ESC European Society of Cardiology

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REVIEW

Head-to-head comparison between recommendations by the ESC and ACC/AHA/HFSA heart failure guidelines

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Recommendations represent the core messages of guidelines, and are particularly important when the body of scientific evidence is rapidly growing, as in the case of heart failure (HF). The main messages from two latest major HF guidelines, endorsed by the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA), are partially overlapping, starting from the four pillars of treatment for HF with reduced ejection fraction. Some notable differences exist, in part related to the timing of recent publications (most notably, the Universal Definition of HF paper and the EMPEROR-Preserved trial), and in part reflecting differing views of the natural history of HF (with a clear differentiation between stages A and B HF in the ACC/AHA/HFSA guidelines). Different approaches are proposed to specific issues such as risk stratification and implantable cardioverter defibrillator use for primary prevention in HFrEF patients with non-ischaemic aetiology. The ACC/AHA/HFSA guidelines put a greater emphasis on some issues that are particularly relevant to the US setting, such as the cost-effectiveness of therapies and the impact of health disparities on HF care. A comparison between guideline recommendations may give readers a deeper understanding of the ESC and ACC/AHA/HFSA guidelines, and help them apply sensible approaches to their own practice, wherever that may be in the world. A comparison may possibly also help further harmonization of recommendations between future guidelines, by identifying why some areas have led to conflicting recommendation, even when ostensibly reviewing the same published evidence.

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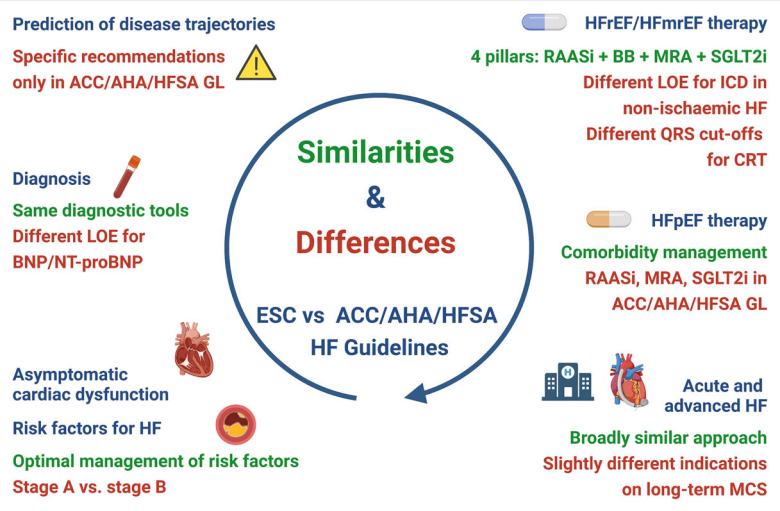
Graphical Abstract



Main similarities and differences between the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) heart failure (HF) guidelines. See text for details. ARNI, angiotensin receptor–neprilysin inhibitor; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; GL, guidelines; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LOE, level of evidence; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

Keywords Clinical practice • Comparison • Guidelines • Heart failure • Recommendations

Guidelines help clinicians select the best management strategies for individual patients, and are particularly important when the body of scientific evidence is rapidly growing, as in the case of heart failure (HF).[1] The main messages from two latest major HF guidelines, endorsed by the European Society of Cardiology (ESC)[1] and the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA),[2] are partially consistent, starting from the four pillars of treatment for HF with reduced ejection fraction (HFrEF) (*Table 1*). Nonetheless, important differences exist (*Table 2* and *Graphical Abstract*). Herein we compare the recommendations by the two guidelines (summarized in online supplementary *Table S1*). We aim to give readers a deeper understanding of the ESC and ACC/AHA/HFSA guidelines, and possibly help the harmonization of recommendations by future guidelines. We do not wish to provide a critical review of guideline contents nor to attempt a synthesis of diverging guideline positions.

Recommendations in the ESC and ACC/AHA/HFSA guidelines: an overview

The ESC guidelines include 129 recommendations, and the ACC/AHA/HFSA guidelines 177.[1,2] Class I/1 recommendations with an intermediate to low level of evidence (B or C) are 61% in the ESC guidelines vs. 72% in the ACC/AHA/HFSA guidelines. Class IIa/2a recommendations with a B or C level are 71% versus 100% (*Table 3*). In other words, the ESC guidelines are less prone to state that an approach 'is recommended or indicated' or 'should be considered' based on a low level of evidence. Furthermore, less Class III/3 recommendations are reported in the ESC guidelines than in the ACC/AHA/HFSA guidelines (5% vs. 14%), but with a higher level of evidence (level A in 36% vs. 16%).

Recommendations on specific topics

Chronic heart failure

Prevention

The ACC/AHA/HFSA guidelines distinguish stage A (presence of risk factors in the absence of even subclinical heart disease) from stage B (asymptomatic heart disease) HF[2] (*Table 4*). Conversely, the ESC guidelines broadly speak of 'prevent(ing) or delay(ing) the onset of HF' and also 'HF hospitalizations'; this last point may suggest that these recommendations are applicable even to patients with stage C (clinical HF).[1] It is actually stated that the Authors

Table 1 'Top 10 Take Home Messages' of the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines and matched messages from the European Society of Cardiology (ESC) guidelines

