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ESC GUIDELINES

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

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Patient Forum

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See the *European Heart Journal* online for supplementary documents that include evidence tables.

Keywords Guidelines • Acute heart failure • Comorbidities • Chronic kidney disease hospitalization • Diagnosis • Ejection fraction • Heart failure • Multidisciplinary management • Natriuretic peptides • Neurohormonal antagonists • Pharmacotherapy • Prevention

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Abbreviations and acronyms

ACE-I	Angiotensin-converting enzyme inhibitor
ADVOR	Acetazolamide in Decompensated Heart Failure with Volume Overload (trial)
AFFIRM-AHF	A Randomized Double-blind Placebo Controlled Trial Comparing the Effects of Intravenous Ferric Carboxymaltose on Hospitalizations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure (trial)
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor–neprilysin inhibitor
aRR	Adjusted risk ratio
CI	Confidence interval
CKD	Chronic kidney disease
CLOROTIC	Combination of Loop Diuretics with Hydrochlorothiazide in Acute Heart Failure (trial)
COACH	Comparison of Outcomes and Access to Care for Heart Failure (trial)
COR	Class of recommendation
CPG	Clinical Practice Guidelines
CREDENCE	Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (trial)
CV	Cardiovascular
DAPA-CKD	Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (trial)
DAPA-HF	Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (trial)
DELIVER	Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (trial)
eGFR	Estimated glomerular filtration rate
EMPA-KIDNEY	EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease (trial)
EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection (trial)
EMPULSE	Empagliflozin in Patients Hospitalized with Acute Heart Failure Who Have Been Stabilized (trial)
ESC	European Society of Cardiology
FIDELIO-DKD	Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (trial)
FIGARO-DKD	Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (trial)
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFnEF	Heart failure with normal ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
IRONMAN	Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency (trial)
i.v.	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LOE	Level of evidence
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
PIVOTAL	Proactive IV Iron Therapy in Haemodialysis Patients (trial)
REVIVED-BCIS2	Revascularization for Ischemic Ventricular Dysfunction (trial)
RR	Risk ratio
SCORED	Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (trial)
SGLT2	Sodium–glucose co-transporter 2
STRONG-HF	Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (trial)
T2DM	Type 2 diabetes mellitus
TRANSFORM-HF	Torsemide Comparison with Furosemide for Management of Heart Failure (trial)
TRILUMINATE Pivotal	Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System Pivotal (trial)

1. Preamble

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. Guidelines are intended for use by health professionals and the European Society of Cardiology (ESC) makes its Guidelines freely available.

ESC Guidelines do not override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and

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regulations applicable in each country to drugs and devices at the time of prescription and, where appropriate, to respect the ethical rules of their profession.

ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated. ESC Policies and Procedures for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines).

Interim Focused Updates are created when the publication of new evidence could influence clinical practice before the next full update of a guideline is published. This Focused Update provides new and revised recommendations for the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. View the full 2021 ESC Guidelines here: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-and-Chronic-Heart-Failure.

The members of the Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. The Task Force performed a critical evaluation of diagnostic and therapeutic approaches, including assessment of the risk–benefit ratio. The strength of every new or updated recommendation and the level of evidence supporting them were weighed and scored according to predefined scales as outlined below. The Task Force followed ESC voting procedures and all approved recommendations were subject to a vote and achieved at least 75% agreement among voting members.

Table 1 **Classes of recommendations**

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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Table 2 **Levels of evidence**

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/guidelines) and have been compiled in a report published in a supplementary document with the guidelines. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC Clinical Practice Guidelines (CPG) Committee supervises and coordinates the preparation of new Guidelines and Focused Updates and is responsible for the approval process. ESC Guidelines and Focused Updates undergo extensive review by the CPG Committee and external experts, including members from across the whole of the ESC region and from relevant ESC Subspecialty Communities and National Cardiac Societies. After appropriate revisions, Guidelines and Focused Updates are signed off by all the experts involved in the Task Force. Finalized documents are signed off by the CPG Committee for publication in the *European Heart Journal*. This Focused Update was developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of writing. Tables of evidence summarizing the findings of studies informing development of the Focused Update are included. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

Off-label use of medication may be presented in this Focused Update if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- The specific situation of the patient. Unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest with regard to the quality, safety, and efficacy of care, and only after the patient has been informed and has provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies, and the ethical rules to which health professionals are subject, where applicable.

2. Introduction

Since the publication of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (HF),[1] there have been several randomized controlled trials that should change patient management ahead of the next scheduled full guidelines. This 2023 Focused Update addresses changes in recommendations for the treatment of HF because of this new evidence. New evidence was considered until 31 March 2023. All major randomized controlled clinical trials and meta-analyses were presented, discussed, and then voted upon for inclusion. Members with declared interests in specific topics were asked to abstain from voting on those topics. The trials were presented and discussed in detail before a consensus was reached about any possible classes of recommendations (COR) (*Table 1*) and levels of evidence (LOE) (*Table 2*) to be assigned.

