypertension) diet [12], as well as diets low in salt (< 1500 mg/day) [12] and a BMI of less than 30 [13] have also been found to reduce progression to symptomatic HF. Hypertension control reduces the risk of developing HF and blood pressure should be targeted at < 130/80 mmHg based on the SPRINT trial, which showed a systolic blood pressure (SBP) goal of < 120 mmHg decreased incident HF by 23% and mortality by 23% compared with an SBP goal of < 140 mmHg [14]. This trial included 9361 participants who were ≥ 50 years old and had hypertension with SBP ≥ 130 mmHg and at least one risk factor for heart disease (age > 75 years old, a Framingham Risk Score for 10-year CV disease risk ≥ 15%, chronic kidney disease, or clinical or subclinical CV disease), and followed them for 5 years to compare the safety and efficacy of intensive lowering of SBP.

SGLT2i Therapy in Patients with Diabetes

The ACC/AHA/HFSA guidelines recommend that patients with type 2 diabetes mellitus (T2DM) and either established CV disease or at high risk of CV disease should be commenced on SGLT2i therapy to improve survival and prevent HF hospitalizations. This recommendation is based on several trials. The CANVAS program compared canagliflozin (n = 5795) to placebo (n = 4347) in patients with T2DM and CV disease or high risk of CV disease [15]. In the primary prevention group, canagliflozin significantly reduced the primary endpoint (incidence of CV death, myocardial infarction (MI), or stroke), HF hospitalizations and progression to albuminuria. Concerns raised in this trial, including increased risk of lower-limb amputations, have not been replicated since, and the black box warning has been removed. The DECLARE-TIMI 58 compared dapagliflozin (n = 8582) to placebo (n = 8578) in patients with T2DM and established CV disease or multiple risk factors. For patients with high CV risk, it was noninferior, but not superior, in reducing major adverse cardiac events, but there was a reduction in blood pressure (BP), HF hospitalizations and improved renal outcomes [16]. The EMPA-REG OUTCOME trial compared empagliflozin (10 mg, n = 2345; 25 mg, n = 2342) to placebo (n = 2333) in patients with T2DM and high risk for CV events and found that empagliflozin resulted in a significant mortality benefit, and was associated with a reduction in HF and all-cause hospitalizations in patients with and without baseline HF [17].

STAGE B: PATIENTS WITH PRE-HF

All recommendations for patients with stage A HF also apply to those with stage B HF. ESC guidelines do not distinguish between stage A and stage B in their recommendations for prevention of HF. Identifying patients with stage B HF allows an opportunity to initiate lifestyle modification and pharmacological therapy that may prevent or delay the transition to symptomatic HF (stage C/D). This is crucial as the Framingham studies have shown a 60% increased risk of death in patients with asymptomatic low LVEF compared to those with normal LVEF, and almost half of these patients remain without symptomatic HF at death [18]. Beneficial pharmacotherapy for asymptomatic LV systolic dysfunction, such as inhibitors of the renin–angiotensin system (RAAS) and beta-blockers, have been predominantly observed in patients with reduced LVEF (LVEF < 35–40%). As such, the recommendations are that patients with LVEF ≤ 40% should be commenced on an angiotensin-converting enzyme inhibitor (ACEi) or, if intolerant, an angiotensin receptor blocker (ARB) to prevent symptomatic HF and reduce mortality, even if asymptomatic. These treatment options are discussed in more detail in the stage C section.

In patients with a recent or remote history of MI, or acute coronary syndrome and LVEF ≤ 40%, statins should be used to prevent symptomatic HF and adverse CV events, and evidence-based beta-blockers should be used to reduce mortality. Asymptomatic patients with an ischemic cardiomyopathy with LVEF ≤ 30%, predicted > 1 year survival and > 40 days post-MI should be considered for an implantable cardiac defibrillator (ICD) to reduce

Table 4 Side effects of HF medications [36]