ACC/AHA/HFSA	ESC
GDMT for HFrEF now includes four medication classes which include SGLT2i	ACEi/ARNI, beta-blocker, MRA and SGLT2i are recommended as cornerstone therapies for HFrEF and may be considered in patients with HFmrEF
SGLT2i have a 2a recommendation in HFmrEF. Weaker recommendations (2b) are made for ARNI, ACEi, ARB, MRA and beta-blockers in this population	
New recommendations for HFpEF are made for SGLT2i (2a), MRAs (2b) and ARNI (2b). Several prior recommendations have been renewed including treatment of hypertension (1), treatment of atrial fibrillation (2a), use of ARBs (2b) avoidance of routine use of nitrates or phosphodiesterase-5 inhibitors (3-no benefit)	In patients with HFpEF, screening and treatment of specific HF aetiologies and comorbidities is recommended
Improved LVEF is used to refer to those patients with a previous HFrEF who now have an LVEF >40%. These patients should continue their HFrEF treatment	–
Value statements were created for select recommendations where high-quality cost-effectiveness studies of the intervention have been published	–
Amyloid heart disease has new recommendations for treatment including screening for serum and urine monoclonal light chains, bone scintigraphy, genetic sequencing, tetramer stabilizer therapy, and anticoagulation	Diagnosis of CA includes search for serum and urine monoclonal light chains, bone scintigraphy and CMR and biopsy, in selected cases. Tafamidis is recommended in patients who have ATTR-CA and NYHA class I–II symptoms to reduce symptoms, cardiovascular hospitalization, and mortality
Evidence supporting increased filling pressures is important for the diagnosis of HF if LVEF is >40%. Evidence for increased filling pressures can be obtained from non-invasive (e.g. natriuretic peptide, diastolic function on imaging) or invasive testing (e.g. haemodynamic measurement)	Definition and diagnosis of HFpEF includes symptoms ± signs of HF, LVEF ≥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
Patients with advanced HF who wish to prolong survival should be referred to a team specializing in HF. A HF specialty team reviews HF management, assesses suitability for advanced HF therapies and uses palliative care including palliative inotropes where consistent with the patient's goals of care	In selected patients with advanced HF refractory to medical therapy, mechanical circulatory support and heart transplantation should be considered
Primary prevention is important for those at risk for HF (stage A) or pre-HF (stage B). Stages of HF were revised to emphasize the new terminologies of 'at risk' for HF for stage A and pre-HF for stage B	Antihypertensive drugs, statins, SGLT2i, healthy lifestyle advice are recommended to prevent or delay the onset of HF
Recommendations are provided for select patients with HF and anaemia/iron deficiency, anaemia, hypertension, sleep disorders, type 2 diabetes, atrial fibrillation, coronary artery disease and malignancy	Recommendations are provided for select patients with HF and anaemia/iron deficiency, hypertension, sleep disorders, type 2 diabetes, atrial fibrillation, coronary artery disease and malignancy

Notes: The 'Top 10 Take Home Messages' are taken from the slide set accompanying the ACC/AHA/HFSA guidelines. The corresponding messages from ESC guidelines either correspond to specific recommendations or a summary of guideline recommendations.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor–neprilysin inhibitor; ATTR-CA, amyloid transthyretin cardiac amyloidosis; CMR, cardiovascular magnetic resonance; CV, cardiovascular; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

Table 2 Most prominent differences between the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines

Topics	Main differences
Prevention	Differentiation between stage A and B with clear recommendations for each stage (ACC/AHA/HFSA) vs. recommendations for patients 'at risk' (ESC)
Diagnostic tools	LOE for NP testing (1 A for ACC/AHA/HFSA, 1 B for ESC)
Characterization of HF aetiology	EMB indicated in 'patients with rapidly progressive HF despite standard therapy' (ESC) or 'when a specific diagnosis is suspected' (ACC/AHA/HFSA)
Risk stratification	NPs and risk prediction tools only recommended by ACC/AHA/HFSA
Drug treatment for HFrEF	- LOE for sacubitril/valsartan (1 A for ACC/AHA/HFSA, 1 B for ESC) - Digoxin only on top of GDMT for HF + sinus rhythm (ESC) or also to patients unable to tolerate GDMT ± sinus rhythm (ACC/AHA/HFSA) - Stronger recommendation for hydralazine/isosorbide dinitrate in ACC/AHA/HFSA (1 A vs. IIa B in ESC)
Drug treatment for HFmrEF	- Different LOE for ACEi, ARB, beta-blockers, MRA, ARNI (C in ESC, B-NR in ACC/AHA/HFSA) - SGLT2i recommended only by ACC/AHA/HFSA
Drug treatment for HFpEF	Diuretics and optimal management of comorbidities (ESC) vs. SGLT2i, ARB, MRA, ARNI (ACC/AHA/HFSA)
Management of HFimpEF	Considered only in ACC/AHA/HFSA
Device treatment	- Stronger recommendation for ICD for primary prevention in non-ischaemic HF in ACC/AHA/HFSA (1 A vs. IIa A in ESC) - Different QRS duration cut-offs, different scenarios
Comorbidities	- Diabetes: sotagliflozin considered only by ESC - Iron deficiency and anaemia: recommendation of periodical screening by ESC only; stronger recommendation for i.v. iron replacement by ESC (IIa A/B vs. 2a B-R) - Formal sleep assessment in patients with suspected sleep-disordered breathing (ACC/AHA/HFSA)
General management, home telemonitoring	Attention to depression, isolation, frailty as determinants of poor HF care (ACC/AHA/HFSA)
Acute HF: management	Timing of follow-up visit: 1 week (ACC/AHA/HFSA) vs. 1–2 weeks (ESC)
Advanced HF	- Renal replacement therapy and ultrafiltration: considered by ESC only - Different indications to long-term MCS
End-of-life care	Formal recommendations by ACC/AHA/HFSA only
Quality of care, cost-effectiveness	Formal recommendations by ACC/AHA/HFSA only
Health disparities	Formal recommendations by ACC/AHA/HFSA only
Specific aetiologies	- Indications to tafamidis (ESC) or broader recommendations on diagnosis and management (ACC/AHA/HFSA) - HF in pregnancy: formal recommendations by ACC/AHA/HFSA only - Cancer therapy-related HF: therapies for HF due to cardiotoxic drugs (ESC: ACEi and beta-blocker, preferably carvedilol; ACC/AHA/HFSA: ARB, ACEi, beta-blocker)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; EMB, endomyocardial biopsy; GDMT, guideline-directed medical therapy; 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; ICD, implantable cardioverter defibrillator; i.v., intravenous; LOE, level of evidence; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NP, natriuretic peptide; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