The Task Force considered and discussed the following new trials and any meta-analyses including them: ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload),[2] CLOROTIC (Combination of Loop Diuretics with Hydrochlorothiazide in Acute Heart Failure),[3] COACH (Comparison of Outcomes and Access to Care for Heart Failure),[4] DAPA-CKD (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease),[5] DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure),[6] EMPA-KIDNEY (EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease),[7] EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction),[8] EMPULSE (Empagliflozin in Patients Hospitalized with Acute Heart Failure Who Have Been Stabilized),[9] FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease),[10] FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease),[11] IRONMAN (Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency),[12] PIVOTAL (Proactive IV Iron Therapy in Haemodialysis Patients),[13,14] REVIVED-BCIS2 (Revascularization for Ischemic Ventricular Dysfunction),[15] STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies),[16] TRANSFORM-HF (Torsemide Comparison with Furosemide for Management of Heart Failure),[17] and TRILUMINATE Pivotal (Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System Pivotal).[18]

Only results that would lead to new or changed class I/IIa recommendations were selected for inclusion in Recommendation Tables. Trials that would have an impact upon recommendations in other ESC Guidelines under preparation have not been included to avoid discordance. This is the case for REVIVED-BCIS2, which will be considered in the upcoming chronic coronary syndrome Guidelines.

In addition to selecting the trials to be included, the Task Force also discussed changing the description of HF with preserved ejection fraction (HFpEF) to HF with normal ejection fraction (HFnEF) and the left ventricular ejection fraction (LVEF) threshold for HFnEF. The Task Force ultimately decided to keep the term HFpEF and left any further changes in terminology to be considered in the next ESC HF Guidelines.

In assigning recommendations, as in the 2021 ESC HF Guidelines, the Task Force focused on the primary endpoints of trials. This means that, for most HF trials, effective treatments reduce the risk of the time to first occurrence of the composite of either HF hospitalization *or* cardiovascular (CV) death (the correct convention for describing such a composite). Of course, that does not mean each component is reduced individually. For total-event trials, where the primary composite outcome included total (first and repeat) HF hospitalizations *and* all CV deaths, the convention for describing this composite, i.e. *and* not *or*, was used. Once again that does not mean that both components were reduced. All the new recommendations are additive to the recommendations of the 2021 ESC HF Guidelines and changed recommendations substitute those of the 2021 ESC HF Guidelines.

After due deliberation, the Task Force decided to update recommendations for the following sections of the 2021 ESC HF Guidelines:

- Chronic HF: HF with mildly reduced ejection fraction (HFmrEF) and HFpEF
- Acute HF
- Comorbidities and prevention of HF.

3. Chronic heart failure

The original 2021 ESC HF Guidelines adopted the classification of chronic HF according to LVEF (*Table 3*).

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Table 3 Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction, and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

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HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEF, left ventricular ejection fraction.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.
[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy, or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.
[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

For those with HFmrEF, with LVEF between 41% and 49%, the Task Force made weak recommendations (COR IIb, LOE C) in the 2021 ESC HF Guidelines for the use of disease-modifying therapies that have class I evidence for use in HF with reduced ejection fraction (HFrEF). These were based on subgroup analyses of trials that were not specifically designed to focus on HFmrEF, including trials where the overall endpoints were statistically neutral. The Task Force made no recommendations for the use of sodium–glucose co-transporter 2 (SGLT2) inhibitors.[1]

For those with HFpEF, the Task Force made no recommendations for the use of disease-modifying HFrEF therapies as clinical trials with angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and angiotensin receptor–neprilysin inhibitors (ARNI) failed to meet their primary endpoints. There were no published trials with SGLT2 inhibitors to consider at the time.[1]

Since then, two trials have become available with the SGLT2 inhibitors empagliflozin and dapagliflozin, in patients with HF and LVEF >40%, that justify an update in the recommendations for both HFmrEF and HFpEF.[6,8]

The first trial to report was the EMPEROR-Preserved trial.[8] It recruited 5988 patients with HF (New York Heart Association [NYHA] class II–IV) whose LVEF was >40% and who had raised plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>300 pg/mL for those in sinus rhythm or >900 pg/mL for those in atrial fibrillation). They were randomized to empagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of CV death or hospitalization for HF. At a median follow-up of 26.2 months, empagliflozin reduced the primary endpoint (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.69–0.90; $P < .001$). The effect was mainly driven by a reduction in HF hospitalizations with empagliflozin and there was no reduction in CV death. The effects were seen in patients with and without type 2 diabetes mellitus (T2DM).[8] The majority of patients were on an ACE-I/ARB/ARNI (80%) and beta-blocker (86%) and 37% were on an MRA.[19]