Medication	Side effect
ACEi	Hypotension
	Cough
	Hyperkalemia
	Renal impairment
	Angioedema
	Rash
	Abnormal LFTs
ARB	First-dose hypotension
	Hyperkalemia
	Diarrhea
	Dyspepsia
	Renal impairment
	Nasal congestion
	Hypersensitivity reactions
	Abnormal LFTs
ARNi	Hyperkalemia
	Raised serum creatinine ± renal impairment
	Hypotension
	Cough
	Anemia
	Angioedema
Beta-blocker	Bradycardia
	Orthostatic hypotension
	Transient worsening of heart failure
	Bronchospasm
	Rare: heart block, impotence, hypersensitivity, thrombocytopenia, abnormal LFTs
MRA	Hyperkalemia
	Hyponatremia + hypochloremia
	Nausea and vomiting
	Gastrointestinal cramps and diarrhea
	Gynecomastia
	Menstrual irregularities
	Renal impairment
	Rare: agranulocytosis, hepatotoxicity, cutaneous vasculitis
SGLT2i	Genital infections
	UTI
	Dyslipidemia
	Hypoglycemia (when used with sulfonylurea or insulin)
	Increased hematocrit
	Increased serum creatinine (related to volume depletion, reversible)
	Volume depletion (hypotension, dehydration)
	Euglycemic ketoacidosis
	Rare: perineal necrotizing fasciitis
Digoxin	Anorexia, nausea, and vomiting
	Blurred vision
	Bradycardia
	Rash
	ECG changes – shortened QRS complexes, atrial or ventricular extrasystoles, paroxysmal atrial tachycardia with AV block, ventricular tachycardia or fibrillation, heart block
	Rare: thrombocytopenia, seizures, psychosis

Table 4 continued

Medication	Side effect
Ivabradine	Transient areas of enhanced brightness in the visual field
	Bradycardia
	Ventricular extrasystoles
Vericiguat	Hypotension
	Anemia
	Nausea, vomiting, and dyspepsia
	Headache

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ARNi* angiotensin receptor–neprilysin inhibitor, *LFTs* liver function tests, *MRA* mineralcorticoid receptor antagonist, *SGLT2i* sodium glucose cotransporter-2 inhibitor, *UTI* urinary tract infection

mortality. This is based on the MADIT-II trial which showed a 31% relative risk reduction in all-cause mortality in patients post-MI with LVEF $\leq$ 30% receiving a prophylactic ICD compared with standard care [19]. Nondihydropyridine calcium channel blockers and thiazolidinediones have been found to be harmful in patients at risk of HF and should be ceased.

STAGE C: SYMPTOMATIC HF

All measures described in stages A and B HF are recommended for patients in stage C.

Non-pharmacological Management

Non-pharmacological management of HF is a focus of the ACC/AHA/HFSA 2022 guidelines with a strong recommendation for regular physical activity and a moderate recommendation for a low-salt diet and cardiac rehabilitation.

Pharmacotherapy for Patients with HFREF

Diuretics are recommended in patients with evidence of fluid retention for symptomatic benefit. The four pillars of HF management (RAAS inhibition, beta-blockade, MRA, and SGLT2i) should be initiated in all patients with HFrEF as tolerated. The ACC/AHA/HFSA guidelines suggest initiation and titration of these agents should be individualized based on the patient's symptoms and signs, function, tolerance, renal function, and comorbidities, however they should be titrated up to the maximum tolerated dose. Optimal benefit comes from initiating all four therapies, rather than sequential maximizing of agents one at a time. The side effects of HF medications are summarized in Table 4.

RAAS Inhibition

Inhibition of the RAAS is recommended to reduce morbidity and mortality, with both ACC/AHA/HFSA and ESC guidelines recommending an ARNi as first-line therapy in hospitalized patients with acute HF or following a trial of an ACEi or ARB in outpatients to ensure the patient tolerates RAAS inhibition. If patients are already treated with an ACEi, a 36-h washout period is recommended prior to introducing the ARNi to reduce the risk of angioedema. Evidence for the use of ARNi is growing with the PARADIGM-HF trial finding sacubitril-valsartan reduced the composite endpoint of CV death and HF hospitalisation by 20% when compared to enalapril in patients with symptomatic HF [5]. Biochemically, the PIONEER-HF trial showed that sacubitril-valsartan reduced natriuretic peptide levels when compared to enalapril [20] and structurally, a meta-analysis showed an improvement in LV modelling parameters [21]. ACEi, or ARB if the patient is intolerant to ACEi, are recommended if an ARNi is not tolerated. The key side effects of ACEi are hypotension, hyperkalemia, angioedema, and cough secondary to accumulation of bradykinin and substance P. ARB's have the same side effects as ACEi, however are less likely to cause angioedema and do not cause due to their