'… decided to focus on the diagnosis and treatment of HF, not on its prevention',[1] and a specific article about HF prevention was published simultaneously.[3]

Both the ESC and ACC/AHA/HFSA recommendations for stage A HF include the treatment of hypertension and type 2 diabetes (through sodium–glucose co-transporter 2 inhibitors [SGLT2i]), as well as counseling on a healthy lifestyle.[1,2] The ESC guidelines further recommend statins 'in patients at high risk of cardiovascular disease or with cardiovascular disease' (1 A). The ACC/AHA/HFSA guidelines mention the possible use of natriuretic peptides (NPs) and validated scores for risk prediction.[2] The ACC/AHA/HFSA guidelines go on to provide several strong recommendations on patients with stage B HF: those with left ventricular ejection fraction (LVEF) <40% should start an angiotensin-converting enzyme inhibitor (ACEi) and a beta-blocker. Patients with a recent myocardial infarction (MI) and LVEF <40% should receive an angiotensin receptor blocker (ARB) if they are intolerant to an ACEi, have a stronger indication to beta-blockers in case of a 'recent or remote' MI, and may benefit from an implantable cardioverter defibrillator (ICD) for primary

Table 3 Categorization of recommendations by class and level

ESC (129 recommendations)				ACC/AHA/HFSA (177 recommendations)					
I	52 (43%)			1	81 (46%)				
IIa	37 (31%)			2a	50 (28%)				
IIb	26 (21%)			2b	21 (12%)				
III	14 (5%)			3	25 (14%)				
A	28 (22%)			A	26 (15%)				
B	41 (32%)			B	105 (59%)				
C	60 (47%)			C	46 (26%)				
I A	20 (16%)	*38% of I*	*71% of A*	1 A	22 (12%)			*27% of 1*	*85% of A*
I B	7 (5%)	*13% of I*	*17% of B*	1 B-R	13 (7%)	1 B	36	*44% of 1*	*34% of B*
				1 B-NR	23 (13%)				
I C	25 (19%)	*48% of I*	*42% of C*	1 C-LD	20 (11%)	1 C	23	*28% of 1*	*50% of C*
				1 C-EO	3 (2%)				
IIa A	3 (2%)	*8% of IIa*	*11% of A*	2a A	0			*0% of 2a*	*0% of A*
IIa B	18 (14%)	*49% of IIa*	*44% of B*	2a B-R	13 (15%)	2a B	39	*78% of 2a*	*37% of B*
				2a B-NR	26 (15%)				
IIa C	16 (12%)	*43% of IIa*	*27% of C*	2a C-LD	8 (2%)	2a C	11	*22% of 2a*	*24% of C*
				2a C-EO	3 (2%)				
IIb A	0 (0%)	*0% of IIb*	*0% of A*	2b A	0			*0% of 2b*	*0% of A*
IIb B	12 (9%)	*46% of IIb*	*29% of B*	2b B-R	9 (5%)	2b B	16	*76% of 2b*	*15% of B*
				2b B-NR	7 (4%)				
IIb C	14 (11%)	*54% of IIb*	*23% of C*	2b C-LD	5 (3%)	2b C	5	*24% of 2b*	*11% of C*
				2b C-EO	0 (0%)				
III A	5 (4%)	*36% of III*	*18% of A*	3: No benefit A	1 (1%)	3 A	4	*16% of 3*	*15% of A*
				3: Harm A	3 (2%)				
III B	4 (3%)	*29% of III*	*10% of B*	3: No benefit B-R	5 (3%)	3 B	14	*56% of 3*	*13% of B*
				3: Harm B-R	6 (3%)				
				3: No benefit B-NR	1 (1%)				
				3: Harm B-NR	2 (1%)				
III C	5 (4%)	*36% of III*	*8% of C*	3: No benefit C-LD	1 (1%)	3 C	7	*28% of 3*	*15% of C*
				3: Harm C-LD	5 (3%)				
				3: No benefit C-EO	1 (1%)				
				3: Harm C-EO	0 (0%)				

Notes: The percentages were calculated out of the total number of recommendations in the corresponding guidelines, except for percentages reported in italic, which were calculated out of the total number of recommendations with the same class or level of evidence.
ACC/AHA/HFSA, American College of Cardiology/American Heart Association/Heart Failure Society of America; ESC, European Society of Cardiology.

prevention if LVEF is <30% and following >40 days from the MI. Other recommendations are about statins for patients with a 'recent or remote history of MI or (acute coronary syndrome)', and thiazolidinediones or non-dihydropyridine calcium channel blockers (contraindicated if LVEF is <50%).[2] The time criterion to identify a 'recent' MI is not specified.[2]

