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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ABSTRACT

The 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 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 in January 2019 in Frankfurt. 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 there 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 SGLT2 inhibitors in type 2 diabetes mellitus; MitraClip for functional mitral regurgitation; atrial fibrillation ablation in HF; tafamidis in cardiac transthyretin amyloidosis; rivaroxaban in HF; ICD's 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 two years, in time for the planned 2021 ESC guidelines on the diagnosis and treatment of acute and chronic heart failure.

INTRODUCTION/PREAMBLE

The ESC has published a series of guidelines on heart failure (HF) over the last 25 years, most recently in 2016[1,2,3,4,5,6]. The next ESC guideline is not due until 2021. Given the amount of new information that has become available since 2016, the 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. 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 AHF and CHF 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 Supplementary Tables 1 and 2). 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 there might change the clinical management of HF. We have avoided re-interpretation of information already considered in the 2016 ESC/HFA guidelines.

A – PHARMACOTHERAPY

1. SGLT2 inhibitors

Consensus recommendation.

- The 2016 Guideline indicated that empagliflozin **should be considered** in patients with T2DM "in order to prevent or delay the onset of heart failure or prolong life"[8].

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

- At this stage, no specific recommendations for the use of SGLT2 inhibitors in patients with established HF can be made.

Supporting evidence. Empagliflozin was compared to placebo in the EMPA-REG OUTCOME 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 regards to reductions in HF hospitalisations for dapagliflozin[10] in the DECLARE-TIMI 58 study and for canagliflozin[11] in the CANVAS programme, that included T2DM with established CV disease or increased CV risk, respectively, but not for all-cause mortality (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 trial[12], which enrolled patients at high risk of CV disease and mild to moderate CKD, canagliflozin reduced HF hospitalization 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] and the DECLARE-TIMI 58 study with canagliflozin[11].

The consensus view was that there is sufficient evidence to consider that the ability of SGLT2 inhibitors to prevent the hospitalisations 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 hospitalisations 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 characterised. 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% CI 0.46-0.80) compared to those without a history of HF at baseline (HR, 0.87; 95% CI, 0.72-1.06).[15]. 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, LVEF, NYHA class or levels of natriuretic peptides are not known[16]. In a post-hoc analysis of DECLARE-TIMI 58, benefits were greater in patients who were classified as HFrEF compared to patients classified as HFpEF, but measurement of LVEF was missing in 25% of patients.[17]

Clinical trials in HF patients with and without T2DM and with HFrEF or HFpEF are ongoing (Table 3). 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, 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 of 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**).

2. Canakinumab

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

Supporting evidence. The CANTOS trial[18] 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 2,173 patients (21.6%) with HF[18,19]. 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 FDA denied regulatory approval for canakinumab for patients with coronary artery disease[20]. A new potential therapeutic area is lung and potentially other forms of cancer[21]. Relevant trials are ongoing.

3. Sacubitril/Valsartan

Consensus recommendation.

- Sacubitril/valsartan **is recommended** as a replacement for ACE-I/ARBs to reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal medical treatment with an ACE-I, a beta-blocker and a MRA.

- Initiation of sacubitril/valsartan rather than an ACE-I or an ARB **may be considered** for patients hospitalised with new-onset HF or decompensated CHF 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, 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 over, and/or with co-morbidities such as T2DM.[22,23,24] Compared with enalapril, administration of sacubitril/valsartan reduced the incidence of diabetes requiring insulin treatment[25], and the incidence of hyperkalaemia in those on an MRA[26]. The rate of decline in eGFR was also found lower with sacubitril/valsartan[27], 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[28].

In the PIONEER-HF trial, patients with HFrEF hospitalized for new-onset (about one third) or worsening CHF (about two thirds) were stabilized and then randomly assigned to receive either sacubitril/valsartan or enalapril; the reduction in NT-proBNP was greater in those assigned to sacubitril/valsartan group at weeks 4 and 8 (the primary endpoint of this biomarker study)[29]. The rates of worsening renal function, hyperkalaemia, symptomatic hypotension and angioedema were similar in the two groups[29] but there were fewer HF related adverse events in patients assigned to sacubitril/valsartan.