A year later, the DELIVER trial reported on the effects of dapagliflozin (10 mg once daily) compared with placebo in 6263 patients with HF (NYHA class II–IV).[6] Patients had to have an LVEF >40% at the time of recruitment, but those who previously had an LVEF ≤40% that had improved to >40% were also enrolled. Outpatients and inpatients hospitalized for HF were eligible. An elevated concentrations of natriuretic peptides were also a mandatory inclusion criterion (≥300 pg/mL in sinus rhythm or ≥600 pg/mL in atrial fibrillation).[6,20,21]

Dapagliflozin reduced the primary endpoint of CV death or worsening HF (HF hospitalization or urgent HF visit) (HR 0.82, 95% CI 0.73–0.92; $P < .001$). Once again, the principal effect was due to a reduction in worsening HF and there was no reduction in CV death. Dapagliflozin also improved symptom burden. The effects were independent of T2DM status.[6] The efficacy of dapagliflozin was consistent in those who remained symptomatic, despite improved LVEF, suggesting that these patients may also benefit from SGLT2 inhibition.[6,22] The benefit of dapagliflozin was also consistent across the range of LVEF studied.[6,23] The background use of therapies for concomitant CV disease was high: 77% were on a loop diuretic, 77% were on an ACE-I/ARB/ARNI, 83% were on a beta-blocker, and 43% were on an MRA.[6]

A subsequent aggregate data meta-analysis of the two trials confirmed a 20% reduction in the composite endpoint of CV death or first hospitalization for HF (HR 0.80, 95% CI 0.73–0.87; $P < .001$). CV death was not reduced significantly (HR 0.88, 95% CI 0.77–1.00; $P = .052$). HF hospitalization was reduced by 26% (HR 0.74, 95% CI 0.67–0.83; $P < .001$). There were consistent reductions in the primary endpoint across the LVEF range studied.[24] Another individual patient data meta-analysis that incorporated data from DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure) in HFrEF with DELIVER confirmed that there was no evidence that the effect of dapagliflozin differed by ejection fraction.[22] This also showed that dapagliflozin reduced the risk of death from CV causes (HR 0.86, 95% CI 0.76–0.97; $P = .01$).[22]

The Task Force discussed the results of these trials in depth, focusing particularly on the fact that they both met their primary endpoints, but they did so by a reduction in HF hospitalizations and not CV death. The Task Force decided to make recommendations on the primary endpoints. That is consistent with all the recommendations made in the 2021 ESC HF Guidelines. The Task Force did not specify NT-proBNP thresholds for treatment, consistent with recommendations for other therapies in the original 2021 ESC HF Guidelines. However, it should be noted that, in the diagnostic algorithm for HF in the 2021 ESC HF Guidelines, raised concentrations of natriuretic peptides are usually implicit to that diagnosis. Taking these two trials into account, the following recommendations have been made for HFmrEF and HFpEF (see *Figs 1 and 2*, respectively).

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Recommendation Table 1 — Recommendation for the treatment of patients with symptomatic heart failure with mildly reduced ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

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CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; SGLT2, sodium–glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

Recommendation Table 2 — Recommendation for the treatment of patients with symptomatic heart failure with preserved ejection fraction

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c] [6,8]	I	A

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CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; SGLT2, sodium–glucose co-transporter 2.
[a]Class of recommendation.
[b]Level of evidence.
[c]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death.

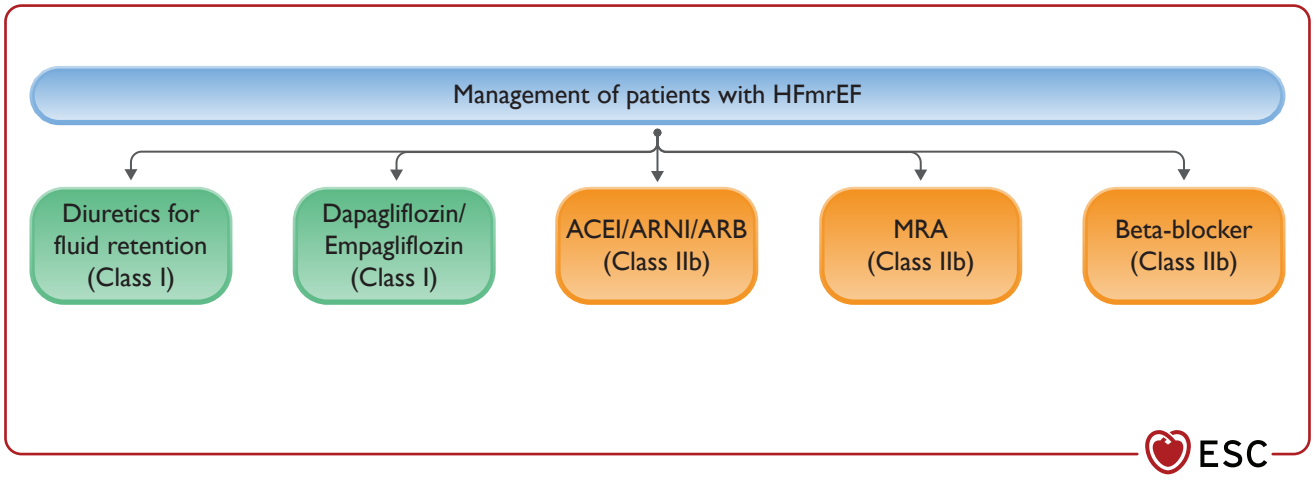

Figure 1 Management of patients with heart failure with mildly reduced ejection fraction. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFmrEF, heart failure with mildly reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

