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Aiming at harmony. Comparing and contrasting International HFrEF Guidelines

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Large randomized controlled trials (RCTs) have led to major changes in the treatment of patients with heart failure and reduced left ventricular ejection fraction (HFrEF) and these advances are included in the recent European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines issued in 2021 and 2022, respectively. According to both guidelines, treatment of patients with HFrEF is based on the administration of four classes of drugs that reduce the primary endpoint of cardiovascular death and HF hospitalizations in RCTs: angiotensin-converting enzyme or angiotensin receptor neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter 2 inhibitors. Specific sequences of treatment are not recommended but emphasis is given to reaching treatment with all four drugs as early as possible. Further treatments are considered in selected patients including ivabradine, hydralazine nitrates, digoxin, and the new agent vericiguat. Specific treatments, mostly new, for cardiovascular and non-cardiovascular comorbidities are also given. The aim of this article is to compare the two recent guidelines issued by the ESC and ACC/AHA/HFSA and show the few differences and the many consistent recommendations, now more numerous given the evidence available for many new treatments.

Introduction

The latest versions of the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines for the management of heart failure (HF) have been recently published, following by 5 months and 1 year, respectively, the Canadian Cardiovascular Society and Canadian Heart Failure Society guidelines.[1–3] In these last years, major randomized clinical trials (RCTs) have given new evidence to radically change management of patients with HF and reduced left ventricular ejection fraction (HFrEF) and the new guidelines reflect this.[1–3] Most of the main recommendations are highly consistent between different guidelines

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although some discrepancies exist. Some of them can be easily explained by the different timing of publication, such as the treatment of patients with HF and preserved ejection fraction (HFpEF). Other aspects, such as consideration of geographical and ethnical differences and different interpretation of the results of RCTs have also had a role. The aim of this study is to compare the recent ESC and ACC/AHA/HFSA guidelines mainly with respect of differences in recommendations of specific treatments. Other aspects, such as the considerations for healthcare costs, given by the ACC/AHA/HFSA, but not by the ESC, guidelines go beyond the aims of this review. In contrast to other recent comparisons,[4] we will focus only on management of the patients with HFrEF.

Definition and classification of HF

Both the ESC and ACC/AHA/HFSA guidelines define HF as a complex syndrome with symptoms and signs resulting from structural and/or functional abnormalities of the heart. The main classification is based on left ventricular ejection fraction (LVEF): HFrEF when LVEF is ≤40%, HF with mildly reduced EF, with LVEF ranging between 41 and 49%, and HFpEF, when LVEF is ≥50%. These definitions and classifications are consistent with guidelines as well as with the recent universal definition of HF.[5] They are based on the large number of favourable RCTs in HF having a reduced EF as the main inclusion criterion.[6]

An additional category included in the ACC/AHA/HFSA guidelines, as well as in the universal definition of HF, is that of HF with improved EF (HFimpEF). To fulfil this definition, patients must have an LVEF ≤40% at baseline and >40% at follow up with a change of ≥10 units from baseline.[2,5] It can also be noted that changes in LVEF might not be unidirectional. A patient may have an improvement followed by a decrease in LVEF, or vice versa, depending on the underlying cause of HF, duration of disease, adherence to the guideline-directed medical therapy (GDMT), or, for instance, re-exposure to cardiotoxic agents. For this reason, the ACC/AHA/HFSA guidelines suggest avoiding the term 'recovered HFrEF' but using HFimpEF as a subgroup of HFrEF.[2] In addition, according to the universal definition of HF, the term 'stable HF' should be substituted by 'HF in remission' to highlight the only temporary duration that any improvement might have, similar to that which occurs in oncology.[5] Continued treatment for HFrEF is strongly recommended in these patients by both guidelines, based on evidence of worsening congestion, cardiac function, and symptoms when treatment is interrupted.[1,2,7-10]

While the ESC guidelines use the traditional symptom-based classification of the New York Heart Association (NYHA), the ACC/AHA/HFSA guidelines emphasize development and progression of HF and use a classification with four stages, from A to D. They were renamed based on the universal definition of HF which mandates symptoms as a key component of the HF syndrome.[2,5] Stage A includes patients at risk of HF. Stage B, now named pre-HF, includes patients with no current or previous symptoms of HF but with evidence of structural heart disease and/or increased filling pressures or with risk factors and increased levels of brain natriuretic peptide (BNP) or persistently elevated cardiac troponin. Stage C defines symptomatic HF and Stage D includes advanced HF. These entities are considered also in the ESC guidelines and in an accompanying paper by the HF Association (HFA) of ESC about prevention.[1,11]

