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CONSENSUS DOCUMENT

Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology

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The European Society of Cardiology (ESC) has published a series of guidelines on heart failure (HF) over the last 25 years, most recently in 2016. Given the amount of new information that has become available since then, the Heart Failure Association (HFA) of the ESC recognized the need to review and summarise recent developments in a consensus document. Here we report from the HFA workshop that was held

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in January 2019 in Frankfurt, Germany. This expert consensus report is neither a guideline update nor a position statement, but rather a summary and consensus view in the form of consensus recommendations. The report describes how these guidance statements are supported by evidence, it makes some practical comments, and it highlights new research areas and how progress might change the clinical management of HF. We have avoided re-interpretation of information already considered in the 2016 ESC/HFA guidelines.

Specific new recommendations have been made based on the evidence from major trials published since 2016, including sodium–glucose co-transporter 2 inhibitors in type 2 diabetes mellitus, MitraClip for functional mitral regurgitation, atrial fibrillation ablation in HF, tafamidis in cardiac transthyretin amyloidosis, rivaroxaban in HF, implantable cardioverter-defibrillators in non-ischaemic HF, and telemedicine for HF. In addition, new trial evidence from smaller trials and updated meta-analyses have given us the chance to provide refined recommendations in selected other areas.

Further, new trial evidence is due in many of these areas and others over the next 2 years, in time for the planned 2021 ESC guidelines on the diagnosis and treatment of acute and chronic heart failure.

Keywords Heart failure • Therapy • Drugs • Devices • Consensus

Introduction/preamble

The European Society of Cardiology (ESC) has published a series of guidelines on heart failure (HF) over the last 25 years, most recently in 2016.[1–6] The next ESC guideline is not due until 2021. Given the amount of new information that has become available since 2016, the Heart Failure Association (HFA) of the ESC recognized the need to review and summarise recent developments in a consensus document. The growing appreciation that HF is caused by a great diversity of aetiologies, with various phenotypes and co-morbidities that affect the response to and, therefore, the choice of therapy creates exciting new opportunities to improve overall and personalised care, to the individual patient.[7]

This document is a report from the HFA workshop that was held in January 2019 in Frankfurt, Germany. The meeting brought together an international group of experts on HF to discuss and evaluate new evidence published after finalisation of the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF that occurred in March 2016 prior to its publication in May 2016.[8] There was no industry support for the meeting or any aspect of the consensus report, and there was no industry representation at the meeting. This expert consensus report is neither a guideline update nor a position statement, but rather a summary and consensus view in the form of consensus recommendations (see also online supplementary *Tables S1* and *S2*). The consensus report uses standard recommendation language to make our opinions understood in context and using comparable language, but it refrains from providing formal (numbered) recommendation classes or evidence levels. In general, the process followed was that the leadership group reviewed the covered field and assessed any new evidence that had been peer-review published since 2016. We opened this to all participants at the meeting and by email, and we agreed by consensus which fields were eligible for new statements via an iterative process to reach eventual consensus on all issues. No voting was required. The report describes how these guidance statements are supported by evidence, it makes some practical comments, and it highlights new research areas and how progress might change the clinical management of HF. We have avoided re-interpretation of information already considered in the 2016 ESC/HFA guidelines.

Pharmacotherapy

Sodium–glucose co-transporter 2 inhibitors

Consensus recommendation

The 2016 guidelines indicated that empagliflozin *should be considered* in patients with type 2 diabetes mellitus (T2DM) in order to prevent or delay the onset of HF or prolong life.[8]

The 2019 expert consensus was that canagliflozin and dapagliflozin *should also be considered* for patients with T2DM and either established cardiovascular (CV) disease or at high CV risk in order to prevent or delay the onset of and hospitalizations for HF.

At this stage, no specific recommendations for the use of sodium–glucose co-transporter 2 (SGLT2) inhibitors in patients with established HF can be made.

Supporting evidence. Empagliflozin was compared to placebo in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial in patients with T2DM and established CV disease. Patients assigned to empagliflozin had a 30% reduction in all-cause mortality, a 38% reduction in CV mortality, and a 35% reduction in HF hospitalizations.[9] Thereafter, similar findings were reported with regard to reductions in HF hospitalizations for dapagliflozin[10] in the DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) study and for canagliflozin[11] in the CANVAS (CANagliflozin cardioVascular Assessment Study) programme, that included T2DM with established CV disease or increased CV risk, respectively, but not for all-cause mortality [hazard ratio (HR) 0.90 and 0.93, respectively] or CV mortality (HR 0.96 and 0.93, respectively). Of note, in none of these trials was the presence of HF at baseline well

characterised or phenotyped, so that any recommendation with regard to treating established HF and T2DM will be necessarily cautious.

Most recently in the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial,[12] which enrolled patients at high risk of CV disease and mild to moderate chronic kidney disease (CKD), canagliflozin reduced HF hospitalisation by 39% ($P < 0.001$) and CV death by 22% ($P = 0.05$). All of these trials required patients to have T2DM, but fewer than 15% had HF at baseline. Inclusion criteria and endpoints varied. Positive results for SGLT2 inhibitors regarding renal protection effects were also reported from the EMPA-REG OUTCOME trial with empagliflozin,[13] the DECLARE-TIMI 58 study with dapagliflozin[10] and the CANVAS programme with canagliflozin.[11]

The consensus view was that there is sufficient evidence to consider that the ability of SGLT2 inhibitors to prevent hospitalizations for HF in patients with T2DM is a class effect. There is insufficient evidence to extend this observation to reductions in either CV or all-cause mortality or to patients without T2DM. Further clarification on whether the reduction in HF hospitalization occurs both in patients with and without pre-existing HF is required. One report from the CANVAS programme suggests that the reduction in hospitalizations for HF was observed only for patients with pre-existing HF.[14]

Subgroup analyses on the primary endpoints of the above mentioned trials have generally found similar relative benefit for patients with and without pre-existing HF, suggesting that the *absolute* benefit in patients with HF may be greater due to their high baseline risk. However, the diagnosis and phenotype of HF have generally not been well characterized. Of 10 142 participants in the CANVAS programme, 14.4% had a history of HF and these patients experienced a greater reduction of CV death or HF hospitalization [HR 0.61, 95% confidence interval (CI) 0.46–0.80] compared to those without a history of HF at baseline (HR 0.87; 95% CI 0.72–1.06).[14] Similar data were reported from the EMPA-REG OUTCOME trial where 706 patients (10.1%) were reported to have HF at baseline. But as in CANVAS, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class or levels of natriuretic peptides are not known.[15] In a post-hoc analysis of DECLARE-TIMI 58, benefits were greater in patients who were classified as HF with reduced ejection fraction (HFrEF) compared to patients classified as HF with preserved ejection fraction (HFpEF), but measurement of LVEF was missing in 25% of patients.[16]

Clinical trials in HF patients with and without T2DM and with HFrEF or HFpEF are ongoing (*Table 1*). These trials have recruited thousands of patients and have not yet been stopped for benefit or harm by their data monitoring committees.

Practical comments. SGLT2 inhibitors are already used for the management of T2DM. After initiating an SGLT2 inhibitor, on average, estimated glomerular filtration rate (eGFR) will deteriorate by 3–5 mL/min, but the long-term rate of decline in eGFR is slowed.[13] These observations await confirmation in the setting of HF.

SGLT2 inhibitors may interact with the effects of loop diuretic agents. Adjustment of the doses of diuretic agents and/or SGLT2 inhibitors may be required. Temporary withdrawal of SGLT2 inhibitors and diuretics and administration of fluids and sodium may be necessary for patients with clinical hypovolaemia or ketoacidosis. Genital infection in the context of treatment with SGLT2 inhibitors can be prevented by better hygiene, and patients should be made aware of the risk of this complication.