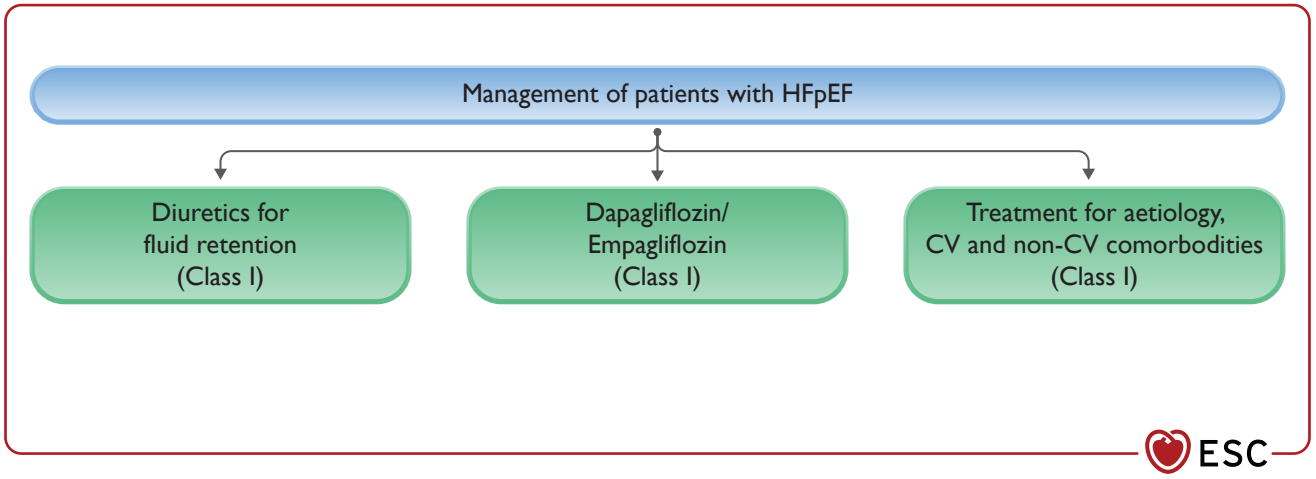

Figure 2 Management of patients with heart failure with preserved ejection fraction. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction.

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4. Acute heart failure

Treatment of acute HF was outlined in the recent 2021 ESC HF Guidelines and a Heart Failure Association scientific statement on HF.[1,25] Since these publications, trials have been conducted with diuretics, as well as on management strategies for patients with acute HF. The results are summarized here.

4.1. Medical therapy

4.1.1. Diuretics

ADVOR was a multicentre, randomized, parallel-group, double-blind, placebo-controlled trial that enrolled 519 patients with acute decompensated HF, clinical signs of volume overload (i.e. oedema, pleural effusion, or ascites), and an NT-proBNP level of >1000 pg/mL or a B-type natriuretic peptide level of >250 pg/mL. They were randomized to receive intravenous (i.v.) acetazolamide (500 mg once daily) or placebo added to standardized i.v. loop diuretic treatment.[2] The primary endpoint of successful decongestion, defined as the absence of signs of volume overload, within 3 days after randomization and without an indication for escalation of decongestive therapy, was achieved in 108 of 256 patients (42.2%) in the acetazolamide group and in 79 of 259 patients (30.5%) in the placebo group (risk ratio [RR] 1.46, 95% CI 1.17–1.82; $P < .001$). Rehospitalization for HF or all-cause death occurred in 76 patients (29.7%) in the acetazolamide group and in 72 patients (27.8%) in the placebo group (HR 1.07, 95% CI 0.78–1.48). Length of hospital stay was 1 day shorter with acetazolamide compared with placebo (8.8 [95% CI 8.0–9.5] vs. 9.9 [95% CI 9.1–10.8] days). No difference between the acetazolamide and placebo groups was found for other outcomes and adverse events.[2] Although these results may support the addition of acetazolamide to a standard diuretic regimen to aid decongestion, further data on outcomes and safety are needed.