Diagnosis

The diagnosis of HF is consistent across different guidelines and remains based on symptoms and signs, detection of elevated BNP or *N*-terminal-proBNP (NT-proBNP) plasma concentrations and on echocardiography.[1,2] Both guidelines suggest the use of advanced imaging techniques, with a major role for cardiac magnetic resonance, and genetic testing in patients with cardiomyopathies. Also, a similar algorithm to establish the diagnosis of cardiac amyloidosis has been proposed.[12] The use of endomyocardial biopsy is limited to patients with a rapid onset of HF symptoms who do not respond to therapy and in whom biopsy may show causes that necessitate specific treatment. All other diagnostic procedures are outlined in both guidelines, and are consistent between them, as well as with previous guidelines.[1,2]

Medical treatment

European Society of Cardiology and ACC/AHA/HFSA guidelines agree and put emphasis on the four pillars of medical treatment of HFrEF (*Figure 1*). Due to robust evidence demonstrating reduction in cardiovascular (CV) mortality and HF hospitalization, both guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACEIs) or the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonist and sodium-glucose co-transporter 2 inhibitors (SGLT2i), dapaglifozin, or empaglifozin [Class of recommendation (CoR) I] for patients with HFrEF who can tolerate them and who do not have contraindications (*Table 1*). The ACC/AHA/HFSA guidelines recommend the use of ACEi only when the use of ARNI is not feasible.[2]

Differences exist in the recommendations for sacubitril/valsartan. ACC/AHA/HFSA recommends sacubitril/valsartan with CoR I, Level of Evidence A (LoE A) for all patients with HFrEF, independent of previous therapy.[2] The ESC guidelines maintain a CoR I for sacubitril/valsartan only as a replacement of ACEI, based on the results of PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in HF) trial, and have a CoR IIb for patients not previously treated with ACEI or ARB.[1] The reason for these recommendations is the lack of data from RCTs including outcomes as a primary endpoint in patients not previously treated with ACEI or ARB. The primary endpoints in these trials were a decrease in NT-proBNP concentrations or the assessment of tolerability of initiating/uptitrating ARNI, respectively.[13,14]

The SGLT2is empagliflozin and dapagliflozin reduced the composite endpoint of CV mortality and HF events and improved quality of life in patients with HFrEF, with or without Type 2 diabetes mellitus (T2DM), on top of GDMT.[15-18] Based on DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in HF) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic HF and a Reduced EF) trials, ESC guidelines recommend dapagliflozin or empagliflozin for all patients with HFrEF to reduce CV mortality and HF hospitalizations (CoR I, LoE A).[1,15,18] The ACC/AHA/