Directions for future development. In T2DM, new onset HF is common and is associated with a high mortality. Further subgroup analyses of existing trials should be conducted to confirm that SGLT2 inhibitors do indeed prevent new-onset HF for patients who did not have HF at baseline. The results of clinical trials of patients with prevalent and well defined HFrEF and HFpEF (with and without T2DM being present at baseline) are awaited before recommending these agents for the management of HF itself, rather than only for the treatment of T2DM (*Table 1*).

Canakinumab

Consensus recommendation

Evidence is not sufficient to provide a recommendation for its use in patients with HF.

Supporting evidence. The CANTOS [Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events)] trial[17] randomized 10 061 patients with prior myocardial infarction and elevated C-reactive protein to canakinumab or placebo. During a median follow-up of 3.7 years, 385 patients were hospitalized due to HF. Canakinumab use was associated with a dose-dependent reduction of hospitalization for HF and of the composite of hospitalization for HF or HF-related mortality. A similar effect was observed in a subgroup of 2173 patients (21.6%) with HF.[17,18] The consensus group considers the results on HF as hypothesis generating.

Practical comments. In CANTOS, canakinumab was given as a subcutaneous injection ensuring high adherence. The substantial annual cost and lack of major benefit limit its use.

Directions for future development. The Food and Drug Administration (FDA) denied regulatory approval for canakinumab for patients with coronary artery disease.[19] A new potential therapeutic area is lung and potentially other forms of cancer.[20] Relevant trials are ongoing.

Sacubitril/valsartan

Consensus recommendation

Sacubitril/valsartan *is recommended* as a replacement for angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB) to reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain

Table 1 Eighteen ongoing randomized trials of sodium–glucose co-transporter 2 inhibitors in patients with heart failure

SGLT2 inhibitor	Trial	Primary outcome	Disease	No. patients
Empagliflozin	EMPEROR-Preserved (NCT03057951)	Time to first CV death or hospitalization for HF	HFpEF	~5500
	EMPEROR-Reduced (NCT03057977)	Time to first CV death or hospitalization for HF	HFrEF	~3350
	EMPERIAL-Reduced (NCT03448419)	Change in 6-min walk distance	HFrEF	300
	EMPERIAL-Preserved (NCT03448406)	Change in 6-min walk distance	HFpEF	300
	Empire HF (NCT03198585)	Change in NT-proBNP	HFrEF	189
	SUGAR (NCT03485092)	Left ventricular end-systolic volume index and left ventricular global longitudinal strain	HFrEF	130
	Effects of Empagliflozin on Exercise Capacity and Left Ventricular Diastolic Function in Patients With Heart Failure With Preserved Ejection Fraction and Type 2 Diabetes Mellitus (NCT03753087)	Change in 6-min walk distance	HFpEF	100
	A Study That Looks at the Function of the Heart in Patients With Heart Failure Who Take Empagliflozin (NCT03332212)	Change in PCr/ATP ratio in the resting state	HF	86
	ELSI (NCT03128528)	Skin sodium content	HFrEF	84
	EMBRACE-HF (NCT03030222)	Change in pulmonary artery diastolic pressure	HF	60
Dapagliflozin	DAPA-HF (NCT03036124)	Time to first CV death, hospitalization for HF, or urgent HF visit	HFrEF	4744
	DELIVER (NCT03619213)	Time to first occurrence of CV death, hospitalization for HF, urgent HF visit	HFpEF	~4700
	PRESERVED-HF (NCT03030235)	Change in NT-proBNP	HFpEF	320
	DETERMINE-Reduced (NCT03877237)	Change in 6-min walk distance	HFrEF	300
	DETERMINE-Preserved (NCT03877224)	Change in 6-min walk distance	HFpEF	400
	DEFINE-HF (NCT02653482)	Change in NT-proBNP	HFrEF	263
Sotagliflozin	SOLOIST-WHF (NCT03521934)	Time to first CV death or hospitalization for HF	HFrEF	4000
Ertugliflozin	ERTU-GLS (NCT03717194)	Global longitudinal strain	HF	120

ATP, adenosine triphosphate; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCr, phosphocreatine; SGLT2, sodium–glucose co-transporter 2.

symptomatic despite optimal medical treatment with an ACE-I, a beta-blocker and a mineralocorticoid receptor antagonist (MRA).

Initiation of sacubitril/valsartan rather than an ACE-I or an ARB *may be considered* for patients hospitalized with new-onset HF or decompensated chronic HF to reduce the short-term risk of adverse events and to simplify management (by avoiding the need to titrate ACE-I first and then switch to sacubitril/valsartan). Because these patients are already at high risk of events, there is no need to check plasma concentrations of natriuretic peptides prior to initiating sacubitril/valsartan. As indicated in the 2016 HF guidelines,[8] ambulatory patients with HFrEF should have an elevated plasma concentration of natriuretic peptides indicating increased risk and the need for more effective therapy.

Supporting evidence. In secondary analyses of PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine

Impact on Global Mortality and Morbidity in Heart Failure), sacubitril/valsartan has been shown to improve survival in a broad range of patients who fulfilled the trial's inclusion/exclusion criteria, including those aged ≥75 years, and/or with co-morbidities such as T2DM.[21–23] Compared with enalapril, administration of sacubitril/valsartan reduced the incidence of diabetes requiring insulin treatment,[24] and the incidence of hyperkalaemia in those on an MRA.[25] The rate of decline in eGFR was also found lower with sacubitril/valsartan,[26] but this is not yet supported by 'slope of decline' analyses. Hypotension occurs more commonly with sacubitril/valsartan than with enalapril. However, patients who develop hypotension still appear to benefit from sacubitril/valsartan.[27]

In the PIONEER-HF (Comparison of Sacubitril/valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial, patients with HFrEF hospitalized for new-onset (about one third) or worsening chronic HF (about two thirds) were stabilized and then randomly assigned to receive either sacubitril/valsartan or enalapril; the reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) was greater in those assigned to sacubitril/valsartan at weeks 4 and 8 (the primary endpoint of this biomarker study).[28] The rates of worsening renal function, hyperkalaemia, symptomatic hypotension and angioedema were similar in the two groups[28] but there were fewer HF-related adverse events in patients assigned to sacubitril/valsartan.

In the open-label TRANSITION (Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event) trial,[29] more than 1000 patients with HFrEF hospitalized for worsening HF were randomized to start sacubitril/valsartan either before (initiated ≥24 h after haemodynamic stabilization) or after discharge (initiated within 14 days after discharge). Safety outcomes were similar for each strategy, indicating no disadvantage to early initiation, which may simplify management from both a clinician and patient perspective. A meaningful proportion of patients, 53% in PIONEER-HF and 24% in TRANSITION, respectively, were ACE-I/ARB naïve prior to sacubitril/valsartan initiation suggesting that the drug has similar efficacy and safety in these patients.

Practical comments. Sacubitril/valsartan is safe and effective in a broad spectrum of patients with HFrEF.[21–25,27,30] Its safety is similar in ACE-I/ARB naïve patients and thus its initiation may be considered also in these patients. In PIONEER-HF,[28] the incidence of hyperkalaemia (≥5.5 mmol/L) was similar for those assigned to enalapril (9.3%) or sacubitril/valsartan (11.6%). Amongst patients receiving MRA in the PARADIGM-HF trial, sacubitril/valsartan reduced the risk of severe hyperkalaemia (>6.0 mmol/L) as compared with enalapril (3.1 vs. 2.2 per 100 patient-years; HR 1.37; $P = 0.02$).[25] Sacubitril/valsartan may slow the rate of decline in eGFR and, in patients with T2DM, improve glycaemic control.[24]

PIONEER-HF required patients to have and NT-proBNP >1600 pg/mL (BNP >400 pg/mL). However, if the diagnosis of HF is certain and the patient has severe enough decompensation to require hospital admission, plasma concentrations of natriuretic peptides will usually be elevated and therefore their measurement might not be necessary. This is a very different situation from patients with ambulatory chronic HF and mild symptoms, in whom the benefit of sacubitril/valsartan is uncertain, if plasma concentrations of natriuretic peptides are not elevated.[31]

Directions for future development. The PIONEER-HF trial provides limited evidence that it is safe to initiate sacubitril/valsartan in ACE-I naïve patients; more evidence would be very welcome. Further results from an extensive trial programme including HFpEF (PARAGON-HF, NCT01920711) and patients with left ventricular dysfunction after myocardial infarction (PARADISE-MI, NCT02924727) may further extend the indications for sacubitril/valsartan. It would also be of interest to understand whether the use of potassium binders can reduce hyperkalaemia and enable more patients to tolerate sacubitril/valsartan at all, or at a higher dose.