The CLOROTIC trial enrolled 230 patients with acute HF and randomized them to oral hydrochlorothiazide (25–100 mg daily, depending on estimated glomerular filtration rate [eGFR]) or placebo, in addition to i.v. furosemide.[3] The trial had two co-primary endpoints, change in body weight and change in patient-reported dyspnoea from baseline to 72 h after randomization. Patients on hydrochlorothiazide had a greater decrease in body weight at 72 h compared with those on placebo (−2.3 vs. −1.5 kg; adjusted estimated difference −1.14 kg, 95% CI −1.84 to −0.42 kg; $P = .002$). Changes in patient-reported dyspnoea were similar between the two groups.[3] An increase in serum creatinine occurred more frequently in patients on hydrochlorothiazide (46.5%) compared with those on placebo (17.2%) ($P < .001$). The rates of HF rehospitalization and all-cause death were similar between groups, as was length of stay.[3] The lack of an impact on clinical outcomes precludes any recommendation in the current guideline update. Further data on outcomes and safety are needed.

4.1.2. Sodium–glucose co-transporter 2 inhibitors

EMPULSE tested the efficacy of the early initiation of empagliflozin in patients hospitalized for acute HF.[9] The primary endpoint was 'clinical benefit', defined using a hierarchical composite of death from any cause, number of HF events, and time to first HF event, or a ≥5 point difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire total symptom score at 90 days, assessed using the win-ratio method. HF events were defined as HF hospitalizations, urgent HF visits, and unplanned outpatient HF visits. An event was considered HF-related only if worsening signs and symptoms of HF were present and an intensification of therapy (defined as an increase in oral or i.v. diuretics, augmentation of a vasoactive agent, or starting a mechanical or surgical intervention) was performed.[9] Patients were randomized in hospital when clinically stable, with a median time from hospital admission to randomization of 3 days, and were treated for up to 90 days. The primary endpoint was achieved in more patients treated with empagliflozin compared with placebo (stratified win ratio 1.36, 95% CI 1.09–1.68; $P = .0054$). Efficacy was independent of LVEF and diabetes status. From a safety perspective, the rate of adverse events was similar between the two treatment groups.[9]

These results are consistent with those shown for SGLT2 inhibitors in patients with chronic HF, regardless of LVEF, and also in those recently hospitalized for HF, once clinically stable.[9,26–28] Caution is, however, needed in patients with T2DM at risk of diabetic ketoacidosis, particularly those treated with insulin when carbohydrate intake is reduced or dose of insulin changed.[29] SGLT2 inhibitors are not indicated in patients with type 1 diabetes.

4.2. Management strategies

Two large trials have been published since the last guidelines: COACH and STRONG-HF.

4.2.1. Admission phase

The COACH trial was a cross-sectional, stepped-wedge, cluster-randomized trial including 5452 patients (2972 during the control phase and 2480 during the intervention phase) enrolled at 10 centres in Ontario, Canada.[4] During the intervention phase, hospital staff used the Emergency Heart Failure Mortality Risk Grade 30 Day Mortality-ST Depression ('EHMRG30-ST') score to ascertain whether patients had a low, intermediate, or high risk of death within 7 days or within 30 days. The study protocol recommended that low-risk patients be discharged early (in ≤3 days) and be treated with standardized outpatient care up to 30-day follow-up, whereas it was advised that intermediate- and high-risk patients be admitted to the hospital. Although early discharge occurred at a similar rate in the intervention and control groups (57% vs. 58%), the trial was successful in showing a 12% reduction in the primary outcome of all-cause death or CV hospitalization in the interventional arm compared with the control arm (HR 0.88, 95% CI 0.78–0.99), consistent with a favourable effect of post-discharge care.[4] The trial may need further confirmation multinationally before any recommendation on its approach can be offered in a guideline.

4.2.2. Pre-discharge and early post-discharge phases

The importance of pre-discharge and early post-discharge assessment in patients admitted to hospital for an episode of acute HF was already stressed in the original 2021 ESC HF Guidelines.[1] The STRONG-HF trial recently showed the safety and efficacy of an approach based on starting and titrating oral medical therapy for HF within 2 days before anticipated hospital discharge and in follow-up visits occurring early after discharge.[16] In this trial, 1078 patients hospitalized for acute HF, not already on full doses of evidence-based HF therapies, who were haemodynamically stable, with elevated NT-proBNP concentrations at screening (>2500 pg/mL), and a >10% decrease in concentration between screening and randomization, were randomly assigned, before discharge, to usual care or high-intensity care. Patients in the high-intensity care group received early and rapid intensification of oral HF treatment with ACE-I (or ARB) or ARNI, beta-blockers, and MRA.[16]

The goal of the first titration visit, which occurred within 48 h before hospital discharge, was to reach at least half of the target doses of recommended medications. Titration to full target doses of oral therapies was attempted within 2 weeks after discharge, with appropriate safety