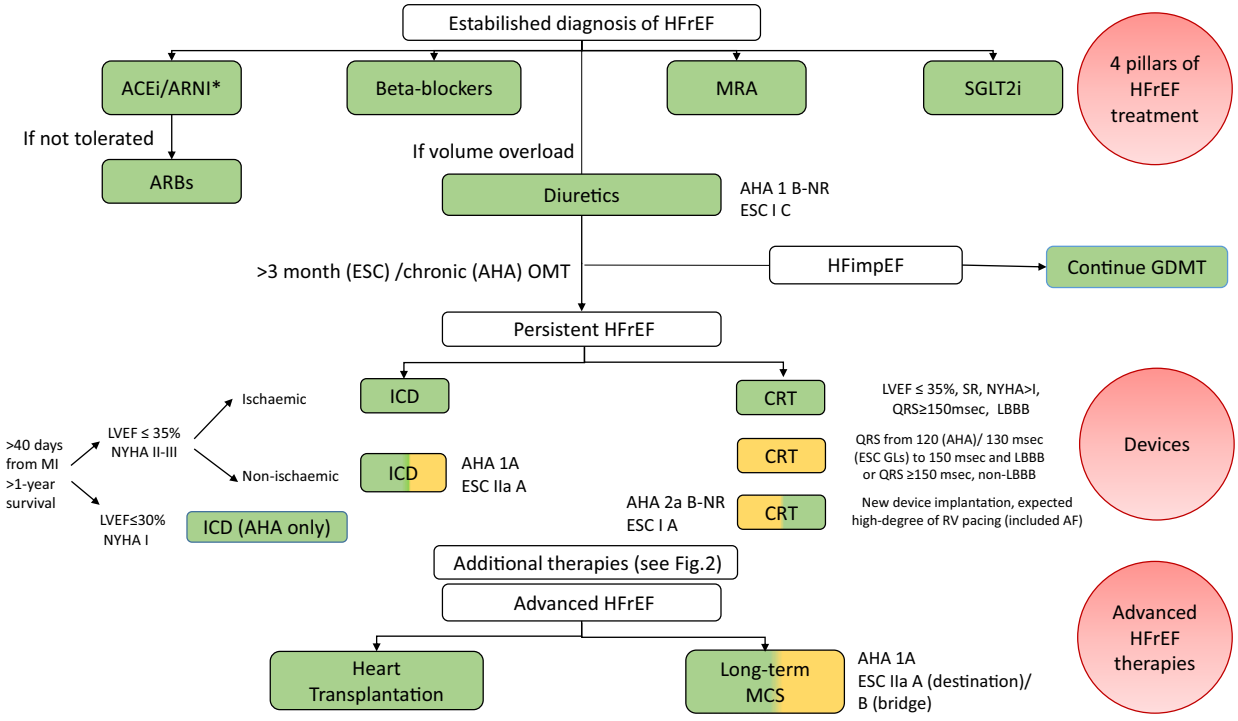

Figure 1 Management of heart failure with reduced ejection fraction a comparison between American College of Cardiology/American Heart Association/Heart Failure Society of America and European guidelines. *The recommendation for angiotensin receptor neprilysin inhibitor in patients receiving angiotensin-converting enzyme inhibitor is I B/1 B in both American College of Cardiology/American Heart Association/Heart Failure Society of America and European guidelines. ACC/AHA/HFSA guidelines recommend sacubitril/valsartan as first line therapy. ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AHA, ACC/AHA/HFSA Heart Association; ARNI, angiotensin neprilysin inhibitor; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; GLs, guidelines; HFimpEF, heart failure with improved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MI, myocardial infarction; MRA, mineralocorticoid antagonists; NYHA, New York Heart Association; OMT, optimal medical therapy; RV, right ventricular; SGLT2i, sodium-glucose co-transporter 2 inhibitors; SR, sinus rhythm.

HFSA guidelines, based on DAPA-HF, EMPEROR-Reduced, and SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes and Worsening HF), have the same CoR but refer more generally to SGLT2i as a class effect for the treatment of HFrEF.[2,15,17,19]

Both guidelines recommend starting therapy with GDMT at low doses and titrating them to the target doses shown to be effective and safe in RCTs, when tolerated.[1,2] Titration is not an issue with SGLT2i as they are administered at single doses in RCTs. Administration of all four drugs that improved outcomes in RCTs is recommended as they act synergistically on different pathways. Tailored treatment is recommended based on the patient's clinical characteristics in the ACC/AHA/HFSA guidelines and in a specific HFA statement.[20] Specific timelines for drug titration are not given. The ACC/AHA/HFSA guidelines recommend titration and optimization of GDMT 'as frequently as every 1–2 weeks depending on the patient's symptoms, vital signs, and laboratory findings'.[2]

The beneficial effects on outcomes of GDMT become significant early and thus any delay in its administration exposes the patient to unnecessary risk. Hospitalizations for HF decompensation can play a major role in the optimization of GDMT. Both the ESC guidelines and the ACC/AHA/HFSA guidelines recommend optimization of GDMT before discharge in patients hospitalized for decompensated HF.[1,2] Based on recent data from RCTs, early initiation of SGLT2i before discharge from hospital is also warranted.[1,2,19,21–26]

Once GDMT with the four pillars of HFrEF treatment is established, additional therapies can be considered in selected patients (*Figures 1* and *2*). Diuretics remain the cornerstone treatment to relieve congestion. They have CoR I LoE C in the ESC guidelines and CoR 1 LoE B-NR in the ACC/AHA/HFSA guidelines, based on the absence of RCTs.[1,2] Both guidelines agree about the use of ivabradine with no major change compared with previous versions of the guidelines.[1,2] ACC/AHA/HFSA guidelines recommend the combination of hydralazine and isosorbide dinitrate to improve symptoms and reduce morbidity and mortality for patients self-identified as African American with NYHA Classes III and IV HFrEF on optimal medical therapy with a CoR 1A.[2] This recommendation is less strong, CoR IIa LoE B, in the ESC guidelines.[1]

