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Management of heart failure: similarities and discrepancies between the European Society of Cardiology and the American Heart Association guidelines

Antonio Luca Maria Parlati[1†], Christian Basile[1†], and Pasquale Perrone-Filardi[1*]

[1]*Dipartimento di Scienze Biomediche Avanzate, Università degli studi di Napoli 'Federico II', Napoli, Italy*

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Recommendations are the fundamental elements of guidelines and are especially significant when the amount of scientific data is expanding fast, as is the scenario of heart failure (HF). Beginning with the four pillars of treatment for HF with reduced ejection fraction, the main messages of the two most recent 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), partially overlap. There are notable differences, in part due to the timing of recent publications, like the Universal Definition of HF and the EMPEROR-Preserved trial, and in part due to differing perspectives on the natural history of HF. Specific challenges, such as risk stratification and the use of implanted cardioverter-defibrillators for primary prevention in HFrEF patients with non-ischaemic aetiology, are approached from a variety of perspectives. The ACC/AHA/HFSA recommendations place increased attention on topics that are especially pertinent to the US context, such as the cost-effectiveness of medications and the impact of health inequalities on HF care. A comparison of guideline suggestions may assist readers get a better grasp of the ESC and ACC/AHA/HFSA guidelines and apply logical ways to their own practice, wherever in the world that may be. A comparison may also contribute to the harmonization of future guidelines' recommendations by highlighting the reasons why certain areas have resulted to different recommendations while seemingly analysing the same published information.

Introduction

In the last decade, the publication of multiple randomized clinical trials investigating new therapeutic molecules in the field of heart failure (HF) has revolutionized treatment, providing the cardiologist with a variety of therapeutic tools.

Sacubitril/valsartan,[1] empagliflozin,[2] and dapagliflozin[3] have been recently shown to significantly reduce the risk of mortality and hospitalizations in patients with HF, while vericiguat[4] and omecamtiv mecarbil[5] proved useful weapons in patients with recent worsening of HF despite optimized medical therapy, further reducing the risk of hospitalization for HF.

The spectrum of drugs useful for HF has thus widened in addition to beta-blockers (BB), angiotensin converting enzyme (ACEi) inhibitors, angiotensin receptor antagonists (ARBs), and mineralocorticoid receptor antagonists (MRA), historic cornerstone of medical therapy for HF with reduced ejection fraction (EF). Innovative implantable devices[6] and new evidence in the field of interventional cardiology[7] have re-pointed the non-pharmacological

[†]The first two authors contributed equally to the study.
*Corresponding author. Via S. Pansini 5, 80131, Naples, Italy. Tel: +39 081 746 2232, Fax: +39 (081) 746 2234, Email: fpperron@unina.it

therapy of HF. The current challenge lies in giving order and proper priority to the various resources available. In this sense, the European Society of Cardiology (ESC)[8] and the American Heart Association (AHA)[9] have drawn up new guidelines for the treatment of HF to provide practical indications for the management of this pathology in light of the new evidence available.

If the overall 'take home messages' overlap between the two guidelines, the two societies entail a different position on some non-negligible points. This manuscript aims to help clinicians reach the best outcomes for their HF patients, highlighting along the way similarities and discrepancies between the two guidelines.

Definition of heart failure

Both guidelines classify HF based on EF and use the same cut-offs to distinguish between HF with reduced EF (EF ≤40%), HF with mildly reduced EF (EF 41–49%), and HF with preserved EF (EF ≥50%). In both cases, the EF value of 40% was merged into the 'HF with reduced EF' category. The novelty introduced by the AHA lies in the establishment of a fourth class called 'HF with improved EF', including those cases that initially present with EF ≤40% but at subsequent clinical checks improve left ventricular systolic function reaching an EF value > 40%. This condition, already introduced by the universal definition of the HF published in 2021 and only marginally mentioned in the ESC guidelines, gains relevance within the AHA guidelines which insist on the concept of the trajectory of HF and the reclassification of HF in the follow-up. Note, however, that for the American definition of 'HF with improved EF' it is sufficient for the patient to increase EF above the 40% threshold value, without mentioning the increase of at least 10 percentage points that is part of the definition proposed in the universal definition[10] (*Table 1*). Considering the intra- and inter-operator variability in the echocardiographic measurement of EF, the choice of the universal definition is at least more representative of an improvement that has substantial clinical relevance and appears more weighted. Dedicated studies have also validated the prognostic role of HF with improved EF according to the latter definition,[11] while studies focused on the AHA proposal and comparison studies are needed to define the real impact of the most recent reclassification of HF with improved EF.