In the open-label TRANSITION trial[30], more than 1,000 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.[22,31,32,33,34,35 36,] Its safety is similar in ACE-I/ARB naïve patients and thus its initiation may be considered also in these patients. In PIONEER[29], the incidence of hyperkalaemia (≥5.5 mmol/L) was similar for those assigned 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 (>6.0mmol/L) as compared with enalapril (3.1 vs 2.2 per 100 patient-years; HR, 1.37; P = .02)[37]. Sacubitril/valsartan may slow the rate of decline in eGFR and, in patients with T2DM, improve glycaemic control[38].

PIONEER-HF required patients to have and NT-proBNP >1,600pg/mL (BNP >400pg/mL). However, if the diagnosis of HF is certain and the patients 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 CHF and mild symptoms, in whom the benefit of sacubitril/valsartan is uncertain, if plasma concentrations of natriuretic peptides are not elevated[39].

Directions for future development. The PIONEER 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 hyperkalemia and enable more patients to tolerate sacubitril/valsartan at all, or at a higher dose.

4. 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 RAASi's 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. Hyperkalemia is an important reason for under-use of life-saving therapy with RAASi's in HF, and it is particularly frequent in patients with more advanced kidney disease and T2DM.[40] Besides PEARL-HF[41], 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 trial[42] 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 50mg 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 uptitration in patients with HF and CKD was studied in 63 normokalaemic (K 4.3-5.1 mmol/L) patients in an open label design[43]. Patients were up-titrated to spironolactone 50mg od and the patiromer dose was adjusted to maintain potassium within the range 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 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 >2,000) is underway investigating its effects on morbidity and mortality (DIAMOND, NCT03888066).

5. 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 trial with acetazolamide is ongoing[44].

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[45].

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 AHF – 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.[4647]

6. Pharmacotherapy in heart failure with mid-range ejection fraction

No prospective trial has been conducted in patients with 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.

6.1. Beta-blockers for HFmrEF

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 cardiovascular 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[48]. In a subgroup of 575 patients with LVEF between 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 cardiovascular death (primary outcomes for this analysis). The absolute reduction in cardiovascular mortality in this subgroup was 4.7% (NNT to prevent one CV death = 21 during a median follow-up of 1.3 years)[48]. 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[48].

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.

6.2. Candesartan for HFmrEF

Consensus recommendation. Candesartan **may be considered** for ambulatory patients with symptomatic HFmrEF in order to reduce the risk of HF hospitalisation 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[49]. In a subgroup of 1,322 patients with an LVEF between 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 cardiovascular death and HF hospitalization (primary outcome for this analysis), the risk of first HF hospitalization and the risk of recurrent HF hospitalizations[49]. Candesartan did not modify the risk of either all-cause or cardiovascular 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[49]. Specific trials in HFmrEF (possibly studied together with HFpEF patients) would be of interest.

6.3. Spironolactone for HFmrEF

Consensus recommendation. Spironolactone **may be considered** for ambulatory patients with symptomatic HFmrEF without contra-indications in order to reduce the risk of cardiovascular death and HF hospitalisation.

Supporting evidence. A post hoc analysis of the TOPCAT trial (spironolactone in HF with LVEF≥45%) suggested that in a subgroup of patients with LVEF between 44–49% (n=520), spironolactone reduced the risk of primary endpoint (defined as cardiovascular death, HF hospitalization, or resuscitated sudden death), which was mostly due to a reduction in cardiovascular mortality with spironolactone and most clearly observed in patients enrolled in North and South America[50].

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[50], 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.

6.4. Intravenous iron for HFmrEF

Consensus recommendation. Evidence is insufficient to provide new practical recommendations.

Supporting evidence. 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[51,52]. Epidemiological evidence emphasises the need for screening for ID in patients with HF, regardless of LVEF, if the blood haemoglobin is <14g/dL.

Clinical trials investigating the effects of intravenous ferric carboxymaltose in ambulatory, patients with symptomatic HF, LVEF ≤45% and ID (FAIR-HF, CONFIRM-HF and EFFECT-HF) included approximately 150 patients with LVEF between 40-45% (HFmrEF).[53,54,55] 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 <14g/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, EudraCT: 2013-002267-25) does not suggest any serious issues[56]. 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)[57] are needed.