mechanism of action. Treatment with beta-blockers reduces the risk of morbidity and mortality in patients with HFrEF, in addition to treatment with an ACEi and diuretic.

Beta Blockade

Beta-blockers have been shown to improve LVEF, reduce symptoms of HF, and improve prognosis. Patients should be initiated on the lowest dose of beta-blocker when euvolemic and clinically stable, and gradually uptitrated to the maximal tolerated dose. Side effects of beta-blockers include bradycardia, orthostatic hypotension, and bronchospasm. They should be used with caution in patients with asthma [22].

MRAs

MRAs are recommended in addition to ACEi and beta-blockers to improve symptoms and reduce all-cause mortality, HF hospitalizations, and sudden cardiac death in all patients with HFrEF. Electrolytes need to be closely monitored as patients may develop hyperkalemia, hyponatremia, and/or hypochloremia while taking MRAs. Gynecomastia is more common in spironolactone than eplerenone, due to its antiandrogen effect [23].

SGLT2i

SGLT2i therapy is a new addition to the pillars of HF management. The DAPA-HF trial [24] and EMPEROR-Reduced trial [25] are landmark studies that demonstrated benefit of SGLT2i versus placebo. Importantly, survival benefits were seen in patients with and without diabetes. Specifically, the DAPA-HF trial, which enrolled patients with HFrEF (irrespective of diabetes status), found a 26% reduction in the primary endpoint (CV death or hospitalization) in patients receiving dapagliflozin compared to those receiving standard care alone. Similarly, the EMPEROR-Reduced trial, which compared empagliflozin with placebo, found a reduction of 25% in the primary endpoint (CV death or HF hospitalization). Secondary outcomes indicate SGLT2i improve HF symptoms, physical function, and quality of life, and led to fewer hospitalizations and an improvement in all-cause mortality [25]. The diuretic/natriuretic properties of SGLT2i may offer additional benefits in reducing congestion and may allow for a reduction in loop diuretic requirement. Although SGLT2i have been shown to increase risk of genital infections, euglycemic ketoacidosis, and volume depletion due to their additive diuretic effect, they are otherwise well tolerated and should not dissuade clinicians from using this class of medication [1].

Other Pharmacotherapeutic Options

In addition to these four drug classes, it is reasonable to commence other medications for HFrEF in certain patient groups. Two key trials, V-HeFT I and A-HeFT, have shown the addition of hydralazine and isosorbide dinitrate to guideline directed medical therapy (GDMT) leads to reduced morbidity and HF hospitalizations, as well as improvement of symptoms in self-identified black patients with HFrEF and NYHA class III-IV [26, 27]. ACC/AHA/HFSA rates this evidence at the highest level (CoR:1), however ESC reports this recommendation as 2a. Ivabradine, an If-channel inhibitor, has reasonable evidence for reducing HF hospitalization and CV death for patients with LVEF $\leq$ 35% on maximal tolerated GDMT when in sinus rhythm with a heart rate $\geq$ 70 bpm. This evidence comes from the SHIFT trial, which showed a reduction in HF hospitalization when patients were commenced on ivabradine due to a reduction in heart rate, however caution should be used as only 25% of patients were on optimal doses of beta-blocker [28]. Given the well-proven mortality benefits of beta-blocker therapy, these agents should be up-titrated to maximal tolerated doses prior to consideration of ivabradine initiation [29, 30]. There is weak evidence for the use of digoxin and soluble guanylate cyclase stimulator (e.g., vericiguat) in patients with progression of HFrEF despite GDMT (or who are unable to tolerate GDMT) to reduce HF hospitalizations. There is only one randomized controlled trial of digoxin in HF, which predated current GDMT. This study

found no effect on mortality with digoxin but modestly reduced risk of death and hospitalization [31]. This has been supported by retrospective analyses and meta-analyses [32–34]. The VICTORIA trial found a 10% reduction in the primary outcome (CV death or HF hospitalization) in patients with LVEF < 45%, NYHA class II-IV, on GDMT with elevated natriuretic peptides and recent HF worsening when taking vericiguat vs. placebo [35].