Another aspect of discrepancy between the two guidelines lies in the definition of HF with mildly reduced EF where for the AHA the demonstration of an EF between 41% and 49% is not sufficient for diagnosis (as instead occurs in the European guidelines), but it requires the evidence of elevated filling pressures of the left ventricle at rest or during exercise with invasive or non-invasive methods. In addition, the AHA guidelines specify that in the HF with preserved EF, the evidence of structural alterations (e.g. increase in left ventricular mass, increase in left atrial volume) is supporting evidence and not a compelling criterion for the diagnosis of HF.

Prognostic stratification

While the ESC guidelines dedicate only a short paragraph to the prevention of HF, the American guidelines spend two large chapters for the stages preceding full-blown HF (stage C), namely patients at risk of developing HF (stage A) and patients with structural or functional changes indicative of HF but without symptoms/signs of HF (subclinical HF; stage B), providing guidance for diagnosis and recommendations for treatment of these conditions. Lifestyle modifications and targeted drug therapy in patients with diabetes mellitus and cardiovascular disease/risk factors and optimal blood pressure control in stage A patients; ACEi and BB for stage B patients are recommended to prevent or delay disease progression to symptomatic HF. In particular, the treatment of patients with asymptomatic left ventricular dysfunction (stage B) can significantly impact prognosis, resulting in a reduced incidence of events in subjects who are at increased risk of developing overt HF and in whom, mostly if young, due to underestimation or progressive adaptation, it is not always easy to define the presence of symptoms. Notably, AHA Guidelines recommend (level IIa) screening of patients at risk of HF (according to validated risk score) using peptides measurements to identify stage B patients, whereas no such recommendation is adopted in ESC Guidelines. Furthermore, a common shared recommendation between the ESC (IA) and AHA (IA) guidelines is the use of sodium/glucose cotransporter 2 inhibitors (SGLT2i) in diabetic patients with HF or at risk of HF, in order to reduce cardiovascular death and worsening kidney function.

Treatment in heart failure with reduced ejection fraction

Shared and undisputed is the therapy based on four classes of drugs that have been shown to be effective in reducing cardiovascular mortality and the rate of hospitalization for HF: ACEi or angiotensin and neprilysin receptor

Table 1 Comparison of the ESC guidelines, AHA guidelines, and the HF universal definition

	ESC (2021)	HF universal definition (2021)	AHA (2022)
HFrEF	EF ≤ 40%		
HFmrEF	EF 41–49% + sign or symptoms of HF	EF 41–49% + sign or symptoms of HF + elevated natriuretic peptides	EF 41–49% + sign or symptoms of HF + elevated left ventricle filling pressures
HFpEF	EF ≥ 50% + sign or symptoms of HF + elevated natriuretic peptides		EF ≥ 50% + sign or symptoms of HF + elevated left ventricle filling pressures
HFimpEF		Baseline EF ≤ 40%, increase of more than 10%, subsequent EF > 40%	Baseline EF ≤ 40%, subsequent EF > 40%

EF, ejection fraction; HF, heart failure.

inhibitors (ARNI), BB, MRA, and SGLT2i. The benefit from quadruple therapy (ARNI/BB/MRA/SGLT2i) was estimated to be 73% in terms of all-cause mortality reduction, justifying the position taken by both guidelines in recommending this therapy in all patients with HF and EF ≤40%.[12] However, the emphasis with which the two most recently introduced drugs in this context (ARNI and SGLT2i) are proposed is different.

The ESC guidelines remain bound to the PARADIGM trial,[1] maintaining a high degree of recommendation (class I), albeit with the level of evidence (B) linked to the publication of a single randomized study, for the use of ARNI only as a replacement for an ACEi. Conversely, the American guidelines indicate ARNI as the inhibitor of choice of the renin-angiotensin system in patients in NYHA class II-III, with the use of ACEi only if ARNI are not feasible due to intolerance or contraindications. Furthermore, the AHA recommends the *de novo* use of ARNI in acute HF hospitalized before discharge, thus emphasizing the results of those studies on sacubitril/valsartan in acute HF, whereas ESC consider a recommendation IIb B for the use of ARNI in the *de novo* HF.[13]

On the other hand, the SGLT2i recognize a common grade of recommendation IA in HF with reduced EF, with the difference that the European guidelines look at the saving of diuretic as an additional advantage deriving from this therapy, while the American guidelines draw attention to the possible adverse effects of SGLT2i in clinical practice, including volume depletion.