According to both the ESC and the ACC/AHA/HFSA guidelines, digoxin may be considered in patients with HFrEF to reduce HF hospitalizations (CoR IIb).[1,2] The ESC guidelines add an indication for digoxin for rate control in patients with HFrEF and atrial fibrillation (CoR IIa LoE C).[1]

Given the results of the VICTORIA (Vericiguat Global Study in Subjects with HFrEF) trial, vericiguat is recommended in patients with NYHA Classes II–IV who have

Table 1 Recommendation for the medical treatment of heart failure and reduced left ventricular ejection fraction: European Society of Cardiology vs. American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines

ESC guidelines		ACC/AHA/HFSA guidelines	
Recommendation	**Class and LoE**	**Recommendation**	**Class and LoE**
An ACEI is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I A	In patients with previous or current symptoms of chronic HFrEF, the use of ACEI is beneficial to reduce morbidity and mortality when the use of ARNI is not feasible.	1 A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I A	In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta-blockers proved to reduce mortality (e.g. bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.	1 A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I A	In patients with HFrEF and NYHA Classes II–IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L.	1 A
Dapagliflozin or empagliflozin is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I A	In patients with symptomatic chronic HFrEF, SGLT2i is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of Type 2 diabetes.	1 A
Sacubitril/valsartan is recommended as a replacement for an ACEI in patients with HFrEF to reduce the risk of HF hospitalization and death.	I B	In patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.	1 B-R
		In patients with HFrEF and NYHA Classes II–III symptoms, the use of ARNI is recommended to reduce morbidity and mortality.	1 A
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.	I C	In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF.	1 B-NR
An ARB is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate an ACEI or ARNI.	I B	In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEI because of cough or angioedema and when the use of ARNI is not feasible, the use of ARB is recommended to reduce morbidity and mortality.	1 A
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACEI/(or ARNI), and an MRA, to reduce the risk of HF hospitalization and CV death.	IIa B	For patients with symptomatic (NYHA Classes II–III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including a beta-blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥70 b.p.m. at rest, ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death.	2a B-R
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 b.p.m. who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACEI (or ARNI) and an MRA.	IIa C		
Soluble guanylate cyclase receptor stimulator vericiguat may be considered in patients in NYHA Classes II–IV who have had worsening HF despite treatment with an ACEI (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization.	IIb B	In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.	2b B-R
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated	IIa B	For patients self-identified as African American with NYHA Classes III and IV HFrEF who are receiving optimal medical therapy, the combination of	1 A

Continued

Table 1 Continued

ESC guidelines		ACC/AHA/HFSA guidelines	
Recommendation	**Class and LoE**	**Recommendation**	**Class and LoE**
left ventricle in NYHA Classes III and IV despite treatment with an ACEI (or ARNI), a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.		hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality.	
Hydralazine and isosorbide dinitrate may be considered in patients with symptomatic HFrEF who cannot tolerate any of an ACEI, an ARB, or ARNI (or they are contraindicated) to reduce the risk of death.	IIb B	In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNI, ACEI, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality.	2b C-LD
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACEI (or ARNI), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).	IIb B	In patients with symptomatic HFrEF despite GDMT (or who are unable to tolerate GDMT), digoxin might be considered to decrease hospitalizations for HF.	2b B-R
Digoxin should be considered when the ventricular rate remains high, despite beta-blockers, or when beta-blockers are contraindicated or not tolerated.	IIa C		

ACEIs include captopril, enalapril, lisinopril, ramipril, and trandolapril. Beta-blockers include bisoprolol, carvedilol, metoprolol succinate (CR/XL), and nebivolol. MRAs include eplerenone and spironolactone. SGLT2 inhibitors include dapagliflozin, empagliflozin, and sotagliflozin (only in patients with T2DM in the ESC guideline).

ARNI, angiotensin receptor neprilysin inhibitor; ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LoE, level of evidence; LVEF, left ventricular ejection fraction; MRA, mineral corticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium-glucose co-transporter 2 inhibitors; SR, sinus rhythm.