7. 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 ATTRm and ATTRwt) in order to improve exercise capacity and quality of life, and to reduce CV hospitalisations and mortality. This recommendation is limited to patients who fulfil the inclusion and exclusion criteria of the ATTR-ACT trial[58] (Table 2). 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 tafamadis 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[5960]. 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: an autosomal dominant inherited disease (ATTRm) and wild-type transthyretin (ATTRwt) which occurs sporadically. ATTR affects 20-30% of people aged >80 years and is more common in patients with HFpEF and/or degenerative aortic stenosis[59,60,61,62,63]. Novel SPECT cardiac imaging with bone-avid tracers (99mTc pyrophosphate (PYP), 3,3-diphosphono1,2-propanedicarboxylic acid (DPD), and hydroxymethylene diphosphonate (HMDP)) help identify cases with high specificity, non-invasively[64], 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. [65]

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[58]. Tafamidis reduced the risk of the combined primary end-point (all-

cause death and cardiovascular-related hospitalization), independently reducing all-cause mortality and the rate of cardiovascular-related hospitalizations. Tafamidis also slowed the rate of decline in both the 6-minute walk distance and quality of life.[59]

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 recognised. 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[66]. We fully support efforts to reduce the high cost of this therapy.

8. Rivaroxaban in heart failure

Consensus recommendation.

- For ambulatory patients with CAD and CHF in NYHA class I/II with an LVEF greater than 30%, addition of rivaroxaban 2.5mg bd to background treatment with aspirin **may be considered** in order to reduce the risk of stroke and CV death.

- For CHF patients with a recent HF hospitalisation 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 trial enrolled 5,022 patients with chronic HFrEF, CAD, a recent HF hospitalisation and no AF[67] 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 (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)[68], demonstrated a significant reduction although rivaroxaban had no effect on HF related hospitalisations or HF deaths. There was an increase in major bleeding (from 2.0% to 3.3%; HR 1.68 (1.18–2.39). The difference was driven mainly by the number of participants with a fall in haemoglobin of >2.0g/dL, with a neutral effect on bleeding requiring hospitalization or resulting in death.

The COMPASS trial enrolled 27,395 patients, of whom 5,902 had HF (predominantly with LVEF ≥40%; n=4,250) and randomly assigned them (double-blind) to aspirin 100mg/day, rivaroxaban 2.5mg bd plus aspirin 100mg/day or rivaroxaban 5mg bd.[69] 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 (0.44–0.76) and all-cause mortality (from 4.1% to 3.4%; HR 0.82 (0.71–0.96), but not myocardial infarction (from 2.2% to 1.9%) or HF hospitalisation (from 2.1% to 2.2%). Major bleeding events were higher on the combination (1.9% versus 3.1%; HR 1.70 [1.40–2.05]), although rarely fatal (10 versus 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 (0.50-0.86)). Benefit was clearest amongst patients with HFpEF/HFmrEF although, statistical tests could not confirm heterogeneity according to LV phenotype. The effect of rivaroxaban 5mg bd compared to aspirin 100mg/day on all-cause mortality approached significance (HR 0.80 (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 (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 CHF patients with a recent HF hospitalisation 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 atrial fibrillation. Relevant ESC guidelines indicate that these patients should receive a DOAC. Rivaroxaban 2.5mg bd is not considered to be an effective dose for the prevention of thrombo-embolic events in patients with atrial fibrillation**.**

In summary, it appears that for patients with CAD rivaroxaban 2.5mg bd 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 remains 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.

9. 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[8,70] 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 (versus placebo) of 62% and 59%, respectively, and in all-cause hospitalizations of 42% for each combination.[71] 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. [71]

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.

10. Approaches to improving guideline adherence for drug therapy in HF

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 hospitalisation and cardiovascular and all-cause mortality. The ESC guidelines provide a framework to deliver evidence-based multidisciplinary care that translates into the better quality of life and improved clinical outcomes in patients with HFrEF. However, adherence to guideline-recommendation 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, an international, prospective, observational, longitudinal survey, amongst 6,669 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)[72]. Similarly, in the BIOSTAT-CHF study, which was specifically designed to study up-titration of ACE-I/ARB and/or beta-blocker and enrolled 2,516 patients with worsening HF, those treated with less than 50% of recommended doses had a greater risk of death and/or HF hospitalization[73].

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[74] may contribute to this goal.

B – DEVICE BASED THERAPIES

11. Implantable cardioverter-defibrillators

Consensus recommendation.

- The consensus group did not identify any new evidence to alter the 2016 guideline recommendations[8] on 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 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.