Potassium binders

Consensus recommendation

Patiromer and ZS-9 *may be considered* in patients with HF with or without CKD to manage hyperkalaemia. In selected patients these therapies may enable use of MRAs and other renin–angiotensin–aldosterone system inhibitors (RAASi) in more patients and at higher doses, but it is not known whether this will improve patient outcomes.

Patiromer and ZS-9 *may be considered in selected patients* with HF with or without CKD in order to enable up-titration of MRA while avoiding hyperkalaemia.

Supporting evidence. Hyperkalaemia is an important reason for under-use of life-saving therapy with RAASi in HF, and it is particularly frequent in patients with more advanced kidney disease and T2DM.[32] Besides PEARL-HF (Evaluation of Patiromer in Heart Failure Patients),[33] a phase-2 trial published in 2011, new evidence is available from trials of patients with CKD and hypertension that also included subgroups of HF patients. The subgroup analysis of the AMETHYST-DN (Patiromer in the Treatment of Hyperkalaemia in Patients With Hypertension and Diabetic Nephropathy) trial[34] included 105 HF patients on RAASi. Per protocol, RAASi dose could not be down-titrated but patiromer could be up-titrated using a study-defined dosing algorithm. Patiromer was effective in maintaining normokalaemia and was well tolerated over 52 weeks of intervention. Findings were similar in groups with mild (K 5.0–5.5 mmol/L; all received spironolactone up to 50 mg on top of RAASi) and moderate (K 5.5–6.0 mmol/L) hyperkalaemia at baseline. The ability of patiromer to enable spironolactone initiation and up-titration in patients with HF and CKD was studied in 63 normokalaemic (K 4.3–5.1 mmol/L) patients in an open label design.[35] Patients were up-titrated to spironolactone 50 mg once daily and the patiromer dose was adjusted to maintain potassium within the range of 3.5–5.5 mmmol/L which at week 8 was achieved in 90% of patients. Both studies followed potassium and renal function regularly and demonstrated that patiromer had a good safety profile. No new evidence is available for ZS-9 in the field of HF.

Practical comments. Patiromer and ZS-9 are approved for clinical use in many European countries and the USA, but in others regulatory approval for local use is incomplete, and hence these drugs are not available everywhere.

Directions for future development. Subgroup results for HF patients enrolled in the AMBER (Spironolactone With Patiromer in the Treatment of Resistant Hypertension in Chronic Kidney Disease) trial are not yet available. A smaller trial of ZS-9 in HF patients to enable RAASi therapy ($n = 280$) has been initiated (PRIORITIZE HF, NCT03532009). A substantial clinical trial of patiromer ($n > 2000$) is underway investigating its effects on morbidity and mortality (DIAMOND, NCT03888066).

Treatment of congestion using diuretics

Consensus recommendation

Evidence is not sufficient to provide new practical recommendations for the use of diuretics.

Supporting evidence. No new evidence was published since 2016 for diuretic therapy. The ADVOR (Acetazolamide in Decompensated Heart Failure With Volume Overload) trial with acetazolamide is ongoing.[36]

Practical comments. With no strong evidence at hand, most of the volume management recommendations are consensus based and must focus on individual patients in whom tailored therapy is necessary. An HFA position statement with emphasis on clinical management was recently published.[37]

Directions for future development. There are several trials ongoing, including ADVOR (testing acetazolamide – NCT03505788), TRANSFORM-HF (testing torsemide vs. furosemide – NCT03296813), EMPA-RESPONSE-AHF (testing empagliflozin in acute HF – NCT03200860), and a trial of metolazone vs. chlorothiazide (NCT03574857). The development of user-friendly systems to deliver subcutaneous furosemide will require evaluation in clinical trials.[38,39]

Pharmacotherapy in heart failure with mid-range ejection fraction

No prospective trial has been conducted in patients with HF with mid-range ejection fraction (HFmrEF) to date. All analyses and related recommendations are based on post-hoc analyses from HFrEF and/or HFpEF trials, with inclusion criteria that included patients now classified as HFmrEF.

Beta-blockers for heart failure with mid-range ejection fraction

Consensus recommendation

A beta-blocker *may be considered* for ambulatory patients with symptomatic HFmrEF in sinus rhythm in order to reduce the risk of all-cause and CV death.

Supporting evidence. Under the auspices of the Beta-blockers in Heart Failure Collaborative Group (BBmeta-HF), individual patient data (IPD) from 11 major HF clinical trials, comparing beta-blockers and placebo, were pooled and meta-analysed.[40] In a subgroup of 575 patients with LVEF 40–49% in sinus rhythm (ischaemic aetiology 91%, NYHA class III–IV 24%, ACE-I/ARB 91%, MRA 6%, diuretics 65%), beta-blockers reduced the risk of all-cause and CV death (primary outcomes for this analysis). The absolute reduction in CV mortality in this subgroup was 4.7% [number needed to treat (NNT) to prevent one CV death = 21 during a median follow-up of 1.3 years].[40] Beta-blockers did not modify the risk of either the first CV hospitalization or the composite of CV death and CV hospitalization (time to first event) in patients with HFmrEF in sinus rhythm. Beta-blockers had no effect on either primary or secondary clinical outcomes in patients with HFmrEF and atrial fibrillation (AF).[40]

Directions for future development. These findings should be interpreted with caution as this was a post-hoc analysis. Specific trials in HFmrEF (possibly studied together with HFpEF patients) would be of interest.

Candesartan for heart failure with mid-range ejection fraction

Consensus recommendation

Candesartan *may be considered* for ambulatory patients with symptomatic HFmrEF in order to reduce the risk of HF hospitalization and CV death.

Supporting evidence. The post-hoc analysis of the pooled data from the CHARM programme compared the impact of candesartan on clinical outcomes in patients with HF across the whole spectrum of LVEF.[41] In a subgroup of 1322 patients with an LVEF 40–49% (ischaemic aetiology 67%, NYHA class III–IV 42%, ACE-I 27%, beta-blocker 58%, MRA 11%, diuretics 74%), candesartan reduced the risk of CV death and HF hospitalization (primary outcome for this analysis), the risk of first HF hospitalization and the risk of recurrent HF hospitalizations.[42] Candesartan did not modify the risk of either all-cause or CV death.

Directions for future development. These findings should be interpreted with caution as this was a post-hoc analysis. However, there was no statistical interaction between LVEF phenotype and candesartan treatment.[42] Specific trials in HFmrEF (possibly studied together with HFpEF patients) would be of interest.

Spironolactone for heart failure with mid-range ejection fraction

Consensus recommendation

Spironolactone *may be considered* for ambulatory patients with symptomatic HFmrEF without contraindications in order to reduce the risk of CV death and HF hospitalization.

Supporting evidence. A post-hoc analysis of the TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function) trial (spironolactone in HF with LVEF ≥ 45%) suggested that in a subgroup of patients with LVEF 44–49% ($n = 520$), spironolactone reduced the risk of the primary endpoint (defined as CV death, HF hospitalization, or resuscitated sudden death), which was mostly due to a reduction in CV mortality with spironolactone and most clearly observed in patients enrolled in North and South America.[42]

Directions for future development. The evidence is based on a post-hoc analysis, in a small subgroup of patients classified as HFmrEF based on measurements of LVEF made by investigators, which will suffer from substantial measurement variability and error, in a clinical trial which overall was neutral. These results do, however, provide the rationale and basis for the design of future trials in patients with HFmrEF,[43] including SPIRIT-HF (EudraCT 2017-000697-11) and SPIRRIT (NCT02901184). Given its well-proven anti-hypertensive effect, spironolactone may be especially useful in patients with poorly controlled hypertension.