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monitoring. Follow-up visits, including physical examination and laboratory evaluation, including NT-proBNP measurement, were performed at 1, 2, 3, and 6 weeks after randomization to assess the safety and tolerability of medical therapy. Patients assigned to high-intensity care were more likely to receive full doses of oral therapies than those in the usual care group (renin–angiotensin system inhibitors 55% vs. 2%, beta-blockers 49% vs. 4%, and MRA 84% vs. 46%). The trial was stopped early for benefit. The primary outcome of HF readmission or all-cause death at 180 days occurred in 15.2% of patients in the high-intensity care group and in 23.3% of patients in the usual care group (adjusted RR [aRR] 0.66, 95% CI 0.50–0.86; $P = .0021$). Readmissions for HF were reduced (aRR 0.56, 95% CI 0.38–0.81; $P = .0011$), whereas all-cause death by day 180 was not (aRR 0.84, 95% CI 0.56–1.26; $P = .42$). Similar rates of serious adverse events (16% vs. 17%) and fatal adverse events (5% vs. 6%) were reported in each group.[16]

Based upon the results of STRONG-HF, high-intensity care for initiation and rapid up-titration of oral HF therapies and close follow-up in the first 6 weeks after discharge for an acute HF hospitalization is recommended to reduce HF readmission or all-cause death. During the follow-up visits, particular attention should be paid to symptoms and signs of congestion, blood pressure, heart rate, NT-proBNP values, potassium concentrations, and eGFR.

STRONG-HF has several limitations. First, the population was carefully selected, based on baseline NT-proBNP concentrations and their decline during hospitalization. Second, the majority of patients in the control group received less than half of full optimal doses of ACE-I/ARB/ARNI and beta-blockers, and, although similar to many real-world clinical settings,[30–33] their relative undertreatment may have favoured the high-intensity care arm. Third, the trial was initiated prior to current evidence and recommendations for SGLT2 inhibitors, which were not mandated in the protocol.

Recommendation Table 3 — Recommendation for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

Recommendation	Class[a]	Level[b]
An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[c,d,e] [16]	I	B

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ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[a]Class of recommendation.

[b]Level of evidence.

[c]In STRONG-HF, the use of ACE-I/ARB/ARNI, beta-blockers, and MRA was evaluated in patients with HFrEF, HFmrEF, and HFpEF.

[d]This recommendation is based on the reduction of the primary endpoint used in the STRONG-HF trial. However, it should be noted that there was a significant reduction only in HF hospitalization and no reduction in CV death or all-cause death alone and that these results were obtained in a specific patient population, not already on full doses of evidence-based HF therapies, who were haemodynamically stable, with elevated NT-proBNP concentrations at screening (>2500 pg/mL), and a >10% decrease in concentration between screening and randomization, according to the enrolment criteria.

[e]Although STRONG-HF was based only on triple therapy with neurohormonal modulators, this recommendation also includes empagliflozin or dapagliflozin based on recent evidence.[6,8,9]

5. Comorbidities

5.1. Chronic kidney disease and type 2 diabetes mellitus

The 2021 ESC HF Guidelines gave recommendations for the prevention of HF in patients with diabetes. This update provides new recommendations for prevention of HF in patients with chronic kidney disease (CKD) and T2DM.[5,7,10,11,34,35]

Previous trials have shown the effects of ARB in preventing HF events in patients with diabetic nephropathy.[36,37] Both the Kidney Disease: Improving Global Outcomes (KDIGO) and the 2022 American Diabetes Association Standards of Medical Care in Diabetes and KDIGO recommendations indicate treatment with an ACE-I or ARB for patients with CKD, diabetes, and hypertension or albuminuria.[38,39]

5.1.1. Sodium–glucose co-transporter 2 inhibitors

Two randomized controlled trials, which were stopped early for efficacy, and a meta-analysis were recently published. DAPA-CKD was a multicentre, double-blind, placebo-controlled, randomized trial including both diabetic and non-diabetic patients with a urinary albumin-to-creatinine ratio ≥200 mg/g and an eGFR of 25–75 mL/min/1.73 m^2, who were randomly assigned 1:1 to dapagliflozin 10 mg once daily or placebo.[5] Overall, 468 of the 4304 patients enrolled (11%) had a history of HF. During a median follow-up of 2.4 years, a reduction in the primary outcome, a composite of sustained decline in eGFR of ≥50%, end-stage kidney disease, or kidney-related or CV death, was reduced by 39% by dapagliflozin compared with placebo (HR 0.61, 95% CI 0.51–0.72; $P < .001$). Also, the risk of the secondary outcome of HF hospitalization or CV death was decreased by dapagliflozin compared with placebo (HR 0.71, 95% CI 0.55–0.92; $P = .009$) with, however, a relatively small absolute risk reduction (4.6% vs. 6.4% with dapagliflozin vs. placebo).[5]

EMPA-KIDNEY enrolled a broader group of patients with CKD, compared with DAPA-CKD, including patients with eGFR 20–45 mL/min/1.73 m^2, even in the absence of albuminuria, or with an eGFR of 45–90 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio ≥200 mg/g. Patients were randomized 1:1 to empagliflozin 10 mg once daily or placebo.[7] Overall, 658 of the 6609 patients enrolled (10%) had a history of HF. During a median follow-up of 2.0 years, a reduction in the primary composite endpoint of progression of kidney disease or CV death was observed.[7] The risk of HF hospitalization or death for CV causes was not reduced significantly (HR 0.84, 95% CI 0.67–1.07; $P = .15$).[7]