In patients with a recent hospitalization for HF and with persistent symptoms despite optimized medical therapy, the initiation of vericiguat can be considered, with the same degree of recommendation between the European and American guidelines (IIb B). Omecamtiv mecarbil, cited by the ESC as a promising drug in the light of the recent trial published, but still not recommended because it is not available on the market, is not even mentioned by the American guidelines. The novelty, however, of the American guidelines is the introduction with recommendation grade IIb B, of new potassium binders among the drugs indicated in the management of HF, to help maintenance and titration of drugs inhibiting the renin-angiotensin-aldosterone system. Finally, the hydralazine/isosorbide dinitrate composition deserves attention as a drug with demonstrated efficacy in the African American population with symptomatic HF which is strongly recommended by the AHA (I A) and less robustly by the European guidelines (IIa B), probably reflecting the different prevalence of African American subjects between America and Europe.

In any case, the commitment of both Cardiology Societies remains in promoting an individual declination of medical therapy for HF based on the characteristics of the individual patient, with an indication not to delay the initiation and optimization of treatment.

Treatment in heart failure with mildly reduced and preserved ejection fraction

In patients with HF with mildly reduced EF, the therapy for HF with reduced EF is substantially re-proposed by both guidelines, with a lower degree of recommendation and lower level of evidence in both ESC (IIb C) and AHA guidelines (2b B-NR), with the exception of SGLT2i that have a higher class of recommendation in the AHA guidelines (2a B-R), due to the availability of the EMPEROR-Preserved trial[14] results.

Instead, treatment of HF with preserved EF is approached differently between AHA and ESC. While Europeans do not provide specific recommendations for the treatment of patients with HF and EF ≥50%, suggesting aetiological research and subsequent treatment aimed at the underlying cause, AHA sees in HF with preserved FE a continuum compared with HF with reduced and mildly reduced EF, proposing the same therapies used therein, although maintaining a low level of recommendation. Underlying this indication are sub-analysis and meta-analysis of large trials that would suggest the efficacy of the renin-angiotensin-aldosterone system inhibitors across the entire spectrum of EF,[15,16,17] albeit with a reduction in the magnitude of benefit as EF increases. As for SGLT2i the degree of recommendation by the AHA is higher (IIa) and includes patients with HF and EF > 40%, according to the results of the EMPEROR-Preserved trial,[14] published at the same time as the European guidelines and therefore not included in the latter (*Table 2*).

As a further novelty within the American guidelines there is the indication of a degree of recommendation for the HF with improved FE that requires the continuation of the medical therapy started to prevent the recurrence of left ventricular dysfunction and HF (I B), an indication suggested by European guidelines but not reinforced by a specific degree of recommendation.

Finally, the large space dedicated within the AHA guidelines to the diagnosis and treatment of a specific aetiology

Table 2 Treatment for HFmrEF and HFpEF, with their respective level of recommendation

	HFmrEF		HFpEF	
	ESC 2021	AHA 2022	ESC 2021	AHA 2022
Diuretics	I	I	I	I
ACEi	IIb	IIb	Not reported	Not reported
ARBs	IIb	IIb	Not reported	IIb
ARNi	IIb	IIb	Not reported	IIb
BB	IIb	IIb	Not reported	Not reported
MRA	IIb	IIb	Not reported	IIb
SGLT2i	Not reported	IIa	Not reported	IIa

of HF with preserved EF, especially amyloid cardiomyopathy, deserves mention. The AHA provides a grade I B recommendation for tafamidis in patients with symptomatic transthyretin cardiac amyloidosis for NYHA class I-III, a more extensive indication than ESC which limits the use of tafamidis to patients in class NYHA I and II.