Supporting evidence. A randomised trial of patients with non-ischaemic symptomatic HF and an LVEF ≤35% (DANISH) did not show that implanting an ICD for primary prevention reduced overall mortality despite a reduction in sudden deaths[75]. Many patients had a broad QRS and were randomised to receive CRT-P or 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 SCD 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 above about 1,000pg/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[76], 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)[77] 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.

12. Atrial fibrillation ablation

Consensus recommendation.

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

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

- Pulmonary vein ablation for persistent atrial fibrillation **may be considered** for patients with HFrEF who have an implanted device (to prevent bradycardia; ICD, CRT or PPM) if achieving and maintaining sinus rhythm is considered likely, especially if the onset of AF was associated with a deterioration in symptoms of HF or the patient has (or is a candidate for) CRT. Pulmonary vein 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 atrial fibrillation (AF) complicating HF continues. Anti-coagulants 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 anti-arrhythmic 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[78]. 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, AVN ablation should be considered,

Patients (n=3,103) with HF and persistent AF were evaluated for inclusion in the CASTLE-AF trial comparing pharmacological rate or rhythm control with pulmonary vein ablation in patients with HFrEF (LVEF <35%) and an ICD or CRT-D device (to prevent post-ablation bradycardia)[79]. Finally, only 363 patients were randomised (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%, hazard ratio 0.62, 95% confidence interval 0.43 – 0.87). The effect was consistent over primary endpoint composites (Hazard ratio of 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 versus 46 deaths in control). Patients with less advanced HF (EF>25%, NYHA class II, <65 years old) potentially derived greater benefit.

The CABANA trial also compared PV ablation to medical therapy[8081]. Only 337 of 2,204 patients randomised had HF at baseline. Overall, the trial was neutral for its primary composite endpoint [HR 0.86, 95% confidence interval 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[82]. In summary, the data suggesting that a rhythm rather than 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 RV pacing after AV node ablation[83]. This may reflect the deleterious effects of RV pacing rather than any benefit of bi-ventricular pacing. The landmark trials all required patients to be in sinus rhythm. CRT may require atrio-ventricular as well as bi-ventricular resynchronisation to be effective. A small, (n=102) un-blinded trial comparing AV node ablation with pharmacological treatment suggested benefit to the ablation strategy but there were too few events to be convincing[84]. 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 RCTs that this improves patient well-being or outcome.[785]

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 70-90bpm. Anti-arrhythmic 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 AVN ablation to increase biventricular capture improves outcomes. AVN 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 RCTs is required comparing "non-aggressive" pharmacological rate control, avoiding amiodarone or Class I anti-arrhythmic agents and higher doses or plasma concentrations of digoxin with the following procedures:

1.) PV (and/or AVN) ablation for paroxysmal AF and HF vs "non-aggressive" pharmacological rate control (and avoiding all of: amiodarone, Class I anti-arrhythmic agents, higher doses or higher plasma concentrations of digoxin)

2.) PV (and/or AVN) 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 anti-arrhythmic agents, higher doses or higher plasma concentrations of digoxin)

3.) PV (and/or AVN) ablation in HF patients with CRT vs usual care

There is also a need for RCTs comparing different rate control strategies, including

4.) High- versus low-dose beta-blocker

5.) Addition of digoxin to beta-blockers. The ongoing DIGIT-HF trial includes patients with AF, but excludes patients in need of rate control with digitalis glycosides. [86]

There is also a need for RCTs investigating

6.) new agents for pharmacological rhythm-control (double-blind versus placebo),

7.) prevention of AF (double-blind versus placebo)

8.) better treatments to prevent atrial fibrillation recurrence (double-blind versus placebo

13. 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[87] selection criteria (Table 3).

Supporting evidence. The MITRA-FR[88] and COAPT[87] trials (recruiting 303 and 614 patients, respectively) included different populations 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 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% versus 87%, p=0.02). In COAPT, the baseline LVEF was 31% (MITRA-FR 33%), the left-ventricular end-diastolic diameter was was 62±7 mm (in MITRA-FR 68±8 mm), 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

hospitalisations by 47% (p<0.001), and all-cause mortality (by 38%, p<0.001) and improved improved average 6min-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 outcome of these two trials at one 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 optimised before deciding on intervention. Treatment with sacubitril/valsartan for HFrEF may also be of some importance as demonstrated recently in the PRIME trial[89]. Of note, the PRIME study was a small (n=118) double-blind RCT comparing sacubitril/valsartan to Valsartan alone in HF patients with chronic functional MR. The primary end-point, the reduction in echo-derived effective regurgitant orifice area, was reached at a borderline level of significance (–0.058±0.095 versus –0.018±0.105 cm^2; P=0.032). The trial was too small to show any clinical benefits and echo derived parameters of MR severity are not considered to constitute evidence of clinical benefit. The ratio of the severity of MR to the severity of LV dilatation may be a key determinant of the response to mitral valve repair; patients with disproportionately severe MR may benefit more.