Diagnosis

The guidelines differ in the level of evidence for B-type NPs (BNP and its N-terminal pro-hormone [NT-proBNP]) as diagnostic tools. BNP/NT-proBNP testing has a 1 A recommendation in the ACC/AHA/HFSA guidelines and a 1 B recommendation in the ESC guidelines, possibly because the ACC/AHA/HFSA guidelines consider a more acute setting ('patients presenting with dyspnoea' vs. 'patients with suspected chronic HF' in the ESC guidelines).[1,2] Therefore, the ACC/AHA/HFSA guidelines seem to rely more on studies establishing the good diagnostic performance of NPs in the emergency department setting,[4,5] while the ESC guidelines might be emphasizing the need for accurate interpretation of NPs in challenging scenarios such as obesity, suspected HF with preserved ejection fraction (HFpEF), atrial fibrillation, or chronic kidney disease.[6]

Characterization of heart failure aetiology

The ESC guidelines consider advanced imaging modalities, exercise testing and invasive coronary angiography and endomyocardial biopsy (EMB).[1] The ACC/AHA/HFSA guidelines adds history and physical examination, laboratory examinations and genetic testing.[2] The ESC guidelines provide multiple recommendations about right heart catheterization to discriminate different HF aetiologies, detect pulmonary hypertension, or confirm the diagnosis of HFpEF.[1] EMB is recommended just 'in patients with rapidly progressive HF despite standard therapy' (ESC)[1] or whenever 'a specific diagnosis is suspected that would influence therapy'

Table 4 Recommendations on heart failure prevention

ESC			ACC/AHA/HFSA			
Tool for prevention	**Class**	**Level**	**HF stage**	**Tool for prevention**	**COR**	**LOE**
Treatment of hypertension	I	A	A	Treatment of hypertension	1	A
Treatment with statins	I	A		SGLT2i for T2DM	1	A
SGLT2i for T2DM	I	A		Healthy lifestyle advice	1	B-NR
Healthy lifestyle advice	I	C		NP screening	2a	B-R
				Validated risk scores	2a	B-NR
			B	ACEi if LVEF <40%	1	A
				Beta-blockers if LVEF <40%	1	C-LD
				ARB if intolerant to ACEi, LVEF <40%, recent MI	1	B-R
				Beta-blockers if LVEF <40% and recent or remote MI or ACS	1	B-R
				ICD if LVEF <30% after >40 days from MI	1	B-R
				Statins if recent or remote MI or ACS	1	A
				No thiazolidinediones if LVEF <50%	3: Harm	C-LD
				No non-dihydropyridine CCBs	3: Harm	C-LD

Note: A summary of the recommendations is provided in online supplementary *Table S1*.
ACC/AHA/HFSA, American College of Cardiology/American Heart Association/Heart Failure Society of America; ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; COR, class of recommendation; ESC, European Society of Cardiology; HF, heart failure; ICD, implantable cardioverter defibrillator; LOE, level of evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NP, natriuretic peptide; SGLT2i, sodium–glucose co-transporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

(ACC/AHA/HFSA).[2] This implies a less restrictive approach to the use of EMB in the US, favouring more research on the aetiology of HF, which is supported by the availability of new aetiological treatments for certain cardiomyopathies such as amyloidosis.

Assessment of the heart failure phenotype and management optimization

The ESC guidelines provide succinct recommendations about blood tests, cardiopulmonary exercise testing (CPET) and right heart catheterization.[1] The ACC/AHA/HFSA guidelines uniquely recommend patient assessment through the New York Heart Association (NYHA) class, the 6-min walk test as an alternative to CPET, the search for signs and symptoms of congestion or advanced HF, and reassessment when the clinical status changes or patients are considered for invasive procedures or device therapy.[2] The ACC/AHA/HFSA guidelines further mention invasive haemodynamic monitoring as a possible guide to HF management.[2]

Prediction of disease trajectories

Only the ACC/AHA/HFSA guidelines consider the prediction of disease trajectories through NPs or validated multivariable risk scores.[2] NP measurement is also recommended after an HF hospitalization.[2]

Drug treatment for heart failure with reduced ejection fraction

Indications for single drug classes

Both guidelines recommend that patients tolerating an ACEi or ARB be switched to the angiotensin receptor–neprilysin inhibitor (ARNI) sacubitril/valsartan.[1,2] The ACC/AHA/HFSA guidelines put more emphasis on sacubitril/valsartan and give it a 1 A recommendation[2] citing studies on acute HF,[7,8] cardiac remodelling[9] and aortic stiffness.[10] Conversely, the ESC guidelines give a I B recommendation to sacubitril/valsartan to 'reduce the risk of HF hospitalization and death', and consider only the PARADIGM-HF trial as evidence.[11]

ARBs are recommended when ARNI and ACEi are contraindicated, not tolerated,[1,2] or 'not feasible', which may be interpreted as including the inability to pay.[2]

The ESC guidelines provide succinct recommendations about beta-blockers and mineralocorticoid receptor antagonists (MRAs), which are both recommended.[1] In the supplementary material, only the beta-blockers bisoprolol, carvedilol, metoprolol succinate and nebivolol are recommended, and the MRAs eplerenone and spironolactone.[1] The ACC/AHA/HFSA guidelines specify that the beta-blockers bisoprolol, carvedilol, sustained-release metoprolol succinate should be prescribed, mention spironolactone and eplerenone, define specific criteria to start MRA treatment, and suggest MRA discontinuation when potassium cannot be maintained <5.5 mEq/L.[2]

SGLT2i are recommended by both guidelines with I/1 A recommendations.[1,2] The ACC/AHA/HFSA recommendation mentions SGLT2i as a drug class,[2] thus theoretically including SGLT2i other than empagliflozin and dapagliflozin.[2]

Overall, the two guidelines agree that the combination of a beta-blocker, an ACEi/ARB/ARNI, an MRA and a SGLT2i represents the mainstay of treatment for HFrEF.