DAPA-CKD, EMPA-KIDNEY, CREDENCE[39a] (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation), and SCORED[39b] (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) were included with HF trials in a recent meta-analysis.[35] The reduction in HF hospitalizations and CV death was similar irrespective of a history of diabetes when both HF and CKD trials were included (HR 0.77, 95% CI 0.73–0.81 in patients with T2DM, and HR 0.79, 95% CI 0.72–0.87 in those without T2DM). However, results were not significant in patients without diabetes when only CKD trials were included (HR for HF hospitalizations and CV death of 0.74, 95% CI 0.66–0.82 in patients with T2DM, and HR of 0.95, 95% CI 0.65–1.40 in patients without T2DM).[35] Based on these results, SGLT2 inhibitors are recommended in patients with CKD and T2DM, and with the additional characteristics of the participants in these trials, including an eGFR >20–25 mL/min/1.73 m^2, to reduce the risk of HF hospitalization or CV death.

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5.1.2. Finerenone

The selective, non-steroidal, MRA finerenone was tested in two trials in patients with diabetic kidney disease. The FIDELIO-DKD trial enrolled 5734 patients with a urinary albumin-to-creatinine ratio 30–300 mg/g, an eGFR 25–60 mL/min/1.73 m^2, and diabetic retinopathy, or a urinary albumin-to-creatinine ratio 300–5000 mg/g and an eGFR 25–75 mL/min/1.73 m^2.[10] The primary outcome of the trial, assessed in a time-to-event analysis, was a composite of kidney failure, a sustained decrease of ≥40% in the eGFR from baseline over a period of ≥4 weeks, or death from renal causes. Kidney failure was defined as end-stage kidney disease or an eGFR <15 mL/min/1.73 m^2; end-stage kidney disease was defined as the initiation of long-term dialysis (for ≥90 days) or kidney transplantation. The primary endpoint of the trial was reduced by finerenone compared with placebo by 18% (HR 0.82, 95% CI 0.73–0.93; $P = .001$), during a median follow-up of 2.6 years.[10] There was no evidence of a reduction in HF hospitalizations with finerenone vs. placebo (HR 0.86, 95% CI 0.68–1.08), although finerenone was associated with a lower occurrence of the key secondary endpoint, a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for HF (HR 0.86, 95% CI 0.75–0.99; $P = .03$).[10] Patients with HFrEF and NYHA class II–IV were excluded from the trial. However, patients with asymptomatic or NYHA class I HFrEF, or with HFmrEF or HFpEF, could be enrolled, so that 7.7% of the patients included had a history of HF. The effects of finerenone on the composite of CV and renal outcomes, including HF hospitalizations, were independent of a previous history of HF.[34]

In the more recent FIGARO-DKD trial, the primary outcome, assessed in a time-to-event analysis, was a composite of death from CV causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for HF.[11] The trial enrolled adult patients with T2DM and CKD treated with a renin–angiotensin system inhibitor at the maximum tolerated dose. CKD was defined according to one of two sets of criteria: persistent, moderately elevated albuminuria (urinary albumin-to-creatinine ratio 30 to <300 mg/g) and an eGFR 25–90 mL/min/1.73 m^2 (i.e. stage 2 to 4 CKD); or persistent, severely elevated albuminuria (urinary albumin-to-creatinine ratio 300–5000 mg/g) and an eGFR >60 mL/min/1.73 m^2 (i.e. stage 1 or 2 CKD). Patients were required to have a serum potassium level of ≤4.8 mmol/L at the time of screening.[11] The trial included 7437 patients randomly assigned to finerenone or placebo.[11] At a median follow-up of 3.4 years, the rate of the primary outcome, CV death, non-fatal myocardial infarction, non-fatal stroke, or HF hospitalization, was lower in the treatment arm compared with placebo (HR 0.87, 95% CI 0.76–0.98; $P = .03$). The benefit was driven by a numerically small, but statistically significant, lower incidence of HF hospitalization with finerenone vs. placebo (3.2% vs. 4.4%; HR 0.71, 95% CI 0.56–0.90), with no differences in CV death.[11] In both FIDELIO-DKD and FIGARO-DKD the occurrence of hyperkalaemia was higher in the finerenone group compared with the placebo group. However, the rate of adverse events was similar between the two arms.

A pre-specified individual patient-level, pooled analysis, including 13 026 patients with diabetic kidney disease followed for a median of 3.0 years from both the FIDELIO-DKD and FIGARO-DKD trials, showed a reduction in the composite CV outcome, including CV death, non-fatal stroke, non-fatal myocardial infarction, and HF hospitalizations, as well as in HF hospitalizations alone with finerenone vs. placebo (HR 0.86, 95% CI 0.78–0.95; $P = .0018$; and HR 0.78, 95% CI 0.66–0.92; $P = .0030$, respectively).[40] Thus, finerenone is recommended for the prevention of HF hospitalization in patients with CKD and T2DM.