Intravenous iron for heart failure with mid-range ejection fraction

Consensus recommendation

Evidence is insufficient to provide new practical recommendations.

Supporting evidence. Iron deficiency (ID) is common in patients with and without anaemia with HFrEF, HFmrEF and HFpEF, and is associated with worse symptoms, quality of life and clinical outcomes of patients with HF across the whole spectrum of LVEF.[43,44] Epidemiological evidence emphasises the need for screening for ID in patients with HF, regardless of LVEF, if blood haemoglobin is <14 g/dL.

Clinical trials investigating the effects of intravenous (IV) ferric carboxymaltose in ambulatory patients with symptomatic HF, LVEF ≤45% and ID [FAIR-HF (A Study to Compare the Use of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency), CONFIRM-HF (A Study to Compare the Use of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency) and EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure)] included approximately 150 patients with LVEF 40–45% (HFmrEF).[45–47] Subgroup analysis by LVEF categories has not been published.

Practical comments. All symptomatic patients with HF should have tests done for ID, if haemoglobin is <14 g/dL.

Directions for future development. Given the high prevalence of ID and its association with an unfavourable outcome in patients with HF regardless of LVEF, more clinical trial evidence for IV iron supplementation is awaited for HFrEF (IRONMAN – NCT02642562, AFFIRM-AHF – NCT02937454, FAIR-HF2 – NCT03036462, HEART-FID – NCT03037931) and HFpEF (FAIR-HFpEF – NCT03074591). Uncertainties also exist about the safety and efficacy of long-term IV supplementation, although a recent trial in patients with CKD [PIVOTAL (UK Multicentre Open-label Randomised Controlled Trial of IV Iron Therapy in Incident Haemodialysis Patients), EudraCT: 2013-002267-25] does not suggest any serious issues.[48] The key trials, so far, have been conducted with ferric carboxymaltose. Whether other iron preparations are similarly effective and safe should be established. Controversy also exists about which test is best for the diagnosis of ID, and whether more than one biomarker measure is required. In addition, more mechanistic studies like Ferric-HF II (EudraCT: 2012-005592-13)[49] are needed.

Tafamidis in cardiac transthyretin amyloidosis

Consensus recommendation

Older patients with symptomatic HF, particularly those with HFpEF (who are not hypertensive) or those who have features of hypertrophic or restrictive cardiomyopathy, or degenerative aortic stenosis and end-diastolic interventricular septal wall thickness exceeding 12 mm, *should be considered for screening* for cardiac transthyretin amyloidosis (ATTR).

Tafamidis *should be considered* in patients with symptomatic HF due to confirmed transthyretin amyloidosis [both autosomal dominant inherited disease (ATTRm) and wild-type transthyretin (ATTRwt)] in order to improve exercise capacity and quality of life, and to reduce CV hospitalizations and mortality. This recommendation is limited to patients who fulfil the inclusion and exclusion criteria of the ATTR-ACT (Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy) trial (*Table 2*).[50] These include confirmation of the presence of amyloid deposits on analysis of biopsy specimens obtained from the heart or other tissues (e.g. fat aspirate, gastrointestinal mucosa sites, salivary glands, or bone marrow).

Special note: the cost of tafamidis is currently extremely high, therefore many patients and health services may currently not be able to pay for it.

Supporting evidence. Amyloidosis includes a variety of pathologies caused by the extracellular accumulation of amyloid fibrils, leading to a progressive damage of the involved organ. When it affects the heart, it may cause HF which is often resistant to treatment and associated with a high mortality.[51,52] Systemic immunoglobulin light-chain amyloidosis (AL) is caused by plasma cell dyscrasias that may (myeloma) or may not (monoclonal gammopathy of uncertain significance) be malignant. This accounts for about 80% of contemporary cases of cardiac amyloid and is rapidly lethal if the underlying cause cannot be reversed. Transthyretin amyloidosis accounts for 15–25% of all cardiac amyloidosis and has a better prognosis, on average, than AL amyloid. Transthyretin amyloidosis has two forms: ATTRm and ATTRwt, which occurs sporadically. ATTR affects 20–30% of people aged >80 years and is

Table 2 Exclusion criteria of the ATTR-ACT trial[58]

1	They had, in the opinion of the investigator, heart failure that was not due to transthyretin amyloid cardiomyopathy
2	New York Heart Association class IV heart failure
3	The presence of light-chain amyloidosis
4	A history of liver or heart transplantation
5	An implanted cardiac device
6	Previous treatment with tafamidis
7	An estimated glomerular filtration rate <25 mL/min/1.73 m^2 of body surface area
8	Liver transaminase levels exceeding two times the upper limit of the normal range
9	Severe malnutrition as defined by a modified body mass index of <600 calculated as the serum albumin level in g/L multiplied by the conventional body mass index (the weight in kg/m^2)
10	Concurrent treatment with non-steroidal anti-inflammatory drugs, tauroursodeoxycholate, doxycycline, calcium channel blockers, or digitalis

more common in patients with HFpEF and/or degenerative aortic stenosis.[51–55] Novel single photon emission computed tomography cardiac imaging with bone-avid tracers (99mTc pyrophosphate, 3,3-diphosphono1,2-propanedicarboxylic acid, and hydroxymethylene diphosphonate (HMDP) help identify cases with high specificity, non-invasively,[56] obviating the need for endomyocardial biopsy. Similarly, the myocardial radiotracer uptake during bone scintigraphy could be used in clinical practice, as this was >99% specific and 86% sensitive to detect cardiac ATTR amyloid.[57]

Tafamidis prevents transthyretin tetramer dissociation and amyloidogenesis. In the ATTR-ACT trial, 441 patients with transthyretin amyloid cardiomyopathy and symptoms of HF received, in a 2:1:2 ratio, 80 mg of tafamidis, 20 mg of tafamidis, or placebo for 30 months. Transthyretin amyloid cardiomyopathy (ATTRwt or ATTRm) was confirmed by the presence of amyloid deposits on tissue biopsies and, in patients without ATTRm, by the presence of transthyretin precursor protein confirmed on immunohistochemical analysis, scintigraphy, or mass spectrometry.[50] Tafamidis reduced the risk of the combined primary endpoint (all-cause death and CV-related hospitalization), independently reducing all-cause mortality and the rate of CV-related hospitalizations. Tafamidis also slowed the rate of decline in both the 6-min walk distance and quality of life.[51]

Practical comments. The high prevalence of undiagnosed transthyretin amyloidosis in older patients with HF, particularly those with HFpEF with or without aortic stenosis, should be recognized. Non-invasive, nuclear imaging simplifies diagnosis, and may in the future serve as preferred screening and diagnostic tool. The major obstacle for widespread implementation of this therapy is the very high cost of therapy.

Directions for future development. Novel selective transthyretin stabilizers (e.g. AG10) and TTR gene silencers are at different stages of development.[58] We fully support efforts to reduce the high cost of this therapy.

Rivaroxaban in heart failure

Consensus recommendation

For ambulatory patients with coronary artery disease (CAD) and chronic HF in NYHA class I/II with an LVEF >30%, addition of rivaroxaban 2.5 mg bid to background treatment with aspirin *may be considered* in order to reduce the risk of stroke and CV death.

For chronic HF patients with a recent HF hospitalization or persistent NYHA class III/IV, initiation of treatment with rivaroxaban *cannot be recommended*, as there is no demonstrable benefit.