Diuretics are recommended to relieve congestion, with a level C recommendation in the ESC guidelines[1] and a level B-NR in the ACC/AHA/HFSA guidelines.[2] The latter guidelines include a recommendation on combination therapy with a thiazide diuretic.[2]

Ivabradine is recommended by both guidelines when resting heart rate is ≥70 bpm despite evidence-based or maximally tolerated beta-blocker doses.[1,2] The ESC guidelines add that

ivabradine might be considered in patients with contraindications to beta-blockers (IIa C).[1]

Hydralazine/isosorbide dinitrate is recommended for use in Black patients on top of optimal medical therapy, with a much stronger recommendation in the ACC/AHA/HFSA guidelines (1 A vs. IIa B).[1,2]

The ESC guidelines recommend vericiguat on top of 'ACEi (or ARNI), a beta-blocker and an MRA'[1] (reflecting the design of the VICTORIA trial),[12] while the ACC/AHA/HFSA guidelines broadly speak of guideline-directed medical therapy,[2] potentially including also SGLT2i, although there are currently no data on the combined efficacy of vericiguat and SGLT2i.

Digoxin may be considered in symptomatic patients on treatment with an ACEi/ARNI, a beta-blocker and an MRA and in sinus rhythm (ESC),[1] or also in patients who are unable to tolerate guideline-directed medical therapy (ACC/AHA/HFSA).[2] The DIG trial predated the era of triple neurohormonal antagonism,[13] possibly explaining the limited consideration for background therapy in the ACC/AHA/HFSA guidelines.[2] While the DIG trial enrolled only patients in sinus rhythm,[13] the ACC/AHA/HFSA guidelines probably do not mention sinus rhythm to acknowledge that digoxin is often used to manage atrial fibrillation.

The ACC/AHA/HFSA guidelines further mention n-3 polyunsaturated fatty acids, potassium binders, and several contraindicated drugs.[2]

Sequence of drug initiation, modalities of drug up-titration and optimization

Both guidelines state that the four pillars of HFrEF treatment are first-line therapies, and leave it to the doctor to decide the order of initiation. Only the ACC/AHA/HFSA guidelines include specific recommendations on drug up-titration, reminding that target doses evaluated in clinical trials should be achieved, and proposing a tentative time schedule for up-titration (every 1–2 weeks under close monitoring).[2] Recommendations on initial doses and up-titration of neurohormonal modulators are given in the supplementary material of the ESC guidelines.[1]

Drug treatment for heart failure with mildly reduced ejection fraction

The ESC guidelines give a I C recommendation for diuretics, and IIb C recommendations for ACEi, ARB, beta-blockers, MRA, and sacubitril/valsartan.[1] The ACC/AHA/HFSA recommendation on ACEi, ARB, beta-blockers, MRA, and sacubitril/valsartan has also a class 2b, but these guidelines weigh differently the evidence (level B-NR), giving greater relevance to the subgroup analyses of trials on HFpEF, which often included a significant proportion of patients with an LVEF that actually fell within the definition of HF with mildly reduced ejection fraction (HFmrEF).[2] SGLT2i are also mentioned (2a B-R)[2] based on the one third of patients from EMPEROR-Preserved having HFmrEF.[14]

Drug treatment for heart failure with preserved ejection fraction

Recommendations about HFpEF treatment diverge widely. The ESC guidelines recommend just diuretics for congestion relief and optimal treatment of comorbidities.[1] The ACC/AHA/HFSA guidelines give a 2a recommendation for SGLT2i, although the only published trial results are on empagliflozin[14] (during revision of this manuscript a press release of the DELIVER trial reported that dapagliflozin also reached its primary endpoint in HFpEF). Furthermore, ARB, MRA and sacubitril/valsartan may be considered based on trials approaching statistical significance for their primary endpoint or showing a significant benefit in a subgroup of patients.[15–17] Routine use of nitrates or phosphodiesterase-5 inhibitors is not recommended.[18] Hypertension and atrial fibrillation are specifically mentioned, while diuretic therapy is not.[2] A strict application of these recommendations may lead to a heterogeneous management of HFpEF patients in Europe and the US.

Management of heart failure with improved ejection fraction

The ACC/AHA/HFSA guidelines follow the new Universal Definition of HF[19] and consider the proposed diagnostic entity of HF with improved ejection fraction (HFimpEF). Patients should not stop therapies recommended for HFrEF to prevent a new deterioration of cardiac function and new HF episodes.[2] The ESC guidelines express a similar message in the text, but not in specific recommendations.[1]

Device treatment

Both guidelines recommend an ICD for primary prevention for patients meeting all the following criteria: ischaemic HF aetiology, NYHA class II–III symptoms, LVEF ≤35%, ≥3 months (ESC) or 'chronic' (ACC/AHA/HFSA) optimal medical therapy, after >40 days from a MI, and with expected survival >1 year.[1,2] The ACC/AHA/HFSA guidelines extend this recommendation to patients with non-ischaemic aetiology,[2] while the ESC guidelines give a IIa A recommendation to this scenario.[1] This is possibly due to different interpretations of the DANISH trial being large enough to withdraw previous recommendation based on a failure to statistically prove a benefit on total mortality, even though sudden cardiac death was reduced in that trial as well.[20] An ICD is contraindicated in patients with NYHA class IV (ESC)[1] or with comorbidities or frailty and expected survival <1 year (ACC/AHA/HFSA).[2] Only the ESC guidelines explicitly recommend an ICD for secondary prevention, and the need to check the appropriateness of generator replacement.[1] The ESC guidelines also give a class IIb recommendation for wearable cardioverter defibrillators for selected HF patients who are at high risk for sudden death but otherwise are not suitable for ICD or as a bridge to an implanted device.[1] Nonetheless, the large VEST trial failed to show a benefit of wearable cardioverter defibrillators in patients with an LVEF ≤35% following a recent acute MI, which likely explains why the ACC/AHA/HFSA do not mention this option.[21]