Recommendation Table 4 — Recommendations for the prevention of heart failure in patients with type 2 diabetes mellitus and chronic kidney disease

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death.[35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

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CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; SGLT2, sodium–glucose co-transporter 2; T2DM, type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

[c]CKD was defined as follows: an eGFR 25–75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio ≥200–5000 mg/g in DAPA-CKD;[5] an eGFR 20–45 mL/min/1.73 m^2 or an eGFR 45–90 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio ≥200 mg/g in EMPA-KIDNEY;[7] an eGFR 25–60 mL/min/1.73 m^2, a urinary albumin-to-creatinine ratio 30–300 mg/g, and diabetic retinopathy, or an eGFR 25–75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio 300–5000 mg/g, in FIDELIO-DKD;[10] and an eGFR 25–90 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio 30 to <300 mg/g, or an eGFR >60 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio 300–5000 mg/g, in FIGARO-DKD.[11]

5.2. Iron deficiency

Recommendations for the diagnosis and treatment of iron deficiency were given in the 2021 ESC HF Guidelines: COR I, LOE C for the diagnosis of iron deficiency, COR IIa, LOE A to improve HF symptoms, exercise capacity, and quality of life, and COR IIa, LOE B to reduce HF hospitalizations, for treatment with ferric carboxymaltose.[1]

A new trial, IRONMAN, has now been published.[12] This was a prospective, randomized, open-label, blinded-endpoint trial including patients with HF, LVEF ≤45%, and transferrin saturation <20% or serum ferritin <100 µg/L who were randomly allocated 1:1 to i.v. ferric derisomaltose or usual care. The patients included were mainly ambulatory, although 14% were enrolled during an HF hospitalization and 18% had an HF hospitalization in the previous 6 months. After a median follow-up of 2.7 years, the rate ratio for the primary endpoint, a composite of total (first and recurrent) HF hospitalizations and CV death, was 0.82 (95% CI 0.66–1.02; $P = .070$). Total hospital admissions for HF were not reduced significantly with ferric derisomaltose vs. usual care (16.7 vs. 20.9 per 100 patient-years; RR 0.80, 95% CI 0.62–1.03; $P = .085$). As in AFFIRM-AHF (A Randomized Double-blind Placebo Controlled Trial Comparing the Effects of Intravenous Ferric Carboxymaltose on Hospitalizations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure),[41] a pre-specified COVID-19 analysis, censoring follow-up on September 2020, showed a reduction in the risk of the primary endpoint with ferric derisomaltose vs. control (HR 0.76, 95% CI 0.58–1.00; $P = .047$). There was a statistically borderline improvement in the Minnesota Living with Heart Failure Questionnaire score with ferric derisomaltose (between treatment difference −3.33, 95% CI −6.67 to 0.00; $P = .050$), but no difference in EQ-5D visual analogue scale or EQ-5D index.[12] Some of these findings in secondary outcomes might be explained by the lack of adjustment for multiple testing.[42] Safety endpoints, i.e. death and hospitalization due to infection, did not differ between the two arms.[12]

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These results have been included in meta-analyses of the randomized controlled trials comparing the effects of i.v. iron therapy with standard of care or placebo in patients with HF and iron deficiency.[43–46] In the analysis by Graham *et al.*[44] including 10 trials with 3373 patients, i.v. iron reduced the composite of total HF hospitalizations and CV death (RR 0.75, 95% CI 0.61–0.93; $P < .01$) and first HF hospitalization or CV death (odds ratio [OR] 0.72, 95% CI 0.53–0.99; $P = .04$). There was no effect on CV (OR 0.86, 95% CI 0.70–1.05; $P = .14$) or all-cause mortality (OR 0.93, 95% CI 0.78–1.12; $P = .47$). Similar results were found in the other meta-analyses.[43,45,46] In the PIVOTAL trial, a high-dose i.v. iron regimen, compared with a low-dose regimen, reduced the occurrence of first and recurrent HF events in patients undergoing dialysis for end-stage CKD.[13,14]

Based on trials and recent meta-analyses,[13,14,41,43,45–49] i.v. iron supplementation is now recommended in patients with HFrEF or HFmrEF, and iron deficiency, to improve symptoms and quality of life, and should be considered to reduce the risk of HF hospitalization. Iron deficiency was diagnosed by a low transferrin saturation (<20%) or a low serum ferritin concentration (<100 µg/L).[12,41] Notably, in IRONMAN, patients were excluded if they had haemoglobin >13 g/dL (for women) and >14 g/dL (for men).[12] The new recommendations are shown below.

Recommendation Table 5 — Recommendations for the management of iron deficiency in patients with heart failure

Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] [12,41,47–49]	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.[c] [12,41,43–46]	IIa	A

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HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Most of the evidence refers to patients with left ventricular ejection fraction ≤45%.

6. Data availability statement

No new data were generated or analysed in support of this research.

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8. Appendix

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