Supporting evidence. The COMMANDER-HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) trial enrolled 5022 patients with chronic HFrEF, CAD, a recent HF hospitalization and no AF[59] and randomised them to rivaroxaban 2.5 mg bid, added to background antiplatelet therapy, mostly aspirin, but including a substantial proportion on dual antiplatelet therapy. The mean follow-up was 21 months. The study was neutral on its primary endpoint of all-cause death, stroke, or acute myocardial infarction. Rivaroxaban did not reduce HF hospitalization but did reduce the rate of stroke from 3.0% to 2.0% (HR 0.66, 95% CI 0.47–0.95). A post-hoc analysis investigating the effect on a broad definition of vascular events (predominantly myocardial infarction, stroke, and sudden death)[60] demonstrated a significant reduction, although rivaroxaban had no effect on HF-related hospitalizations or HF deaths. There was an increase in major bleeding (from 2.0% to 3.3%; HR 1.68, 95% CI 1.18–2.39). The difference was driven mainly by the number of participants with a fall in haemoglobin of >2.0 g/dL, with a neutral effect on bleeding requiring hospitalization or resulting in death.

The COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) trial enrolled 27 395 patients, of whom 5902 had HF (predominantly with LVEF ≥40%; $n = 4250$) and randomly assigned them (double-blind) to aspirin 100 mg/day, rivaroxaban 2.5 mg bid plus aspirin 100 mg/day or rivaroxaban 5 mg bid.[61] Patients with NYHA class III/IV HF or a LVEF <30% were excluded. Mean follow-up was 23 months. Overall, compared to aspirin alone, the combination reduced stroke (from 1.6% to 0.9%; HR 0.58, IC 95% 0.44–0.76) and all-cause mortality (from 4.1% to 3.4%; HR 0.82, IC 95% 0.71–0.96), but not myocardial infarction (from 2.2% to 1.9%) or HF hospitalization (from 2.1% to 2.2%). Major bleeding events were higher on the combination (1.9% vs. 3.1%; HR 1.70, 95% CI 1.40–2.05), although rarely fatal (10 vs. 15 events). Rivaroxaban was neither superior to aspirin alone nor inferior to the combination. The combination exerted similar relative effects for patients with and without HF but the absolute gain was greater for patients with HF. For patients with HF, the combination reduced all-cause mortality from 6.5% to 4.4% (HR 0.66, 95% CI 0.50–0.86). Benefit was clearest amongst patients with HFpEF/HFmrEF, although

statistical tests could not confirm heterogeneity according to left ventricular phenotype. The effect of rivaroxaban 5 mg bid compared to aspirin 100 mg/day on all-cause mortality approached significance (HR 0.80, 95% CI 0.61–1.03). Amongst patients with HF, major bleeding events were higher on the combination (2.5%) compared to aspirin alone (1.8%; HR 1.36, 95% CI 0.88–2.09); although the risk appeared somewhat less than for patients without HF (3.3 vs. 1.9%, HR 1.79, 95% CI 1.45–2.21), tests for statistical heterogeneity were not significant.

For chronic HF patients with a recent HF hospitalization or persistent NYHA class III/IV, based on COMMANDER-HF, *initiation of treatment* with rivaroxaban cannot be recommended. However, *stopping of pre-existing therapy* with rivaroxaban in such patients cannot be recommended, as there is no related evidence.

Practical comments. A large proportion of patients with advanced HF have non-valvular AF. Relevant ESC guidelines indicate that these patients should receive a direct oral anticoagulant. Rivaroxaban 2.5 mg bid is not considered to be an effective dose for the prevention of thromboembolic events in patients with AF.

In summary, it appears that for patients with CAD rivaroxaban 2.5 mg bid in addition to low-dose aspirin reduces the risk of vascular events in patients without HF and with mild HF. However, for patients with advanced HF, myocardial dysfunction and congestion rather than vascular events determine outcome.

Directions for future development. These trials provide insights into the contribution of vascular events to the outcome of patients at various points across a broad spectrum of HF. The benefit and safety of aspirin in patients with HF remain in doubt, which should be addressed by further clinical trials. The strong trend for a reduction in mortality with rivaroxaban alone compared to aspirin alone (and its non-inferiority to combination therapy) should be investigated further.

Fixed dose drug combinations in heart failure

Consensus recommendation

Evidence is insufficient to provide new practical recommendations.

Supporting evidence. The incremental use of combinations of disease-modifying therapies has resulted in the progressive improvement in clinical outcomes for patients with HFrEF.[8,62] In a network analysis, the most effective combinations for HFrEF were (i) sacubitril/valsartan + beta-blocker + MRA, and (ii) ACE-I + beta-blocker + MRA + ivabradine, leading to reductions in all-cause mortality (vs. placebo) of 62% and 59%, respectively, and in all-cause hospitalizations of 42% for each combination.[63] The administration of fixed-dose combinations improves compliance, blood pressure control and clinical outcomes in patients with hypertension but this has not yet been demonstrated for HF.[63]

Directions for future development. Many guideline-recommended medications remain underutilized in community practice and many fail to reach target doses. Simplifying medication regimens and reducing total pill intake may be welcomed by patients and health professionals and improve adherence. Prospective trials investigating the effects of fixed-dose combinations should be encouraged.

Approaches to improving guideline adherence for drug therapy in heart failure

Consensus recommendation

Evidence is insufficient to provide new practical recommendations.

Supporting evidence. The 2016 ESC guidelines[8] state that implementation of multidisciplinary strategies in order to improve adherence to guideline-recommended medicines is recommended for patients with HFrEF in order to reduce the risk of HF hospitalization and CV and all-cause mortality. The ESC guidelines provide a framework to deliver evidence-based multidisciplinary care that translates into better quality of life and improved clinical outcomes in patients with HFrEF. However, adherence to guideline recommendations remains suboptimal for many reasons, including provider and patient education, lack of sufficient resources to advise patients, some patients' reluctance to take more medication, side effects and cost. A substantial group of patients with HF do not receive appropriate pharmacotherapy with adequate doses, and receives intracardiac devices without prior optimization of pharmacotherapy.

In QUALIFY (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY), an international, prospective, observational, longitudinal survey, amongst 6669 outpatients with HFrEF after recent HF hospitalization, good adherence for treatment with ACE-I, ARB, beta-blocker, MRA and ivabradine, with a prescription of at least 50% of recommended doses (which, however, is still less than what is achieved in many trials), was associated with a better clinical outcomes during 6-month follow-up (e.g. reduced mortality).[64] Similarly, in the BIOSTAT-CHF (a systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure) study, which was specifically designed to study up-titration of ACE-I/ARB and/or beta-blocker and enrolled 2516 patients with worsening HF, those treated with less than 50% of recommended doses had a greater risk of death and/or HF hospitalization.[65]

Directions for future development. There is a need to develop more practical strategies to improve adherence to guidelines. They should be based on multidisciplinary models, involving HF teams, structured referral schemes, telemedicine (using home-based methodology or also implantable pulmonary artery pressure and left atrial pressure monitoring systems), synchronized education of patients and health care providers, care standardization, quality control and audit. The development of centres of excellence, such as those recently described for the treatment of advanced HF,[66] may contribute to this goal.

Device-based therapies

Implantable cardioverter-defibrillators

Consensus recommendation

The consensus group did not identify any new evidence to alter the 2016 guideline recommendations[8] on implantable cardioverter-defibrillator (ICD) implantation in patients with HFrEF and CAD.

The consensus view was that *one may consider not to implant* an ICD in patients with non-ischaemic HFrEF who (i) are aged >70 years, or (ii) have advanced symptoms (NYHA class III/IV), or (iii) have life-shortening co-morbidity (e.g. severe lung disease or Stage IV CKD) and hence are likely to die for reasons other than sudden arrhythmic death (SAD).

Supporting evidence. A randomised trial of patients with non-ischaemic symptomatic HF and an LVEF ≤35% [DANISH (Danish ICD Study in Patients With Dilated Cardiomyopathy)] did not show that implanting an ICD for primary prevention reduced overall mortality despite a reduction in sudden deaths.[67] Many patients had a broad QRS and were randomised to receive cardiac resynchronization therapy (CRT) with a pacemaker (CRT-P) or a defibrillator (CRT-D) (58% of participants) but, similar to the main trial, no difference in mortality was observed in this subgroup. For patients aged <59 years, implantation of an ICD almost halved mortality but for those aged 59–67 years mortality was reduced by only 25% and for those aged 68 years or older, there was a 19% excess mortality. ICDs probably reduce sudden cardiac death throughout the age spectrum but fail to reduce all-cause mortality in older patients due to high rates of death due to worsening HF and non-cardiac co-morbidities. Patients with an NT-proBNP >1000 pg/mL did not benefit from an ICD. Pharmacological therapy should be optimized before a decision is made to implant an ICD. The risk of deferring ICD implantation by a few months in order to optimise therapy is low.