Recommendations for cardiac resynchronization therapy (CRT) implantation are quite different, particularly for less well-established indications (*Table 5*). QRS cut-offs are 130 ms in the ESC and 120 ms in the ACC/AHA/HFSA guidelines, and each guideline proposes its own recommendations reflecting the general notion that CRT may prevent or relieve left ventricular dysfunction

Table 5 Indications to cardiac resynchronization therapy

ESC			ACC/AHA/HFSA					
Patient profile	**Class**	**Level**	**Patient profile**	**COR**	**LOE**	**Patient profile**	**COR**	**LOE**
Symptomatic HF, sinus rhythm, QRS ≥150 ms, LBBB, LVEF ≤35%	I	A	NYHA class II–III or ambulatory IV, sinus rhythm, QRS ≥150 ms, LBBB, LVEF <35%	1	B-R	NYHA class I, sinus rhythm, QRS ≥150 ms, LBBB, LVEF <30% + ischaemic HF	2b	B-NR
Symptomatic HF, sinus rhythm, QRS ≥150 ms, no LBBB, LVEF ≤35%	IIa	B	NYHA class II–III or ambulatory IV, sinus rhythm, QRS ≥150 ms, no LBBB, LVEF <35%	2a	B-R			
Symptomatic HF, sinus rhythm, QRS 130–149 ms, LBBB, LVEF ≤35%	IIa	B	NYHA class II–III or ambulatory IV, sinus rhythm, QRS 120–149 ms, LBBB, LVEF <35%	2a	B-NR			
Symptomatic HF, sinus rhythm, QRS 130–149 ms, no LBBB, LVEF ≤35%	IIb	B	NYHA class III or ambulatory IV, sinus rhythm, QRS 120–149 ms, no LBBB, LVEF <35%	2b	B-NR	NYHA class I–II, sinus rhythm, QRS <150 ms, no LBBB, LVEF <35%	3: No Benefit	B-NR
QRS <130 ms, no indications to pacing	III	A	QRS <120 ms				3: No Benefit	B-R
HFrEF (regardless of QRS/NYHA class) with indication to RV pacing (±AF)	I	A						
Conventional PM/ICD, worsening HF following RV pacing	IIa	B						
			Expected RV pacing >40%				2a	B-NR
			Indications to RV pacing + LVEF 36%–50%				2a	B-R
			AF + LVEF <35% + criteria for ventricular pacing/CRT *or* total RV pacing				2a	B-NR

Note: A summary of the recommendations is provided in online supplementary *Table S1*.
ACC/AHA/HFSA, American College of Cardiology/American Heart Association/Heart Failure Society of America; AF, atrial fibrillation; COR, class of recommendation; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; HF, heart failure; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LOE, level of evidence; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PM, pacemaker; RV, right ventricular.

from chronic right ventricular pacing.[1,2] The ACC/AHA/HFSA guidelines even propose some scenarios of CRT implantation in patients with NYHA class I or I–II.[2] As a result, the strength of recommendation may differ greatly even in the same scenario: for example, a patient with LVEF 38% and need for right ventricular pacing would have a I A indication to CRT in Europe and a 2a B-R indication in the US.

Comorbidities

Atrial fibrillation

Guideline recommendations about the need for anticoagulation and drug choice are similar.[1,2] The ESC guidelines identify the indications to cardioversion, and cite drug options for heart rate control.[1] For both guidelines catheter ablation should be considered when there is an association between atrial fibrillation episodes and HF decompensations.[1,2] The ACC/AHA/HFSA guidelines recommend atrioventricular nodal ablation and CRT for 'patients with atrial fibrillation and LVEF <50%' when rate control cannot be achieved.[2] This procedure has a 2a recommendation in the ACC/AHA/HFSA guidelines[2] versus a IIb recommendation in the ESC guidelines.[1]

Diabetes

Both guidelines recommend SGLT2i in patients with HFrEF and type 2 diabetes mellitus (T2DM).[1,2] The ESC guidelines specifically mention sotagliflozin,[1] despite the early discontinuation of the SOLOIST-WHF trial, the lack of a subgroup analysis specifically investigating the HFrEF subgroup, and the specific setting explored (recent HF decompensation).[22] The ACC/AHA/HFSA guidelines extend the indication to all patients with HF and T2DM.[2] The ESC

guidelines also recommend SGLT2i in patients with 'T2DM at risk of (cardiovascular) events',[1] while the ACC/AHA/HFSA guidelines recommend SGLT2i in a dedicated section on HF prevention.

Anaemia and iron deficiency

The ESC guidelines recommend to periodically screen for anaemia and iron deficiency,[1] while the ACC/AHA/HFSA guidelines do not.[2] Both guidelines recommend intravenous iron replacement to treat iron deficiency, but ESC guidelines specifically refer to intravenous ferric carboxymaltose.[1,2] The ACC/AHA/HFSA guidelines deem such replacement 'reasonable' (2a B-R),[2] while the ESC guidelines identify two scenarios, and give a level A recommendation for symptomatic patients with LVEF <45%.[1] As a consequence, the use of iron replacement therapy is more likely to become a part of the standard of care in Europe than in the US, particularly for patients with HFrEF or HFmrEF.