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

14. 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 the HF itself, and treatments directed at the CSA should be reviewed and avoided, unless compelling symptomatic indications for treatment of the CSA exist, in which case positive pressure airway mask therapy should be avoided and phrenic nerve stimulation **may be considered** as an alternative.

Supporting evidence. HFrEF patients with predominantly CSA suffered an increase in mortality in SERVE-HF[90], so that it is essential to know if such patients have CSA prior to starting positive airway pressure therapy. One small trial (Pivotal trial[91]) showed promise for phrenic nerve stimulation (PNS) for the treatment of severe central sleep apnoea. However, the randomised 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 AHI and symptoms, although blinding may have been imperfect; two deaths occurred in each group.

Practical comments. PNS 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 on-going 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 phrenic nerve stimulation is required before making recommendations for broader use in the HF population.

15. Cardiac contractility modulation

Consensus recommendation. CCM **may be considered** in patients with HFrEF (LVEF between 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 trial[92], CCM increased peak VO2 by 0.84 (95% Bayesian credible interval: 0.123 to 1.552) ml O2/kg/min (the primary end-point), 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 sub-group 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 cardiovascular death and HF hospitalizations reduced from 10.8% to 2.9% ($p = 0.048$).

Practical comments. CCM is now approved in the US 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 <130msec and are therefore not indicated for CRT.

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

16. 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 – LVAD device, a HeartMate III rather than HeartMate II device **should be considered**.

Supporting evidence. ROADMAP[93] 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[94] 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[95] is a pivotal trial for HeartMate III vs HeartMate II. Use of HeartMate III was associated with better 2-year survival and fewer adverse events.

C – DISEASE MANAGEMENT AND LIFE STYLE

16. Multidisciplinary heart failure management programs

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

Supportive evidence. Although evidence on the effectiveness of multidisciplinary HF management program was established in the 2016 guidelines[8], new studies have been published since then, often investigating the optimal components and intensity of these programs. In 2017, van Spall et al.[96] published a network meta-analysis of 53 RCTs, 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.[97]

published an IPD meta-analysis of 20 studies, including 5,624 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 multi-disciplinary HF disease management programmes, barriers and opportunities for their implementation and interactions and synergies with a variety of health care systems would be valuable.

17. Salt/sodium intake

Consensus recommendation. There is no robust new evidence on the benefits of manipulating salt intake on clinical status amongst either out-patients or in-patients.

Supportive evidence. A recent systematic review,[98] 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 heart failure with reduced intake of dietary salt, no clinically relevant data on whether reduced dietary salt intake affected outcomes such as cardiovascular-associated or all cause mortality, cardiovascular-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 the sodium restriction in HF patients

18. Exercise based cardiac rehabilitation

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

Supportive evidence. A new meta-analysis[99] and an updated Cochrane meta-analysis[100] identified 44 trials that included 5,783 people with HFrEF 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 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[101].

19. Telemedicine

Consensus recommendation. Home telemonitoring using an approach that is similar to the one used in TIM-HF2 **may be considered** for patients with HF in order to reduce the risk recurrent cardiovascular and HF hospitalizations and cardiovascular death.

Supporting evidence. The TIM-HF2 trial[102] included 1,571 patients and demonstrated that remote telemonitoring including home assessment of weight, blood pressure, ECG 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[103] identified 25 relevant trials and found that telemonitoring reduced all-cause mortality by about 20% and HF hospitalisation 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 healthcare provision. Remote monitoring should not be impersonal. As with many interventions, the cost/benefit 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.

Section D. Summary and outlook

It is approximately three years since the cut-off date for clinical trial data to be considered in the most recent HFA guidelines on HF[8] and it will be more than another two years before we have the next ESC guidelines on HF (in 2021). As such this expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology gives us a chance to review significant developments in pharmacotherapy, interventions, device therapy and general care relevant to the management of HF. As stated before, this expert consensus report does not aim to be a guideline update nor a position statement.