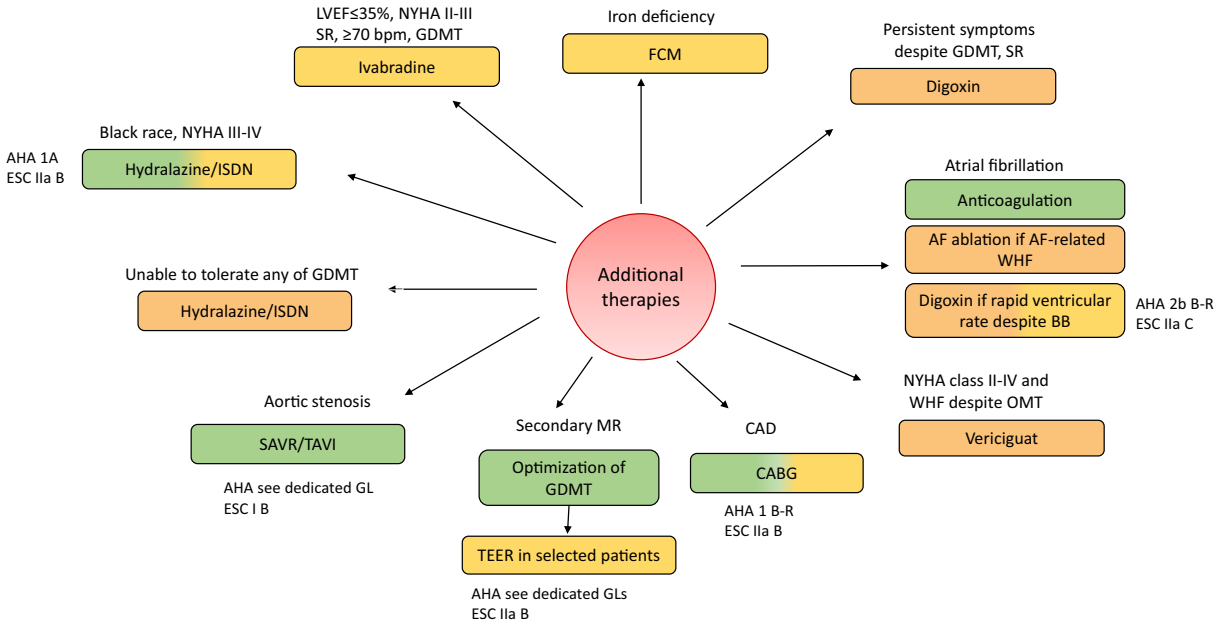

Figure 2 Additional therapies in specific subgroups of patients. AF, atrial fibrillation; AHA, ACC/AHA/HFSA Heart Association; BB, beta-blockers; CAD, coronary artery disease; CABG, coronary artery bypass grafting; ESC, European Society of Cardiology; FCM, ferric carboxymaltose; GDMT, guideline-directed medical treatment; GLs, guidelines; ISDN, isosorbide dinitrate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; OMT, optimal medical therapy; SAVR, surgical aortic valve replacement; SR, sinus rhythm; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair; WHF, worsening heart failure.

worsening HF despite GDMT to reduce the risk of CV mortality or HF hospitalization with no difference in the CoR and LoE between the two guidelines (CoR IIb, LoE 2b B).[1,2,27]

Device therapy

Both guidelines recommend with CoR I A an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death in patients with ischaemic HF aetiology, after >40 days from a MI, NYHA Classes II and III symptoms, LVEF ≤35%, ≥3 months (ESC) or on 'chronic' (ACC/AHA/HFSA) optimal medical therapy, and with expected survival >1 year.[1,2] In patients with a non-ischaemic aetiology, ESC guidelines now provide a weaker CoR for ICD implantation, compared with the ACC/AHA/HFSA guidelines (IIa vs. I), based on the interpretation of the results of the DANISH trial.[1,2,28] Furthermore, ACC/AHA/HFSA guidelines give a CoR I with LoE B-R for patients with an ischaemic aetiology, ≥ 40 days after MI, with LVEF ≤30% and NYHA Class I, rather than II and III, symptoms despite GDMT, with expected survival >1 year.[2] Only the ESC guidelines mention the indication for ICD for secondary prevention (CoR I, LoE A).