Valvular heart disease

The ACC/AHA/HFSA guidelines basically remind to dedicated guidelines on the topic,[2] whereas the ESC guidelines specifically recommend surgical aortic valve replacement or transcatheter aortic valve implantation for severe aortic stenosis.[1] Percutaneous correction of secondary mitral regurgitation should be considered if the patient 'fulfil criteria for achieving a reduction in HF hospitalizations' (basically corresponding to the inclusion criteria of COAPT).[23] It may be considered to improve symptoms or as a bridge to transplantation or mechanical circulatory support (MCS) in the patients not fulfilling these criteria.[1]

Coronary artery disease

The ACC/AHA/HFSA guidelines mention surgical revascularization in 'selected patients with HF, reduced LVEF (<35%), and suitable coronary anatomy'.[2] The 35% LVEF cut-off basically corresponds to the inclusion criterion of STICH (LVEF ≤35%).[24] The ESC guidelines refer to HFrEF, and propose coronary revascularization (preferably surgical) in patients with chronic coronary syndrome.[1] Nonetheless, these seemingly different recommendations substantially translate into a similar approach in clinical practice, considering the broad definition of chronic coronary syndrome by the ESC, which also includes patients with new-onset HF or left ventricular dysfunction and suspected coronary artery disease as well as asymptomatic subjects in whom coronary artery disease is detected at screening.[1]

Other comorbidities

Only the ACC/AHA/HFSA guidelines advise up-titration of anti-hypertensive drugs, a sleep assessment in patients with suspected sleep-disordered breathing (including the differentiation between obstructive and central sleep apnoea), and continuous positive airway pressure in patients with obstructive sleep apnoea,[2] underscoring the importance of sleep disorders as comorbidities in HF.

Exercise training and rehabilitation

Guidelines agree that physical activity is recommended to all patients with HF to improve functional status, exercise performance, quality of life (QOL) (ACC/AHA/HFSA and ESC), and to reduce HF hospitalization (ESC).[1,2] A cardiac rehabilitation programme is recommended for all patients with chronic HF 'who are able in order to improve exercise capacity, QOL, and reduce HF hospitalization', and should be considered in patients 'with more severe disease, frailty, or comorbidities' (ESC) or in 'patients with HF' (ACC/AHA/HFSA).[1,2]

General management, home telemonitoring

An HF management programme, pulmonary artery pressure monitoring, and vaccination against respiratory illnesses have similar recommendations.[1,2] Both guidelines recommend 'self-management strategies' (level A in ESC, B-R in ACC/AHA/HFSA).[1,2] The ESC guidelines also consider non-invasive home telemonitoring.[1]

Acute heart failure: management

The ACC/AHA/HFSA guidelines focus on the main principles of care for patients with acute HF, and stress that patients need tailored discharge instructions, and clear plans for home management and for diuretic dose adjustment.[2] A 1-week follow-up visit is recommended.[2] The ESC guidelines give detailed instructions on patient management during the acute phase and recommend treatment of iron deficiency.[1] Congestion should be excluded before discharge, and disease-modifying drugs should be started.[1] A first follow-up visit is recommended after 1 to 2 weeks.[1]

Advanced heart failure

The ACC/AHA/HFSA guidelines emphasize the need for management by specialized teams, and include a recommendation about fluid restriction in patients with congestion and hyponatraemia.[2] Only the ESC guidelines provide recommendations about renal replacement therapy and ultrafiltration.[1]

The ACC/AHA/HFSA guidelines discuss more extensively the indications to intravenous inotropes.[2] They give to continuous intravenous inotropic support a class 2a indication as a bridge to MCS or heart transplantation and a class 2b recommendation for ineligible patients as palliative therapy.[2] The ESC guidelines are slightly more restrictive and just give a class IIb recommendation to 'continuous inotropes and/or vasopressors' as a bridge to MCS or heart transplantation.[1]

The indications for short-term MCS are broadly similar.[1,2] The ESC guidelines specifically consider intra-aortic balloon pump, and propose long-term MCS for patients with advanced HF, not eligible for heart transplantation, without right ventricular dysfunction, and with good compliance to treatment.[1] These recommendations never go beyond a class IIa.[1] The ACC/AHA/HFSA guidelines give a class 1 indication to long-term MCS in select patients with advanced HFrEF with NYHA class IV symptoms and dependent on continuous intravenous inotropes or temporary MCS.[2] Long-term MCS as a bridge to transplant is contemplated just by the ESC guidelines.[1]

Heart transplantation has a I/1 C recommendation in both guidelines.[1]

End-of-life care

The ACC/AHA/HFSA guidelines include several recommendations about end-of-life care, stating that palliative and supportive care should be provided, care discontinuation should be discussed beforehand, advanced care directives can be useful, palliative care consultation and referral to hospice care should be considered.[2] Conversely, the ESC guidelines do not provide specific recommendations on these topics, albeit end-of-life and palliative care are extensively discussed in the text, without significant differences between the two guidelines.

Quality of care, cost-effectiveness

The ACC/AHA/HFSA guidelines recommend that patient-reported outcome measures be evaluated through validated questionnaires, adherence to guidelines be verified, institutions participate in quality improvement programmes.[2] Quality indicators are listed in the ESC guidelines and discussed in a companion article.[1,25]

Health disparities

Only the ACC/AHA/HFSA panel felt the need for specific recommendations about social determinants of inequal access to optimal HF care.[2]

Specific aetiologies

Both guidelines pay particular attention to some specific aetiologies. Cardiac amyloidosis (CA), pregnancy and cancer therapy-related toxicity are considered in both documents.