Specific new recommendations have been made based on the evidence from major trials published since 2016, including SGLT2 inhibitors in T2DM; MitraClip for functional MR; atrial fibrillation ablation in HF; Tafamidis in cardiac transthyretin amyloidosis; Rivaroxaban in HF; ICD's 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 refine our guidance statements in selected other areas.

Further, new trial evidence is due in many of these areas and others over the next two years, in time for the planned 2021 guidelines.

AUTHOR CONTRIBUTION

All authors contributed to the discussions that lead to the consensus document. SDA with the help of EAJ, ML and MSA wrote the first draft of the manuscript, and all authors contributed to critical revision of the paper and approved the final version of the manuscript for submission to EJHF.

CONFLICTS OF INTEREST

PMS: reports no COI.

PP: reports personal fees for consultancy and honoraria for lectures from: Vifor Pharma, Novartis, Boeringer-Ingelheim, Respicardia, and AstraZeneca.

SDA: reports grant support and personal fees from Vifor Int., grant support from Abbott Vascular, and personal fees from ASTRA, Bayer, Boehringer Ingelheim, Impulse Dynamics, Novartis, Respicardia, Servier, and Actimed.

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RAdB: reports that the UMCG, which employs Dr. De Boer has received research grants and/or fees from AstraZeneca, Abbott, Bristol-Myers Squibb, Novartis, Novo Nordisk, and Roche. Dr. de Boer is a minority shareholder of scPharmaceuticals, Inc. Dr. de Boer received personal fees from Abbott, AstraZeneca, MandalMed Inc, and Novartis.

HD: reports no COI.

TBG: Honoraria for lectures and/or consulting: Novartis, Abbott.

LH: reports no COI.

TJ: reports to be a member of advisory board of Sensible Medical and has received fees from Novartis.

EAJ: reports personal fees for consultancy and honoraria for lectures from: Vifor Pharma, Novartis, Roche Diagnostics, Servier, Berlin-Chemie, Boeringer-Ingelheim, Pfizer, AstraZeneca.

MSA: reports personal fees from Servier.

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MV: reports no COI.

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GF: participated in Committees of trials and Registries sponsored by Medtronics, BI, Novartis, Vifor, Servier

AJSC: In the last 3 years Professor Coats declares having received honoraria and/or lecture fess from: Astra Zeneca, Menarini, Novartis, Nutricia, Respicardia, Servier, Stealth Peptides, Vifor, Actimed, Faraday, and WL Gore.

Abbreviations

ACE-I – angiotensin-converting enzyme inhibitors

ADVOR – Acetazolamide in Decompensated Heart Failure With Volume OveRload

AHF – acute heart failure

AHI – Apnea–Hypopnea Index

AF – atrial fibrillation

AFFIRM-AHF – Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency

AL – amyloidosis

AMETHYST-DN – Patiromer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy

ARBs – angiotensin receptor blockers

ARNI – angiotensin receptor-neprilysin inhibitor

ATTR – cardiac transthyretin amyloidosis

ATTR-ACT – Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy

ATTRm – hereditary cardiac transthyretin amyloidosis

ATTRwt – wild-type cardiac transthyretin amyloidosis

AVN ablation– atrioventricular node ablation

BIOSTAT-CHF study – BIOlogy Study to TAilored Treatment in Chronic Heart Failure

BNP – b-type natriuretic peptide

CABANA trial – Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial

CAD – coronary artery disease

CANTOS trial – Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events)

CANVAS – CANagliflozin cardioVascular Assessment Study

CASTLE-AF trial – Catheter Ablation vs. Standard Conventional Treatment in Patients With LV Dysfunction and AF

CCM – Cardiac contractility modulation

CHARM – Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity

CHF – chronic heart failure

CKD – chronic kidney disease

COAPT trial – Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation

COMMANDER HF trial – 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

COMPASS trial – Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease

CONFIRM-HF – A Study to Compare the Use of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency

CREDENCE trial – Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy

CRT – cardiac resynchronization therapy

CRT-D – cardiac resynchronization therapy defibrillator

CRT-P – cardiac resynchronization therapy pacemaker

CSA – central sleep apnoea

CV – cardiovascular

DANISH – Danish ICD Study in Patients With Dilated Cardiomyopathy

DECLARE-TIMI 58 trial – Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events