Imaging in heart failure guidelines

Echocardiography

ESC and AHA guidelines recommend with evidence class, respectively, of IA and IC transthoracic echocardiography (TTE) in all patients with suspected HF. In fact, due to its broad availability, low cost, and safety, echocardiography is the most used technique for the diagnosis, prognosis, and treatment selection of HF. In addition to rest TTE,[18] exercise, and pharmacological stress echocardiography[19] are used for the assessment of inducible ischaemia in those who are eligible for coronary revascularization with the same class of recommendation between ESC and AHA guidelines (2b-B).[20]

In the ESC guidelines in cancer patients undergoing cardiotoxic chemotherapy, new parameters like speckle tracking and global longitudinal strain (GLS) can be used to determine subclinical LV dysfunction, as suggested by the SUCCOUR trial.[21] There is no mention of the cardio-oncology use of GLS in the AHA guidelines, this may be due to the different interpretation of the SUCCOUR trial results as the cardioprotective treatment based on changes in GLS compared with treatment based on EF led to the same decrease in EF (primary endpoint), but with fewer patients developing cardiac dysfunction, defined as a symptomatic EF reduction of >5% or >10% asymptomatic to <55%, at the end of the study. The recently introduced ESC cardio-oncology guidelines[22] further strengthen this message suggesting the use of GLS in all patients with cancer having echocardiography (IC).

However, both ESC and AHA suggest the use of GLS without a specific class of recommendation for detecting subclinical LV dysfunction in the follow-up of HF patients.

Cardiac magnetic resonance

In ESC and AHA guidelines, cardiac magnetic resonance (CMR) is recommended with an IC evidence class in patients with a poor echocardiographic acoustic window. Furthermore, for the characterization of myocardial tissue in suspected cardiomyopathies, ESC (IC) and AHA (IIa-B) guidelines both suggest the use of CMR, however with a different level of evidence based on the AHA consideration of the OUTSMART-HF trial.[23] Additionally, the role of late gadolinium enhancement (LGE) to distinguish between ischaemic and non-ischaemic myocardial dysfunction is differently recognized: while ESC guidelines suggest the use of LGE with an IIa class of recommendation, in AHA guidelines the class of recommendation is 2b-B, for CMR as well as other imaging technique like PET and SPECT, based on meta-analysis[24] and a sub-analysis of the PARR-2 trial.[25] In fact, the width and the distribution of LGE in the myocardium can help evaluate the underlying aetiology of the HF since there are specific patterns connected to different pathological conditions (*Figure 1*).

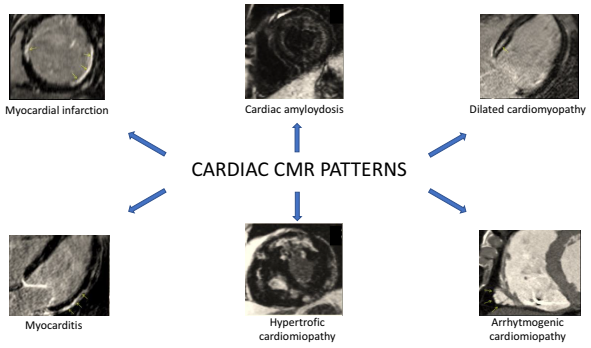

Figure 1 Various types of cardiac magnetic resonance pattern according to the aetiology.

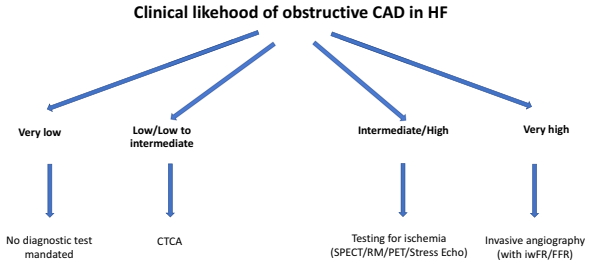

Figure 2 Diagnostic tools for ischaemia evaluation in heart failure patients according to clinical pre-test likelihood.

Coronary computed tomography angiography

ESC guidelines recommend with IIa class of recommendation to perform coronary computed tomography angiography (CCTA) in HF patients with a low to intermediate pre-test probability of coronary artery disease (CAD) or those with equivocal non-invasive stress tests to rule out the presence of CAD taking advantage of the high negative predictive value of the test. Conversely, AHA guidelines, while underlying the role of CCTA to detect and characterize CAD according to IMAGE-HF 1C trial,[26] do not report any clear recommendation for the use of CCTA in CAD, reserving the execution of CCTA with an IC evidence class in patients for whom echocardiography is inadequate in order to precisely assess the EF (Figure 2).

Conclusion

In recent decades, few fields of medicine have seen the substantial improvement of pharmacological therapy and diagnostic tools observed for HF. ESC and AHA Guidelines represent key documents for the implementation of evidence-based new approaches for the management of patients in clinical practice. Although some discrepancy in recommendations is expected due to differences in epidemiological and ethnic context as well as health system organization among different countries, harmonization among different cardiac societies' guidelines should be pursued to strengthen the impact in disseminating and implementing new evidence in the global scientific and clinical community.