The benefit of the ICD is determined by the risk of sudden cardiac death over the risk of non-sudden cardiac death incorporating the high co-morbidity burden in HF patients. The rate of SAD appears to be declining, possibly due to improvements in pharmacological care,[68] which might reduce the absolute effect of ICDs on mortality. For patients with a LVEF ≤35% who do not have CAD, the most recent trial reported an annual risk of SAD of about 1% in patients who were assigned not to receive an ICD.

Practical comments. For younger patients (e.g. <70 years), implantation of an ICD is recommended provided the patient is considered unlikely to die of a cause other than SAD in the following 5 years (predicted reduction in mortality over 5 years of up to 5%).

Directions for future development. More trials comparing CRT-P and CRT-D are required, such as RESET-CRT (NCT03494933). The VEST trial (Vest Prevention of Early Sudden Death)[69] showed a reduction in mortality although not SAD in patients with an acute myocardial infarction and an LVEF <35%. Trials for patients with HF may be warranted although, given the generally low annual risk of SAD, this intervention may only be useful for some highly selected patient groups.

Atrial fibrillation ablation

Consensus recommendation

Pulmonary vein (PV) ablation of patients with HF and symptomatic paroxysmal AF *may be considered*, if paroxysms cause troublesome symptoms despite implementation of guideline-recommended pharmacological and device therapy.

Atrio-ventricular (AV) node ablation, usually with bi-ventricular rather than right ventricular pacing, *may be considered* if paroxysms provoke severe symptoms and PV ablation has failed or is not possible.

Pulmonary vein ablation for persistent AF *may be considered* for patients with HFrEF who have an implanted device (to prevent bradycardia; ICD, CRT or permanent pacemaker) if achieving and maintaining sinus rhythm is considered likely, especially if the onset of atrial AF was associated with a deterioration in symptoms of HF or the patient has (or is a candidate for) CRT. PV ablation is less likely to be successful in patients with long-standing AF and severe right and or left atrial dilatation.

Atrio-ventricular node ablation *is not recommended* in patients with CRT and AF with controlled heart rate due to a lack of evidence of clinical benefit that ablation is superior to pharmacological rate control.

Supporting evidence. The debate on whether rate or rhythm control is the better strategy for managing AF complicating HF continues. Anticoagulants should be continued even if sinus rhythm is restored because the risk of recurrent AF is high. An optimal rate control strategy must avoid excessive heart rate reduction as well as toxic antiarrhythmic agents, potentially including higher doses of amiodarone or plasma concentrations of digoxin. A modest dose of beta-blocker may be the safest option for rate control in patients with AF, even if beta-blockers do not appear to improve outcome when titrated to conventional target doses.[70] A rate control strategy for persistent AF avoids the need for procedures and potentially toxic drugs and the problems that relapse into AF can cause. For those with symptomatic paroxysmal AF and HF there is a stronger rationale for a rhythm control strategy.

There is no substantial trial investigating PV or AV node ablation for paroxysmal AF in patients with HF. However, where there is a clear association between paroxysmal AF and marked worsening of symptoms which persist despite guideline-recommended therapy, then PV ablation or, if that fails, AV node ablation should be considered.

Patients ($n = 3103$) with HF and persistent AF were evaluated for inclusion in the CASTLE-AF (Catheter Ablation vs. Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) trial comparing pharmacological rate or rhythm control with PV ablation in patients with HFrEF (LVEF <35%) and an ICD or CRT-D device (to prevent post-ablation bradycardia).[71] Finally, only 363 patients were randomized (about 50 patients per year) of whom only 317 received

their assigned strategy. PV ablation often failed, with a residual burden of AF of about 25%. Neither patients nor investigators were blind to assigned management strategy and 33 patients were lost to follow-up. A reduction in the primary composite endpoint of death from any cause or hospitalization for worsening HF was reported for the intervention arm patients (28% vs. 45%; HR 0.62, 95% CI 0.43–0.87). The effect was consistent over primary endpoint composites (HR 0.53 and 0.56, respectively, $P \leq 0.01$ for both). After 3 years of follow-up, at which time there were fewer than 100 patients in each group, a difference in mortality appeared (24 deaths with ablation vs. 46 deaths in control). Patients with less advanced HF (LVEF >25%, NYHA class II, <65 years old) potentially derived greater benefit.

The CABANA (Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial also compared PV ablation to medical therapy.[72,73] Only 337 of 2204 patients randomized had HF at baseline. Overall, the trial was neutral for its primary composite endpoint (HR 0.86, 95% CI 0.65–1.15). The point-estimate was somewhat better for patients with HF (HR 0.61, 95%CI 0.35–1.08), and was associated with an improvement in quality of life at 12 months.

A meta-analysis of older trials reported 18 deaths amongst patients assigned to control compared to 9 assigned to ablation.[74] In summary, the data suggesting that a rhythm rather than a rate control strategy is superior is not robust for patients with persistent AF. The trials were not blinded and the patients highly selected. Further trials are required.

Several trials show that bi-ventricular pacing is superior to right ventricular pacing after AV node ablation.[75] This may reflect the deleterious effects of right ventricular pacing rather than any benefit of bi-ventricular pacing. The landmark trials all required patients to be in sinus rhythm. CRT may require AV as well as bi-ventricular resynchronization to be effective. A small, ($n = 102$) unblinded trial comparing AV node ablation with pharmacological treatment suggested benefit to the ablation strategy but there were too few events to be convincing.[76] Accordingly, the consensus opinion was to avoid this strategy until more evidence of benefit is obtained.

Although AV node ablation will increase bi-ventricular capture, there is no evidence from adequately designed randomized controlled trials that this improves patient well-being or outcome.[77]

Practical comments. Ensure that the patient is receiving an effective anticoagulant regimen. The optimal resting ventricular rate for patients with HF and AF may be 70–90 bpm. Antiarrhythmic agents should generally be avoided other than to control symptomatic paroxysmal AF; PV ablation may be a better strategy than amiodarone/dronedarone, the latter is contraindicated in HF. Ablation is best reserved for patients with paroxysmal AF where episodes cause marked worsening of symptoms despite guideline-recommended therapy at optimal doses. There is little evidence of benefit from CRT in the absence of sinus rhythm or that AV node ablation to increase bi-ventricular capture improves outcomes. AV node ablation should be an intervention of last resort. PV ablation to restore sinus rhythm is preferred in patients with CRT. Neither the safety nor efficacy of PV ablation for persistent AF and HF in the absence of back-up pacing has been demonstrated.

Directions for future development. The group believes that a series of randomized controlled trials is required comparing 'non-aggressive' pharmacological rate control, avoiding amiodarone or Class I antiarrhythmic agents and higher doses or plasma concentrations of digoxin with the following procedures:

1 PV (and/or AV node) ablation for paroxysmal AF and HF vs 'non-aggressive' pharmacological rate control (and avoiding all of: amiodarone, Class I antiarrhythmic agents, higher doses or higher plasma concentrations of digoxin).
2 PV (and/or AV node) ablation for persistent AF and HF with or without a back-up pacing device vs 'non-aggressive' pharmacological rate control (and avoiding all of: amiodarone, Class I antiarrhythmic agents, higher doses or higher plasma concentrations of digoxin).
3 PV (and/or AV node) ablation in HF patients with CRT vs. usual care.
4 There is also a need for randomized controlled trials comparing different rate control strategies, including:

   (i) high- vs. low-dose beta-blocker;
   (ii) addition of digoxin to beta-blockers. The ongoing DIGIT-HF (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure) trial includes patients with AF, but excludes patients in need of rate control with digitalis glycosides.[78]

5 There is also a need for randomized controlled trials investigating:

   (i) new agents for pharmacological rhythm control (double-blind vs. placebo);
   (ii) prevention of AF (double-blind vs. placebo);
   (iii) better treatments to prevent AF recurrence (double-blind vs. placebo).