DIAMOND – Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure

EFFECT-HF – Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure

eGFR – estimated glomerular filtration rate

EMPA-REG OUTCOME trial – BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients

EMPA-RESPONSE-AHF – Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure

ENDURANCE trial – The HeartWare™ Ventricular Assist System as Destination Therapy of Advanced Heart Failure

ESC – European Society of Cardiology

FAIR-HF – A Study to Compare the Use of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency

FAIR-HF2 – Intravenous Iron in Patients With Systolic Heart Failure and Iron Deficiency to Improve Morbidity & Mortality

FAIR-HFpEF – Effect of IV Iron in Patients With Heart Failure With Preserved Ejection Fraction

FDA – Food and Drug Administration

FiX-HF 5C trial – Evaluate Safety and Efficacy of the OPTIMIZER® System in Subjects With Moderate-to-Severe Heart Failure

HF – heart failure

HFA – Heart Failure Association

HFmrEF – heart failure with mid-range ejection fraction

HFrEF – heart failure with reduced ejection fraction

HFpEF – heart failure with preserved ejection fraction

HR – hazard ratio

ICD – implantable cardioverter defibrillator

ID – iron deficiency

IPD – individual patient data

IRONMAN – Intravenous Iron Treatment in Patients With Heart Failure and Iron Deficiency

kg – kilogram

LVAD – left ventricular assist device

LVEF – left ventricular ejection fraction

min – minute

MITRA-FR trial – Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation

mL – milliliter

MOMENTUM 3 – Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3™ IDE Clinical Study

MR – mitral regurgitation

MRA – mineralocorticoid receptor antagonist

NNT – number needed to treat

NT-proBNP – N-terminal pro b-type natriuretic peptide

NYHA – New York Heart Association

O2 – oxygen

PARADIGM-HF trial – This Study Will Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure

PARADISE-MI – Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI

PARAGON-HF trial – Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction

PEARL-HF – Evaluation of Patiromer in Heart Failure Patients

PIONEER-HF trial – Comparison of Saocubitril/valsartaN Versus Enalapril on Effect on ntpRo-bnp in Patients Stabilized From an Acute Heart Failure Episode.

PIVOTAL trial – UK Multicentre Open-label Randomised Controlled Trial Of IV Iron Therapy In Incident Haemodialysis Patients

Pivotal trial – A Randomized Trial Evaluating the Safety and Effectiveness of the remedē® System in Patients With Central Sleep Apnea

PNS - phrenic nerve stimulation

PPM – permanent pacemaker

PRIME study – Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation

PRIORITIZE HF – Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure

PV ablation– pulmonary vein ablation

QUALIFY survey – QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY

RAAS-I – renin angiotensin aldosterone system inhibitors

RESET-CRT – Re-evaluation of Otimal Re-synchronisation Therapy in Patients with CHF

Reshape-HF2 – A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation

ROADMAP trial – Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device (LVAD) and Medical Management

SAD – sudden arrhythmic death

SERVE-HF – Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure

SGLT2 – Sodium glucose transporter 2

SPECT – single photon emission computed tomography

SPIRIT-HF – SPIRonolactone In the Treatment of Heart Failure

SPIRRIT-HFPEF – Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction

T2DM – type 2 diabetes

TIM-HF2 – Telemedical Interventional Management in Heart Failure II

TOPCAT trial – Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function

TRANSFORM-HF – ToRsemide compArisoN With furoSemide FORManagement of Heart Failure

TRANSITION trial – Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event

TTR – transthyretin

VEST trial – Vest Prevention of Early Sudden Death

ZS-9 – sodium zirconium cyclosilicate

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Table 1

Eighteen Ongoing Randomised Trials of SGLT2-inhibitors in Patients with Heart Failure

SGLT2 inhibitor	Trial name	Primary outcome	Disease	N
Empagliflozin	EMPEROR-Preserved[1]	Time to first CV death or hospitalization for HF	HFpEF	ca. 5500
Dapagliflozin	DAPA-HF[2]	Time to first CV death, hospitalization for HF, or urgent HF visit	HFrEF	4744
Dapagliflozin	DELIVER[3]	Time to first occurrence of CV death, hospitalization for HF, urgent HF visit	HFpEF	ca. 4700
Sotagliflozin	SOLOIST-WHF[4]	Time to first CV death or hospitalization for HF	HFrEF	4000
Empagliflozin	EMPEROR-Reduced[5]	Time to first CV death or hospitalization for HF	HFrEF	ca. 3350
Dapagliflozin	PRESERVED-HF[6]	Change of NT-proBNP	HFpEF	320