Cardiac resynchronization therapy (CRT) is recommended for symptomatic patients with LVEF ≤35%, sinus rhythm, left bundle branch block, and QRS duration ≥150 ms (CoR I, LoE A) in both guidelines. Further differences are reported in *Table 2*. Of note, the QRS width minimum cut-off for CRT implantation is 120 ms in the ACC/AHA/HFSA guidelines vs. 130 ms in the ESC ones.[1–3]

Advanced heart failure

Both the AHA/ACC/HFSA and the ESC guidelines define 'stage D HF/advanced HF' using the 2018 HFA of ESC definition, which is based on four distinct criteria.[29] The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification is used in both versions for the indication to long-term mechanical circulatory support (MCS) implantation.[1–3]

Continuous or intermittent intravenous inotropic support is recommended for patients with advanced HF as a bridge to transplantation or long-term MCS as well as palliative care in the patients in whom these procedures are contraindicated. However, the ESC guidelines do not go beyond a CoR IIb, whereas the ACC/AHA/HFSA guidelines have a stronger CoR 2a when inotropic agents are used as a bridge to transplantation or MCS.[1,2] Heart transplantation has a IC/1C recommendation in both guidelines.

The indications for short-term MCS are similar, whereas those for long-term MCS differ. For long-term MCS, ESC guidelines never go beyond CoR IIa with LoE A for destination therapy and B as a bridge to transplantation. Conversely, the AHA/ACC/HFSA guidelines recommend long-term MCS to improve functional status, quality of life, and survival in selected patients with advanced HFrEF and NYHA Class IV symptoms who are deemed as dependent on continuous intravenous inotropes or temporary MCS with CoR 1A. A CoR 2A is kept for the other patients with no major difference from the ESC guidelines.[1,2]

Cardiovascular comorbidities

With respect to atrial fibrillation, oral anticoagulation has a CoR I and pulmonary vein ablation a CoR IIa in both guidelines. Pulmonary vein ablation should be considered when there is a clear association between paroxysmal or persistent AF and worsening of HF symptoms, which persist despite medical therapy (*Figure 2*). Ablation of the atrioventricular node and permanent pacing has a CoR IIb in the ESC guidelines and a CoR IIa in the ACC/AHA/HFSA ones.[1,2]

Both guidelines recommend optimization of GDMT in patients with severe secondary mitral regurgitation and HFrEF with surgery, in patients with an indication for concomitant coronary artery bypass surgery (CABG), and transcatheter edge-edge mitral valve repair in those patients who fulfil the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for HF Patients With Functional Mitral Regurgitation) trial inclusion criteria, with a CoR IIa to reduce HF hospitalizations (*Figure 2*).[30]

There are few data from RCTs regarding the effects of coronary revascularization in patients with HFrEF. The two guidelines provide different CoRs for coronary revascularization based on different interpretations of the STICH (Surgical Treatment for Ischemic Heart Failure) trial and its long-term follow up.[31,32] Thus, ACC/AHA/HFSA guidelines recommend CABG in 'selected patients with HF, LVEF <35%, and suitable coronary anatomy' (Class I LoE B-R).[2] The ESC guidelines give a CoR IIa for CABG in patients with persistent symptoms of angina (or an angina equivalent) and coronary anatomy suitable for revascularization and a CoR IIb for revascularization to improve outcomes.[1]

Non-cardiovascular comorbidities

Both guidelines recommend periodic screening for anaemia and iron deficiency with iron replacement therapy with ferric carboxymaltose in patients with iron deficiency, with or without anaemia, to improve symptoms, exercise capacity, and quality of life and to reduce rehospitalizations in patients with a recent HF hospitalization, according to the AFFIRM-AHF results.[1,2,33]

The ACCE/AHA/HFSA guidelines give a CoR 2B to treatment of hyperkalaemia with potassium-lowering agents in patients on ACEI therapy. The ESC guidelines also give indications for treatment of hyperkalaemia.[1,2]

Both guidelines give the same recommendations for sleep disordered breathing. Treatment of predominant central sleep apnoea with adaptive servoventilation is contraindicated because of increased mortality in RCTs. Obstructive sleep apnoea can be treated with continuous positive airway pressure, bi-level positive airway pressure, and adaptive servoventilation, although none of these interventions has been shown to have beneficial effects on outcomes in HF.[1,2]