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Data availability

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References

1. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR *et al*. Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
2. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P *et al*. EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**: 1413–1424.
3. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA *et al*. DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
4. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J *et al*. VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2020;**382**: 1883–1893.
5. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD *et al*. GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med* 2021;**384**: 105–116.
6. Adamo M, Fiorelli F, Melica B, D'Ortona R, Lupi L, Giannini C *et al*. COAPT-like profile predicts long-term outcomes in patients with secondary mitral regurgitation undergoing MitraClip implantation. *JACC Cardiovasc Interv* 2021;**14**:15–25.
7. Patel PA, Nadarajah R, Ali N, Gierula J, Witte KK. Cardiac contractility modulation for the treatment of heart failure with reduced ejection fraction. *Heart Fail Rev* 2021;**26**:217–226.
8. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M *et al*. ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
9. 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**:e895–1032.
10. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid M, 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. *Eur J Heart Fail* 2021;**23**:352–380.
11. Manca P, Stolfo D, Merlo M, Gregorio C, Cannatà A, Ramani F *et al*. Transient versus persistent improved ejection fraction in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2022;**24**: 1171–1179.
12. Bassi NS, Ziaeian B, Yancy CW, Fonarow GC. Association of optimal implementation of sodium-glucose cotransporter 2 inhibitor therapy with outcome for patients with heart failure. *JAMA Cardiol* 2020;**5**: 948–951.
13. Velazquez EJ, Morrow DA, DeVore AD, Velazquez EJ, Morrow DA, DeVore AD *et al*. PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;**380**: 1090.
14. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M *et al*. EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;**385**:1451–1461.
15. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N *et al*. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42.
16. Solomon SD, Vaduganathan M, Claggett B, Packer M, Zile M, Swedberg K *et al*. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation* 2020;**141**:352–361.
17. Sancassiani F, Carta MG, Montisci R, Preti A, Machado S, Moro MF *et al*. Takotsubo syndrome is associated with mood disorders and antidepressants use, not with anxiety and impairment of quality of life due to the psychiatric disorder. *CP & EMH* 2018;**14**:26–32.
18. Osto E, Tona F, Angelini A, Montisci R, Ruscazio M, Vinci A *et al*. Determinants of coronary flow reserve in heart transplantation: a study performed with contrast-enhanced echocardiography. *J Heart Lung Transplant* 2009;**28**(5):453–460.
19. Montisci R, Cecchetto G, Ruscazio M, Snenghi R, Portale A, Viel G *et al*. Early myocardial dysfunction after chronic use of anabolic androgenic steroids: combined pulsed-wave tissue Doppler imaging and ultrasonic integrated backscatter cyclic variations analysis. *J Am Soc Echocardiogr* 2010;**23**(5):516–522.
20. Gimelli A, Lancellotti P, Badano LP, Lombardi M, Gerber B, Plein S *et al*. Non-invasive cardiac imaging evaluation of patients with chronic systolic heart failure: a report from the European Association of Cardiovascular Imaging (EACVI). *Eur Heart J* 2014;**35**:3417–3425.
21. Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J *et al*. & SUCCOUR Investigators Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol* 2021;**77**: 392–401.
22. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J *et al*. ESC Scientific Document Group 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J* 2022;**43**:4229–4361.
23. Paterson DI, Wells G, Erthal F, Mielniczuk L, O'Meara E, White J *et al*. & IMAGE-HF Investigators OUTSMART HF: A randomized controlled trial of routine versus selective cardiac magnetic resonance for patients with nonischemic heart failure (IMAGE-HF 1B). *Circulation* 2020;**141**: 818–827.
24. McCrohon JA, Moon JC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ *et al*. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. *Circulation* 2003;**108**:54–59.
25. D'Egidio G, Nichol G, Williams KA, Guo A, Garrard L, deKemp R *et al*. & PARR-2 Investigators Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. *J Am Coll Cardiol Img* 2009;**2**:1060–1068.
26. Chow BJW, Coyle D, Hossain A, Laine M, Hanninen H, Ukkonen H *et al*. IMAGE-HF Investigators Computed tomography coronary angiography for patients with heart failure (CTA-HF): a randomized controlled trial (IMAGE-HF 1C). *Eur Heart J Cardiovasc Imaging* 2021;**22**:1083–1090.