The ESC guidelines provide recommendations on tafamidis treatment for patients with amyloid transthyretin CA (ATTR-CA).[1] These recommendations refer to the population setting investigated in the ATTR-ACT trial and a subgroup analysis showing a greater survival benefit in patients with NYHA class I–II symptoms.[1,26] The ACC/AHA/HFSA guidelines recommend tafamidis also in patients with NYHA class III symptoms and add that tafamidis should be considered in 'select patients'.[2] The ACC/AHA/HFSA guidelines further recommend that: (i) patients with suspected CA should undergo the search for a monoclonal protein and then bone tracer scintigraphy, (ii) *TTR* gene mutations should be searched in ATTR-CA, and (iii) all patients with CA and atrial fibrillation should be anticoagulated.[2] The ESC guidelines provide an algorithm for the diagnosis of CA.[1]

The ESC guidelines provide an algorithm for the management of HF patients before and during pregnancy, but do not include any specific recommendations.[1] The ACC/AHA/HFSA guidelines include three level C-LD (limited data) recommendations about counselling for women with a history of HF or cardiomyopathy, anticoagulation for peripartum cardiomyopathy and severe systolic HF, and drugs to be avoided.[2]

Cancer patients to receive cardiotoxic drugs should receive a baseline cardiovascular assessment if they have a 'history or risk factors of (cardiovascular) disease' (ESC),[1] or 'cardiovascular risk factors or known cardiac disease' (ACC/AHA/HFSA).[2] The ESC guidelines also recommend that all patients starting cardiotoxic drugs be evaluated, with a lower level of evidence.[1] Monitoring is recommended by the ACC/AHA/HFSA guidelines, and might include serial troponin measurement.[2] Although not in any recommendation, increased surveillance with ECG and cardiac biomarkers during treatment and reassessment after completion of cancer therapy are recommended in patients at medium to high risk in an ESC guideline algorithm.[1] Cancer therapy-related cardiomyopathy is defined as an absolute LVEF reduction ≥10% to <50% in the ESC guidelines,[1] and simply as LVEF <50% in the ACC/AHA/HFSA guidelines.[2] When it develops, 'interruption, discontinuation, or continuation' of treatment should be considered (ACC/AHA/HFSA guidelines),[2] together with 'ACEi and a beta-blocker (preferably carvedilol)' (ESC)[1] or 'ARB, ACEi, and beta-blockers' (ACC/AHA/HFSA).[2]

Main differences between the ESC and ACC/AHA/HFSA guidelines

As discussed above, the ESC and ACC/AHA/HFSA guidelines are broadly consistent, although differing slightly concerning both some conceptual aspects as well as class of recommendations/level of evidence (*Table 2*). Two main reasons of divergence can be identified. First, the two guidelines were published at different time points, therefore the ACC/AHA/HFSA guidelines also incorporate more recently published trials, such as EMPEROR-Preserved, and more recently defined pathophysiological entities, such as HFimpEF. The other reason for conceptual divergence mostly reflects the different importance towards certain topics given by the two writing committees. For example, the ACC/AHA/HFSA guidelines pay more attention on the role of biomarkers beyond diagnostic tools, and to end-of-life care, QoL care, cost-effectiveness, and health disparities, whereas the ESC guidelines are keener on giving specific recommendations on the management of certain comorbidities, such as iron deficiency and end-stage renal disease in advanced HF.

As for the differences in terms of class of recommendation/level of evidence, the two guidelines mainly diverge because the two writing committees chose to give or not more relevance to certain observational studies or subgroup/*post hoc* analyses of clinical trials. In this regard, the recommendation for ARNI in HFrEF is emblematic, with ESC guidelines giving a I B recommendation citing only the evidence from PARADIGM-HF, whereas the ACC/AHA/HFSA guidelines providing a 1 A recommendation reporting the data on the effects of ARNI in acute HF as well as on cardiac remodelling and aortic stiffness. Similarly, in the case of HFmrEF, the ESC guidelines give a IIb C recommendations for ACEi, ARB, beta-blockers, MRA, and ARNI, while the ACC/AHA/HFSA guidelines provide a greater level of evidence (B-NR), giving more importance to the subgroup analyses of trials on HFmrEF/HFpEF.

Conclusions

Many recommendations by the ESC and ACC/AHA/HFSA guidelines are broadly consistent. Some prominent differences reflect

the timing of publication (with the incorporation of the Universal Definition of HF and the new results about empagliflozin in HFpEF in the ACC/AHA/HFSA guidelines), a different vision of the natural history of HF (with a clear differentiation between stage A and B HF in the ACC/AHA/HFSA guidelines), and also heterogeneous approaches to specific issues (e.g. primary prevention ICD for non-ischaemic HF). The ACC/AHA/HFSA guidelines provided 48 more recommendations encompassing also topics such as end-of-life care, cost-effectiveness and health disparities. Future writing panels may consider balancing the arguably stricter 'evidence only' approach of the ESC guidelines with the more pragmatic 'evidence supplemented by clinical advice' attitude of the ACC/AHA/HFSA guidelines. Statement harmonization will require a consensus agreement between the ESC and ACC/AHA/HFSA for the exact definition of the class and level of evidence, and possibly inter-societies writing panels, as the one recently producing the Universal Definition of HF.[19]

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

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