Diuretics

Loop diuretics such as frusemide or bumetanide are the preferred diuretic agent for use in most patients with HF. The ACC/AHA/HFSA guidelines also recommend the addition of a thiazide (e.g., chlorthalidone or hydrochlorothiazide) for refractory fluid retention unresponsive to high-dose loop diuretics alone. With the exception of mineralocorticoid receptor antagonists (MRA) (e.g., spironolactone), the effects of diuretics on morbidity and mortality are uncertain, but their symptomatic benefits are well established.

Device Therapy

Both guidelines agree that implantable cardiac defibrillators (ICD) are effective at reducing sudden cardiac death (SCD), and improving cardiac function and quality of life, in selected patients with HF. For primary prevention, regardless of etiology, the ACC/AHA/HFSA guidelines strongly recommend an ICD to reduce the risk of SCD and all-cause mortality in patients with symptomatic HFrEF of ischemic or non-ischemic etiology, with an LVEF ≤ 35% despite ≥ 3 months of optimal medical management if their life expectancy is > 1 year (CoR: 1) [1].

The ESC guidelines state ICDs are strongly recommended in ischemic cardiomyopathy (CoR: 1), but are only reasonable to consider in non-ischemic etiology (CoR: 2a) [4]. These conclusions are based on several studies. The MADIT-II trial specifically investigated patients with previous MI, LVEF ≤ 35% with non-sustained ventricular tachycardia (VT) and found a mortality benefit of ICDs [19]. In comparison, the DEFINITE trial included only non-ischemic patients with LVEF ≤ 35% and frequent premature ventricular contractions (PVCs) or non-sustained VT, and found a non-significant mortality benefit [37]. In the SCD-HEFT trial, which included patients with ischemic and non-ischemic cardiomyopathy with an LVEF ≤ 35% and NYHA class II-III, there was a benefit with ICD compared with amiodarone or placebo alone [38]. More recently, the DANISH trial, which only enrolled patients with non-ischemic cardiomyopathy and LVEF ≤ 35% to ICD or standard care found no reduction in total mortality despite a modest absolute risk reduction in sudden death [39]. The ACC/AHA/HFSA guideline authors questioned the significance of this result as 58% of patients in each limb received CRT, potentially mitigating the benefit of an ICD [1].

Cardiac resynchronization therapy (CRT) is strongly recommended for symptomatic patients (NYHA class II-IV on best medical management) who have LVEF ≤ 35%, sinus rhythm, left bundle branch block (LBBB) with a QRS of ≥ 150 ms to reduce total mortality and hospitalizations, and improve symptoms and quality of life (CoR: 1). These findings were shown in the MIRACLE trial, COMPANION trial, CARE-HF trial, REVERSE trial, and RAFT trial [40–44]. In patients without a LBBB or QRS duration between 130 and 149 ms, the available evidence for CRT demonstrates a moderate level of certainty (CoR: 2a) [40, 42–45]. The evidence is uncertain for patients who are asymptomatic (CoR: 2b) [45].

ACC/AHA/HFSA guidelines state that CRT is not recommended when QRS is < 120 ms, compared with < 130 ms in the ESC guidelines. In addition, ACC/AHA/HFSA guidelines find CRT reasonable if the LVEF is 36–50% and the patient has high degree atrioventricular block, based on the BLOCK-HF trial [46].

These variations in recommendations highlight the nuanced interpretation of available evidence. It is important for healthcare professionals to consider the specific patient characteristics and individualize the decision-making process when determining the appropriateness of CRT for patients.