MitraClip

Consensus recommendation

Referral of patients with HF and secondary (i.e. functional) mitral regurgitation to a multidisciplinary HF team that will decide on management *is recommended*.

Reduction in mitral regurgitation using a MitraClip device *may be considered* for patients with HFrEF who fulfil the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) selection criteria (*Table 3*).[79]

Supporting evidence. The MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation)[80] and COAPT[79] trials (recruiting 303 and 614 patients, respectively) included different populations

Table 3 Inclusion/exclusion criteria from the COAPT trial[87]

Inclusion criteria (all must be present)

1 Symptomatic secondary mitral regurgitation (3+ or 4+ by independent echocardiographic core laboratory assessment) due to cardiomyopathy of either ischaemic or non-ischaemic aetiology
2 Subject has been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure
3 New York Heart Association functional class II, III or ambulatory IV
4 Subject has had at least one hospitalization for heart failure in the 12 months prior to enrolment and/or a corrected[a] BNP ≥300 pg/mL or a corrected[a] NT-proBNP ≥1500 pg/mL
5 Local heart team has determined that mitral valve surgery will not be offered as a treatment option, even if the subject is randomized to the control group
6 Left ventricular ejection fraction ≥20% and ≤50%
7 Left ventricular end-systolic dimension ≤70 mm
8 The primary regurgitant jet is non-commissural, and in the opinion of the MitraClip implanting investigator can successfully be treated by the MitraClip (if a secondary jet exists, it must be considered clinically insignificant)
9 Creatine kinase-MB obtained within prior 14 days is less than the local laboratory upper limit of normal
10 Transseptal catheterization and femoral vein access is feasible per the MitraClip implanting investigator
11 Age ≥18 years
12 Subject or guardian agrees to all provisions of the protocol, including the possibility of randomization to the control group and returning for all required post-procedure follow-up visits, and has provided written informed consent

Exclusion criteria (all must be absent)

1 Untreated clinically significant coronary artery disease requiring revascularization
2 CABG, PCI, or TAVR within the prior 30 days
3 Aortic or tricuspid valve disease requiring surgery or transcatheter intervention
4 COPD requiring continuous home oxygen therapy or chronic outpatient oral steroid use
5 Cerebrovascular accident within prior 30 days
6 Severe symptomatic carotid stenosis (>70% by ultrasound)
7 Carotid surgery or stenting within prior 30 days
8 ACC/AHA Stage D heart failure
9 Presence of any of the following: estimated PASP >70 mmHg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the cath lab is able to reduce PVR to <3 Wood Units or between 3 and 4.5 Wood Units with v wave less than twice the mean of PCWP
10 Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischaemic or non-ischaemic aetiology
11 Infiltrative cardiomyopathies (e.g. amyloidosis, haemochromatosis, sarcoidosis)
12 Haemodynamic instability requiring inotropic support or mechanical heart assistance
13 Physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe right ventricular dysfunction
14 Implant of CRT or CRT-D within the last 30 days
15 Mitral valve orifice area <4.0 cm^2 by site-assessed transthoracic echocardiography
16 Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets, or sufficient reduction in mitral regurgitation by the MitraClip
17 Haemodynamic instability defined as systolic pressure <90 mmHg with or without afterload reduction, cardiogenic shock, or the need for inotropic support or intra-aortic balloon pump or other haemodynamic support device
18 Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months
19 Life expectancy <12 months due to non-cardiac conditions
20 Modified Rankin Scale ≥4 disability
21 Status 1 heart transplant or prior orthotopic heart transplantation
22 Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure
23 Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
24 Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e. non-compliant, perforated)
25 Active infections requiring current antibiotic therapy
26 Transoesophageal echocardiography is contraindicated or high risk
27 Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically
28 Pregnant or planning pregnancy within the next 12 months
29 Currently participating in an investigational drug or another device study that has not reached its primary endpoint
30 Subject belongs to a vulnerable population or has any disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures

ACC, American College of Cardiology; AHA, American Heart Association; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TAVR, transcatheter aortic valve replacement.
[a]'Corrected' refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in body mass index above a reference of 20 kg/m^2.

and reported very different results on the clinical efficacy of MitraClip. In COAPT, patients assigned to MitraClip were more likely to be prescribed ACE-I, ARB or angiotensin receptor–neprilysin inhibitor (ARNI) at baseline (72% compared to 63%, $P = 0.02$). By 12 months this difference had increased (77% compared to 63%, $P = 0.002$) and more patients assigned to MitraClip were receiving beta-blockers (93% vs. 87%, $P = 0.02$). In COAPT, the baseline LVEF was 31% (vs. 33% in MITRA-FR), the left ventricular end-diastolic diameter was 62 ± 7 mm (vs. 68 ± 8 mm in MITRA-FR), and the effective regurgitant orifice area was on average 40 ± 15 mm^2 (vs. 31 ± 10 mm^2 in MITRA-FR). Over 24 months, COAPT reduced HF hospitalizations by 47% ($P < 0.001$) and all-cause mortality by 38%

($P < 0.001$) and improved average 6 min-walking test distance by >50 m ($P < 0.001$). Over a follow-up of 12 months, no such benefits were observed in MITRA-FR. However, the outcomes of these two trials at 1 year were not statistically different.[7] Longer-term follow-up for the MITRA-FR trial might reveal a deferred benefit.

Practical comments. If interventional therapy is considered, a multidisciplinary team involving HF specialists, interventionalists, imaging experts and cardiac surgeons should be involved in patient evaluation and decision making. Medical therapy should be optimized before deciding on intervention. Treatment with sacubitril/valsartan for HFrEF may also be of some importance as demonstrated recently in the PRIME (Pharmacological Reduction of Functional, Ischaemic Mitral Regurgitation) trial.[81] Of note, the PRIME study was a small ($n = 118$) double-blind randomized controlled trial comparing sacubitril/valsartan to valsartan alone in HF patients with chronic functional mitral regurgitation. The primary endpoint, the reduction in echo-derived effective regurgitant orifice area, was reached at a borderline level of significance (-0.058 ± 0.095 vs. -0.018 ± 0.105 cm^2; $P = 0.032$). The trial was too small to show any clinical benefits and echo-derived parameters of mitral regurgitation severity are not considered to constitute evidence of clinical benefit. The ratio of the severity of mitral regurgitation to the severity of left ventricular dilatation may be a key determinant of the response to mitral valve repair; patients with disproportionately severe mitral regurgitation may benefit more.

Directions for future development. The Reshape-HF2 trial (NCT02444338) is ongoing and will have more patient-year follow-up than either published trial.

Treatment of central sleep apnoea

Consensus recommendation

Patients with HF and suspected sleep apnoea who are being considered for positive pressure airway mask therapy *are recommended* to undergo a specialized sleep study in order to diagnose the characteristics of the sleep apnoea present, in particular whether the sleep apnoea is predominantly obstructive or central in nature.

In patients with predominantly central sleep apnoea (CSA) and concomitant HFrEF, evidence is insufficient to recommend CSA therapy for any putative benefit in HF itself, and treatments directed at CSA should be reviewed and avoided, unless compelling symptomatic indications for treatment of CSA exist, in which case positive pressure airway mask therapy should be avoided and phrenic nerve stimulation (PNS) *may be considered* as an alternative.

Supporting evidence. HFrEF patients with predominantly CSA suffered an increase in mortality in SERVE-HF (Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure),[82] so that it is essential to know if such patients have CSA prior to starting positive airway pressure therapy. One small trial [Pivotal (A Randomized Trial Evaluating the Safety and Effectiveness of the remedē® System in Patients With Central Sleep Apnea)][83] showed promise for PNS for the treatment of severe CSA. However, the randomized trial included only 151 patients (73 assigned to PNS) of whom only 96 had HF (48 assigned to PNS – and perhaps only half of these had HFrEF) and follow-up was for only 6 months. PNS improved apnoea-hypopnoea index and symptoms, although blinding may have been imperfect; two deaths occurred in each group.