Conclusion

Generally, there is a high consistency between the ESC and ACC/AHA/HFSA guidelines with respect to the treatment of HFrEF. Strong evidence supports the administration of

Table 2 Recommendation for device implantation in heart failure and reduced left ventricular ejection fraction: European Society of Cardiology vs. American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines

ESC guidelines		ACC/AHA/HFSA guidelines	
Recommendation	**Class and LoE**	**Recommendation**	**Class and LoE**
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after a MI.	I A		
ICD—Primary prevention			
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Classes II and III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially >1 year with good functional status.	I A	In patients with non-ischaemic DCM or ischaemic heart disease at least 40 days post-MI with LVEF ≤35% and NYHA Class II or III symptoms on chronic GDMT, who have reasonable expectation of meaningful survival for >1 year, ICD therapy is recommended for primary prevention of SCD to reduce total mortality.	1 A
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Classes II and III) of a non-ischaemic aetiology, and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially >1 year with good functional status.	IIa A	As above	
—		In patients at least 40 days post-MI with LVEF ≤30% and NYHA Class I symptoms while receiving GDMT, who have reasonable expectation of meaningful survival for >1 year, ICD therapy is recommended for primary prevention of SCD to reduce total mortality.	1 B-R
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals, the patient's needs and clinical status may have changed.	IIa B		
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	IIb B		
Cardiac resynchronization therapy			
CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I A	For patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS duration ≥150 ms, and NYHA Class II, III, or ambulatory IV symptoms on GDMT, CRT is indicated to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL	1 B-R
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high-degree AV block in order to reduce morbidity. This includes patients with AF.	I A	For patients on GDMT who have LVEF ≤35% and are undergoing placement of a new or replacement device implantation with anticipated requirement for significant (>40%) ventricular pacing, CRT can be useful to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL.	2a B-NR
		In patients with high-degree or complete heart block and LVEF of 36–50%, CRT is reasonable to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL.	2a B-R
		In patients with AF and LVEF ≤35% on GDMT, CRT can be useful to reduce total mortality, improve symptoms and QOL, and increase LVEF, if: (i) the patient requires ventricular pacing or otherwise meets CRT criteria and (ii) atrioventricular nodal ablation or	2a B-NR

Continued

Table 2 Continued

ESC guidelines		ACC/AHA/HFSA guidelines	
Recommendation	**Class and LoE**	**Recommendation**	**Class and LoE**
		pharmacological rate control will allow near 100% ventricular pacing with CRT.	
CRT should be considered for symptomatic patients with HF in SR with a QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa B	For patients who have LVEF ≤35%, SR, a non-LBBB pattern with a QRS duration ≥150 ms, and NYHA Class II, III, or ambulatory Class IV symptoms on GDMT, CRT can be useful to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL	2a B-R
CRT should be considered for symptomatic patients with HF in SR with a QRS duration of 130–149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa B	For patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS duration of 120 to 149 ms, and NYHA Class II, III, or ambulatory IV symptoms on GDMT, CRT can be useful to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL.	2a B-NR
Patients with an LVEF ≤35% who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a significant proportion of RV pacing should be considered for 'upgrade' to CRT.	IIa B		
CRT may be considered for symptomatic patients with HF in SR with a QRS duration of 130–149 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb B	For patients who have LVEF ≤35%, sinus rhythm, a non-LBBB pattern with QRS duration of 120–149 ms, and NYHA Class III or ambulatory Class IV on GDMT, CRT may be considered to reduce total mortality, reduce hospitalizations, and improve symptoms and QOL.	2b B-NR
		For patients who have LVEF ≤30%, ischaemic cause of HF, sinus rhythm, LBBB with a QRS duration ≥150 ms, and NYHA Class I symptoms on GDMT, CRT may be considered to reduce hospitalizations and improve symptoms and QOL.	2b B-NR

AF, atrial fibrillation; AV, atrioventricular; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; OMT, optimal medical therapy; QOL, quality of life; RV, right ventricular; SCD, sudden cardiac death; SR, sinus rhythm.

four classes of drugs to improve outcomes and quality of life of the patients with HFrEF. Some minor differences remain with regards to additional therapies for specific subgroups and the indications for devices.