Table 5 Comparison of key differences between 2022 ACC/AHA/HFSA and 2021 ESC HF guidelines

ACC/AHA/HFSA	ESC
Staging	
Differentiation between stages A and B, with clear recommendations for each stage	Recommendations for patients 'at risk'
Investigations	
CMR imaging can be useful for non-ischemic cardiomyopathy but would not be recommended routinely unless suggested to be necessary from TTE and clinical findings	CMR imaging for characterization of myocardial tissue in suspected infiltrative disease, Fabry disease, inflammatory disease (e.g., myocarditis), LV non-compaction, amyloid, sarcoidosis, and hemochromatosis
Management of HFrEF	
Stronger recommendation for hydralazine/isosorbide mononitrate in self-reported Black people	
Stronger recommendation of ICD for primary prevention in non-ischemic heart failure	
Management of HFmrEF	
SGLT2i recommended	
Management of HFimpEF	
Only considered in ACC/AHA/HFSA guideline	
Management of HFpEF	
SGLT2i, ARNi (or ACEi/ARB), MRA for management of HFpEF	Diuretics and optimal management of comorbidities
Other	
Formal recommendation for palliative care	
	Formal recommendation for telemonitoring

ACC American College of Cardiology, *ACEi* angiotensin-converting enzyme inhibitor, *AHA* American Heart Association, *ARB* angiotensin receptor blocker, *ARNi* angiotensin receptor–neprilysin inhibitor, *ESC* European Society of Cardiology, *CMR* cardiac magnetic resonance, *HFSA* Heart Failure Society of America, *HFimpEF* heart failure with improved ejection fraction, *HFmrEF* heart failure with mildly reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *ICD* implantable cardiac defibrillator, *LV* left ventricular, *MRA* mineralcorticoid receptor antagonist, *SGLT2i* sodium glucose cotransporter-2 inhibitor, *TTE* transthoracic echocardiogram

Multidisciplinary Team Involvement

Both the ACC/AHA/HFSA and ESC guidelines emphasize the critical role of a multidisciplinary team (MDT) approach in the management of HF. These guidelines recognize the value of involving various healthcare professionals, including cardiologists, nurses, pharmacists, dieticians, mental health clinicians, social workers, primary care clinicians, and additional specialists. Both guidelines assign the highest level of evidence (CoR: 1) to support the implementation of an MDT approach.

The inclusion of an MDT approach in the 2022 guidelines is emphasized significantly compared to previous recommendations. It acknowledges the role of non-pharmacological interventions, such as dietary modifications, fluid management, and exercise, alongside the prescription and adherence to GDMT.

By adopting an MDT approach, healthcare professionals can collectively address the multifaceted aspects of HF management. This collaborative approach enables comprehensive patient care, optimized non-pharmacological

strategies, and ensures appropriate implementation of GDMT in accordance with the guidelines.

Telemonitoring

The guidelines differ slightly on the recommendations for telemonitoring. The ACC/AHA/HFSA guidelines suggests that telemonitoring is not recommended, however, and that further research is required. The ESC guidelines suggest telemonitoring may be reasonable to reduce the risk of recurrent CV and HF hospitalizations, and CV death (CoR: 2b). Emerging data have shown promise in smartphone-based options for telemonitoring [47], and this is likely to be a focus in future guidelines.

HFmrEF Management

Both guidelines highlight that no prospective randomized controlled trials (RCTs) have been performed specifically for patients with HFmrEF, although there is evidence from subgroup analysis or post hoc analysis from previous HF trials. As such, strong recommendations cannot be made. ACC/AHA/HFSA and ESC guidelines both suggest that ACEi, ARB, or ARNi in addition to beta-blocker and MRA may be considered to reduce risk of HF hospitalizations and death (CoR: 2b). These recommendations are new since previous guidelines. The BBmeta-HF trial [48] found beta-blockers reduced all-cause mortality and CV mortality in patients with HFmrEF. Similarly, PARAGON-HF trial for patients with LVEF 45–57% suggested benefit of sacubitril-valsartan versus valsartan alone [49]. Subgroup analysis of patients with HFmrEF from the CHARM trial found candesartan reduced the risk of CV death and HF hospitalization [50]. The TOPCAT trial found spironolactone reduced the risk of the primary composite endpoint of CV death, HF hospitalization or resuscitated sudden death in patients with HFmrEF on subgroup analysis [51].