Empagliflozin	EMPERIAL-reduced[7]	Change in 6-minute walk distance	HFrEF	300
Empagliflozin	EMPERIAL-Preserved[8]	Change in 6-minute walk distance	HFpEF	300
Dapagliflozin	DETERMINE-reduced[9]	Change in 6-minute walk distance	HFrEF	300
Dapagliflozin	DETERMINE-preserved[10]	Change in 6-minute walk distance	HFpEF	400
Dapagliflozin	DEFINE-HF[11]	Change of NT-proBNP	HFrEF	263
Empagliflozin	Empire HF[12]	Change of NT-proBNP	HFrEF	189
Empagliflozin	SUGAR[13]	Left Ventricular End Systolic Volume Index and left ventricular global longitudinal strain	HFrEF	130
Ertugliflozin	ERTU-GLS[14]	Global Longitudinal Strain	HF	120
Empagliflozin	NCT03753087[15]	Change in 6-minute walk distance	HFpEF	100
Empagliflozin	NCT03332212[16]	Change in PCr/ATP ratio in the resting state	HF	86

Empagliflozin	ELSI[17]	Skin sodium content	HFrEF	84
Empagliflozin	EMBRACE-HF[18]	Change in pulmonary artery diastolic pressure	HF	60

Table 2

Inclusion/exclusion criteria of the ATTR-ACT trial (copied from[19])

Exclusion Criteria:

1. they had, in the opinion of the investigator, heart failure that was not due to transthyretin amyloid cardiomyopathy
2. New York Heart Association (NYHA) 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 lower than 25 ml per minute per 1.73 m2 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 (mBMI) of less than 600 calculated as the serum albumin level in grams per liter multiplied by the conventional BMI (the weight in kilograms divided by the square of the height in

meters)

10. concurrent treatment with nonsteroidal antiinflammatory drugs, tauroursodeoxycholate, doxycycline, calcium-channel blockers, or digitalis.

Table 3

Inclusion/exclusion criteria from the COAPT trial (copied from[20])

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 ischemic or non-ischemic etiology
2. Subject has been adequately treated per applicable standards, including for coronary artery disease, LV dysfunction, mitral regurgitation and heart failure
3. NYHA functional class II, III or ambulatory IV
4. Subject has had at least one hospitalization for heart failure in the 12 months prior to enrollmentand/or a corrected* BNP ≥300 pg/ml or a corrected NT-proBNP ≥1500 pg/ml
5. Local heart team has determined that MV 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 be successfully be treated by the MitraClip (if a secondary jet exists, it must be considered clinically insignificant)
9. CK-MB obtained within prior 14 days is less than thelocal laboratory ULN
10. Transseptal catheterization and femoral vein access is feasible per the MitraClip implanting investigator
11. Age 18 years or older
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 mm Hg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the cath lab is able to reduce the 12PVR to <3 Wood Units or between 3 and 4.5Wood Units with v wave less than twice the mean of the PCWP•Hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology•Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis)
10. Hemodynamic instability requiring inotropic support or mechanical heart assistance
11. Physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe right ventricular dysfunction
12. Implant of CRT or CRT-D within the last 30 days
13. Mitral valve orifice area <4.0 cm2by site-assessed TTE

14. Leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in mitral regurgitationby the MitraClip.
15. Hemodynamic 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 hemodynamic support device.
16. Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months.
17. Life expectancy <12 months due to non-cardiac conditions
18. Modified Rankin Scale ≥4 disability.
19. Status 1 heart transplant or prior orthotopic heart transplantation
20. Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure.
21. Echocardiographic evidence of intracardiac mass, thrombus or vegetation
22. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated)
23. Active infections requiring current antibiotic therapy
24. Transesophageal echocardiography (TEE) is contraindicated or high risk

25. Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically
26. Pregnant or planning pregnancy within next 12 months
27. Currently participating in an investigational drug or another device study that has not reached its primary endpoint.
28. 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*“Corrected” refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m2in body mass index above a reference of 20 kg/m2).

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[2] https://clinicaltrials.gov/ct2/show/NCT03036124

[3] https://clinicaltrials.gov/ct2/show/NCT03619213

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[9] https://clinicaltrials.gov/ct2/show/NCT03877237

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