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References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131.
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM *et al*. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;**145**:e895–e1032.
3. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N *et al*. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. *Can J Cardiol* 2021;**37**:531–546.
4. Bayes-Genis A, Aimo A, Metra M, Anker S, Seferovic P, Rapezzi C *et al*. Head-to-head comparison between recommendations by the ESC and ACC/AHA/HFSA heart failure guidelines. *Eur J Heart Fail* 2022;**24**:916–926.
5. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N *et al*. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of

Heart Failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380.
6. Lund LH, Pitt B, Metra M. Left ventricular ejection fraction as the primary heart failure phenotyping parameter. *Eur J Heart Fail* 2022;**24**: 1158–1161.
7. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S *et al*. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019;**393**:61–73.
8. Halliday BP, Owen R, Gregson J, Vassiliou VS, Chen X, Wage R *et al*. Myocardial remodelling after withdrawing therapy for heart failure in patients with recovered dilated cardiomyopathy: insights from TRED-HF. *Eur J Heart Fail* 2021;**23**:293–301.
9. Dovancescu S, Pellicori P, Mabote T, Torabi A, Clark AL, Cleland JGF. The effects of short-term omission of daily medication on the pathophysiology of heart failure. *Eur J Heart Fail* 2017;**19**:643–649.
10. Dauw J, Martens P, Tersalvi G, Schouteden J, Deferm S, Gruwez H *et al*. Diuretic response and effects of diuretic omission in ambulatory heart failure patients on chronic low-dose loop diuretic therapy. *Eur J Heart Fail* 2021;**23**:1110–1119.
11. Piepoli MF, Adamo M, Barison A, Bestetti RB, Biegus J, Bohm M *et al*. Preventing heart failure: a position paper of the Heart Failure Association in collaboration with the European Association of Preventive Cardiology. *Eur J Heart Fail* 2022;**24**:143–168.
12. Rapezzi C, Aimo A, Serenelli M, Barison A, Vergaro G, Passino C *et al*. Critical comparison of documents from scientific societies on cardiac amyloidosis: JACC state-ofthe-art review. *J Am Coll Cardiol* 2022; **79**:1288–1303.
13. Morrow DA, Velazquez EJ, DeVore AD, Desai AS, Duffy CI, Ambrosy AP *et al*. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial. *Circulation* 2019;**139**:2285–2288.
14. Senni M, Wachter R, Witte KK, Straburzynska-Migaj E, Belohlavek J, Fonseca C *et al*. Initiation of sacubitril/valsartan shortly after hospitalisation for acutely decompensated heart failure in patients with newly diagnosed (de novo) heart failure: a subgroup analysis of the TRANSITION study. *Eur J Heart Fail* 2020;**22**:303–312.
15. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA *et al*. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
16. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S *et al*. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. *Circulation* 2020;**141**:90–99.
17. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P *et al*. Cardiovascular and renal outcomes with Empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
18. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ *et al*. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-reduced trial. *Eur Heart J* 2021;**42**:1203–1212.
19. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK *et al*. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384**:117–128.
20. Rosano GMC, Moura B, Metra M, Bohm M, Bauersachs J, Ben Gal T *et al*. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2021;**23**:872–881.
21. Cunningham JW, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS *et al*. Dapagliflozin in patients recently hospitalized with heart failure and mildly reduced or preserved ejection fraction. *J Am Coll Cardiol* 2022;**80**:1302–1310.
22. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ *et al*. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-reduced trial. *Circulation* 2021;**143**:326–336.
23. Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A *et al*. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail* 2020;**22**:713–722.
24. Rao VN, Murray E, Butler J, Cooper LB, Cox ZL, Fiuzat M *et al*. In-hospital initiation of sodium-glucose cotransporter-2 inhibitors for heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2021; **78**:2004–2012.
25. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS *et al*. Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2022;**24**:431–441.
26. Voors AA, Damman K, Teerlink JR, Angermann CE, Collins SP, Kosiborod M *et al*. Renal effects of empagliflozin in patients hospitalized for acute heart failure: from the EMPULSE trial. *Eur J Heart Fail* 2022. doi: 10.1002/ejhf.2681.
27. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J *et al*. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;**382**:1883–1893.
28. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E *et al*. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
29. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G *et al*. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:1505–1535.
30. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM *et al*. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
31. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A *et al*. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;**364**:1607–1616.
32. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA *et al*. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016;**374**:1511–1520.
33. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J *et al*. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* 2020;**396**:1895–1904.