The ACC/AHA/HFSA guideline finds stronger evidence for SGLT2i to be beneficial in decreasing HF hospitalizations (CoR: 2a), whereas the ESC guidelines do not include them for HFmrEF. There are no significant trials for ICD or CRT in patients with HFmrEF and are therefore not recommended.

HFpEF Management

Both guidelines agree that there are no treatments that have been shown to reduce mortality in patients with HFpEF. There are, however, marginal benefits on HF hospitalizations for some pharmacological treatments, specifically diuretics and SGLT2i. These recommendations are primarily based on the EMPEROR-Preserved, TOPCAT, CHARM, and PARAGON-HF trials [49–52]. Both the ACC/AHA/HFSA 2022 HF guideline and the ESC 2021 HF guideline recommend diuretics to reduce congestion and improve symptoms.

New recommendations for treatment for HFpEF from the ACC/AHA/HFSA 2021 guidelines include the use of SGLT2i based on the recent EMPEROR-Preserved trial, which demonstrated a reduction in the composite outcome of CV death or hospitalization in patients on empagliflozin (n = 2997) vs. placebo (2991) who had HFpEF and a NYHA II-IV and had been hospitalized with HF in the last 12 months (CoR: 2a) [52]. The benefit was similar irrespective of their diabetes status. The ACC/AHA/HFSA guidelines also suggest ARB, ARNi, and MRAs can be considered (CoR: 2b). This is in contrast to the ESC guidelines where SGLT2i are indicated in patients with type 2 diabetes mellitus only (CoR: 1). This difference is likely due to the timing of publication, as ESC guidelines were published at a similar time to the EMPEROR-Preserved trial [52]. Recently, the ACC released an expert consensus decision pathway for management of HFpEF, which highlights GDMT in more detail [53].

STAGE D: ADVANCED HF

Many patients with HF will progress to advanced HF, with persistently severe symptoms despite optimal medical management. Both the ACC/AHA/HFSA and ESC guidelines use the 2018 HFA-ESC criteria for the definition of advanced HF, highlighting that a severely

reduced LVEF is common but not required for diagnosis of advanced HF [54]. The ACC/AHA/HFSA guideline emphasizes the importance of referring patients with advanced HF who wish to prolong survival to a specialist HF team to review management and assess suitability for advanced therapies. Mechanical circulatory support and heart transplantation is recommended for carefully selected patients to improve functional status, quality of life, and survival. Patients who are eligible and awaiting these should be considered for continuous intravenous inotropic support as a "bridge therapy" (CoR: 2a).

Palliative Care

The ACC/AHA/HFSA guidelines recommend all patients with HF should receive palliative and supportive care to improve quality of life (CoR:1), with the suggestion that patients' who have stage D HF, uncontrolled symptoms, multimorbidity, frailty, or cognitive impairment be referred to specialist palliative care (CoR:2a). There is no such suggestion in the ESC guidelines. Both the ACC/AHA/HFSA and ESC guidelines support the use of inotropes in the palliative setting for symptom relief (CoR: 2b). These recommendations are echoed in the ESC guideline, however the evidence has not been assessed.

CONCLUSIONS

The 2022 ACC/AHA/HFSA and 2021 ESC heart failure (HF) guidelines serve as essential resources for clinicians, providing them with the most current and evidence-based recommendations for the optimal diagnosis and treatment of patients at all stages of HF. The 2022 guidelines also address previously unexplored areas, such as patients at risk for HF and those with pre-HF. Notably, the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) has emerged as a significant development, with its recommended use across all stages of HF, including HFpEF.

Table 5 provides a comprehensive overview of the key differences in recommendations across the guidelines, emphasizing the need for clinicians to be aware of these variations to ensure appropriate patient management.

By staying updated with these guidelines, healthcare professionals can deliver optimal care to patients with HF, considering the latest evidence and advancements in the field. Furthermore, efforts to close the gap between evidence and implementation of guideline directed medical therapy [55, 56] will be vital in improving patient outcomes and future guideline development.

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