Practical comments. Phrenic nerve stimulation received FDA approval in 2018 and is also reimbursed in a number of European countries. Further clinical trials are required before making positive recommendations. The learning curve for this new therapeutic approach is considered to be 3–10 cases for experienced interventionalists. Patients can on occasion feel the stimulation, an effect which reduces over a few weeks. The device is designed to stimulate only during sleep, thereby reducing the chance of ongoing stimulation awareness.

Directions for future development. The prevalence of CSA to some degree depends on the disease definition and HF severity. A study to investigate the impact on morbidity and mortality of PNS is required before making recommendations for broader use in the HF population.

Cardiac contractility modulation

Consensus recommendation

Cardiac contractility modulation (CCM) *may be considered* in patients with HFrEF (LVEF 25–45%) and a narrow QRS complex (<130 ms) in order to improve exercise capacity, quality of life and alleviate HF symptoms.

Supporting evidence. In the FiX-HF 5C (Evaluate Safety and Efficacy of the OPTIMIZER® System in Subjects With Moderate-to-Severe Heart Failure) trial,[84] CCM increased peak oxygen uptake by 0.84 [95% Bayesian credible interval: 0.123–1.552 mL O_2/kg/min (the primary endpoint), and the Minnesota Living With Heart Failure questionnaire] ($P < 0.001$), NYHA functional class ($P < 0.001$), and 6-min hall walk ($P = 0.02$). This trial used an FDA-approved design and analysis to confirm the results on an earlier subgroup analysis. Although its limitations, i.e. the unblinded nature, and a small sample size (160 patients), with short follow-up duration (24 weeks), not powered to look at outcomes, the point-estimate showed the composite of CV death and HF hospitalizations reduced from 10.8% to 2.9% ($P = 0.048$).

Practical comments. Cardiac contractility modulation is now approved in the USA and Europe. CCM may be used to improve symptoms and exercise capacity in selected HFrEF patients with troublesome symptoms despite pharmacological therapy who have a QRS duration of <130 ms and are therefore not indicated for CRT.

Directions for future development. A study to investigate the impact of CCM on morbidity and mortality is being planned.

Mechanical ventricular assist devices

Consensus recommendation

There is limited evidence to make new recommendations. For patients with advanced HF that are considered for implantation of a HeartMate left ventricular assist device, a HeartMate 3 rather than HeartMate II device *should be considered*.

Supporting evidence. ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management)[85] tested the HeartMate II vs. optimized medical therapy as destination therapy. No difference for survival was found, but use of HeartMate II was associated with better functional capacity and quality of life. ENDURANCE (The HeartWare™ Ventricular Assist System as Destination Therapy of Advanced Heart Failure)[86] tested the HeartMate HVAD system vs. HeartMate II in patients with advanced HF eligible for heart transplantation, and showed non-inferiority for the HVAD system; however, stroke and device malfunction rates were increased with this system. MOMENTUM 3 (Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3™ IDE Clinical Study)[87] is a pivotal trial for HeartMate 3 vs. HeartMate II. Use of HeartMate 3 was associated with better 2-year survival and fewer adverse events.

Disease management and lifestyle

Multidisciplinary heart failure management programmes

Consensus recommendation

As already stated in the 2016 ESC HF guidelines, it *is recommended* that HF patients are enrolled in a multidisciplinary HF management programme. Both home-based and clinic-based programmes can improve outcomes. Self-management strategies are encouraged.

Supportive evidence. Although evidence on the effectiveness of multidisciplinary HF management programmes was established in the 2016 guidelines,[8] new studies have been published since then, often investigating the optimal components and intensity of these programmes. In 2017, van Spall *et al.*[88] published a network meta-analysis of 53 randomized controlled trials, concluding that both nurse home visits and disease management clinics reduced all-cause mortality compared to usual care; nurse home visits being most effective. Jonkman *et al.*[89] published an IPD meta-analysis of 20 studies, including 5624 patients, and concluded that self-management interventions in HF patients improve outcomes despite heterogeneity, diversity in intensity, content and personnel who deliver the intervention.

Directions for future development. Studies addressing the benefits of multidisciplinary HF disease management programmes, barriers and opportunities for their implementation and interactions and synergies with a variety of health care systems would be valuable.

Salt/sodium intake

Consensus recommendation

There is no robust new evidence on the benefits of manipulating salt intake on clinical status amongst either outpatients or inpatients.

Supportive evidence. A recent systematic review[90] identified nine trials involving 479 unique participants, none including more than 100 patients; results were inconclusive. Although there was a trend toward improvement in the clinical signs and symptoms of HF with reduced intake of dietary salt, no clinically relevant data on whether reduced dietary salt intake affected outcomes such as CV-associated or all-cause mortality, CV-associated events, hospitalization, or length of hospital stay were found.

Direction for future development. Several trials investigating salt restriction in HF are in progress. Sodium, chloride and water balance are all important. Oedema and congestion are volumetrically mainly due to water. Many patients with severe HF have hyponatraemia. Ensuring that net loss of water exceeds that of salt may be important for the management of oedema. Well-designed, adequately powered studies are needed to reduce uncertainty about sodium restriction in HF patients.

Exercise-based cardiac rehabilitation

Consensus recommendation

It *is recommended* that patients with HFrEF are enrolled in an exercise-based cardiac rehabilitation programme to reduce the risk of HF hospitalization.

Supportive evidence. A new meta-analysis[91] and an updated Cochrane meta-analysis[92] identified 44 trials that included 5783 people with HFrEF and both showed that exercise rehabilitation reduced hospital admissions overall, as well as for HF. The effect on health-related quality of life is uncertain due to lower-quality evidence. However, neither the participants nor the investigators were blind to intervention and many older patients with HF will have been excluded due to their inability to comply with trial requirements.

Directions for future development. Further evidence is needed to show whether exercise rehabilitation benefits older, frailer patients and those with HFpEF (currently under investigation) as well as the impact of and alternative delivery settings including home- and using technology-based programmes.[93]

Telemedicine

Consensus recommendation

Home telemonitoring using an approach that is similar to the one used in TIM-HF2 (Telemedical Interventional Management in Heart Failure II) *may be considered* for patients with HF in order to reduce the risk recurrent CV and HF hospitalizations and CV death.

Supporting evidence. The TIM-HF2 trial[94] included 1571 patients and demonstrated that remote telemonitoring including home assessment of weight, blood pressure, electrocardiogram and general health status in the context of a 24/7 support system, reduced the proportion of days lost due to unplanned CV (mainly HF) hospitalizations or death ($P = 0.046$). This study also documented a reduction in all-cause mortality for patients managed using telemedicine (HR 0.70; $P = 0.028$).

Of note, through an oversight, the 2016 ESC guidelines[8] failed to refer to a systematic Cochrane review of home telemonitoring published in late 2015 (after the guideline had done its major literature search). This Cochrane review[95] identified 25 relevant trials and found that telemonitoring reduced all-cause mortality by about 20% and HF hospitalization by about 30%.

Practical comments. Home telemonitoring may be used to enhance patient education and motivation and delivery of care but must be adapted to work in synergy with existing health care provision. Remote monitoring should not be impersonal. As with many interventions, the cost/benefit ratio needs to be adequately assessed.

Directions for future development. Further research is required and will be facilitated by advances in sensor and communication technology, smart algorithms and machine-learning and the growing number of effective interventions that require monitoring. The TIM-HF2 intervention protocol should be tested in other countries and different health care systems.

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Supplementary Information

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

Table S1. List of consensus recommendations regarding the management of patients with heart failure: pharmacotherapy.

Table S2. List of consensus recommendations regarding the management of patients with heart failure: interventions, devices, and management strategies.

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