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

Evidence tables

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

Study first author surname and year	**Add endnote reference for study**	**Details and quality of evidence**				**Summary of key findings**		
		Population and study type (meta-analysis of RCTs, single RCT, case-control, retrospective cohort, etc.)	**Number of patients**	**Intervention and control**	**Key inclusion & exclusion criteria**	**Relevant outcome(s)**	**Key findings Important biases**	**Conclusion(s)**
Anker, SD 2021	8	Single RCT	5988	Empagliflozin 10mg/placebo	CHF, NYHA>II, LVEF>40%, NTproBNP>300pg/ml in SR or >900pg/ml in AF	CV death or or hospitalization for HF, (time to the first event)	415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001) Main effect on hospitalisations: Total number of hospitalizations for HF was lower in the empagliflozin group than in the placebo group (407	Met primary endpoint NNT to prevent one primary endpoint=60

							with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001) Main effect on reduction in hospitalisations. Rate of decline of eGFR lower in empagliflozin group	
Solomon, SD 2022	6	Single RCT	6263	Dapagliflozin 10mg/placebo	CHF, NYHA II-IV, LVEF>40% (previous LVEF<40%, included if >40% at enrolment). NT-ProBNP>300pg/ml in Sr or >600pg/ml in AF, either ambulatory or hospitalised, structural heart disease (LVH or LA enlargement)	Time to event: occurrence of worsening HF or CV death,	Primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (HR, 0.82; 95% [CI], 0.73 to 0.92; P<0.001). Worsening HF occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (HR, 0.79; 95% CI, 0.69 to 0.91)	Met primary endpoint NNT to prevent one primary endpoint=61

							CV death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (HR, 0.88; 95% CI, 0.74 to 1.05).	
Vaduganathan, M 2022	24	Aggregate data meta-analysis	12251	Dapagliflozin or Empagliflozin versus placebo	Patients included in the DELIVER and EMPEROR-P trials	CV or first hospitalisation for HF	Reduced CVD or first hospitalisation for HF. HR 0·80 [95% CI 0·73-0·87]) with consistent reductions in both components: CV (0·88 [0·77-1·00]) and first hospitalisation for HF (0·74 [0·67-0·83])	CV reduction was a trend (p not<0.05)
Mebazaa A 2022	16	Patients admitted to hospital with acute heart failure. RCT	1078	High-intensity care (HIC) or usual care (UC). HIC involved the up-titration of treatments to 100% of recommended doses within 2 weeks of discharge and four scheduled outpatient visits over the 2 months	Patients were eligible for inclusion if they were aged 18–85 years; had been admitted to hospital within 72 h before screening for acute heart failure, defined as dyspnoea at rest and pulmonary congestion on chest x-ray, and other	The primary endpoint was 180-day readmission to hospital due to heart failure or all-cause death.	The study was stopped early per the data and safety monitoring board's recommendation because of greater than expected between-group differences. The primary endpoint occurred	Met primary endpoint

				after discharge that closely monitored clinical status, laboratory values, and NT-proBNP concentrations. UC followed usual local practice.	signs or symptoms of heart failure (eg, oedema or positive rales on auscultation); were haemodynamically stable; had elevated NT-proBNP concentrations at screening (>2500 pg/mL) and a more than 10% decrease in concentration between screening and before randomisation (but still >1500 pg/mL); and had not been treated with optimal doses of oral heart failure therapies within 2 days before anticipated hospital discharge for acute heart failure. Patients were excluded if they had a clear intolerance to high doses of β blockers, ACE inhibitors, or ARBs. There were no inclusion criteria based on left ventricular ejection fraction (LVEF).		in 74 (15.2% down-weighted adjusted Kaplan-Meier estimate) of 506 patients in the HIC group and 109 (23.3%) of 502 patients in the UC group (adjusted risk difference 8.1% [95% CI 2.9–13.2]; p=0.0021; risk ratio 0.66 [95% CI 0.50–0.86]).	

Heerspink 2020	5	Patients with CKD RCT	4304	Dapagliflozin 10 mg/placebo	CKD was the main inclusion criterion. It was defined as estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000	The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Among secondary outcomes: the composite of death from cardiovascular causes or HF hospitalization	The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of death from cardiovascular causes or hospitalization for HF was 0.71 (95%	Met primary endpoint + secondary endpoint (CVD or HFH)

							CI, 0.55 to 0.92; P = 0.009)	
Herrington, 2023	7	Patients with CKD RCT	6609	Empagliflozin 10 mg/placebo	CKD was the main inclusion criterion. It was defined as estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m2 of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m2 with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200.	The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes. Among the secondary endpoints: HF hospitalization or CV death.	During a median of 2 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). Results were consistent among patients with or without diabetes. The risk of death for CV causes or HF hospitalizations was not significantly reduced (HR 0.84, 95% CI 0.67–1.07; P = 0.15)	Met primary endpoint. No differences in CVD or HFH

Nuffield Department of Population Health Renal Studies Group, 2022	35	Meta-analysis study level of RCT comparing SGLT2i vs placebo including CKD trials.	90409	SGLT2i/placebo	SGLT2 inhibitor trials that were double-blind, placebo-controlled, performed in adults (age ≥18 years), large (≥500 participants per group), and at least 6 months in duration were included.	The main efficacy outcomes were kidney disease progression (standardised to a definition of a sustained ≥50% decrease in estimated glomerular filtration rate [eGFR] from randomisation, a sustained low eGFR, end-stage kidney disease, or death from kidney failure), acute kidney injury, and a composite of cardiovascular death or hospitalisation for heart failure.	Compared with placebo, SGLT2 inhibitor reduced the risk of kidney disease progression by 37% (relative risk [RR] 0·63, 95% CI 0·58–0·69) with similar RRs in patients with and without diabetes. In the 4 CKD trials, RRs were similar irrespective of primary kidney diagnosis. SGLT2 inhibitors reduced the risk of cardiovascular death or hospitalisation for heart failure by 23% (0·77, 0·74–0·81) with similar effects in those with and without diabetes.	Reduction in kidney progression and CV death or HFH.
Bakris, 2020	10	Patients with CKD and type 2 Diabetes.	5734	Finerenone/placebo	Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in	The primary composite outcome was kidney failure,	During a median follow-up of 2.6 years, a primary outcome event	Met primary endpoint. Finerenone better than

		RCT			milligrams and creatinine measured in grams) of 30 to less than 300, an estimated glomerular filtration rate (eGFR) of 25 to less than 60 ml per minute per 1.73 m2 of body surface area, and diabetic retinopathy, or they had a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75 ml per minute per 1.73 m2. All the patients were treated with renin–angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects.	defined as a a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes. The key secondary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.	occurred in 504 of 2833 patients (17.8%) in the finerenone group and 600 of 2841 patients (21.1%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P = 0.001). A key secondary outcome event occurred in 367 patients (13.0%) and 420 patients (14.8%) in the respective groups (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; P = 0.03). However, There was no evidence of a reduction in HF hospitalizations with finerenone versus placebo (HR 0.86, 95% CI 0.68–1.08).	placebo for the secondary endpoint including HFH, but not for HFH as a single endpoint.
Filippatos, 2022	34	Patients with CKD and type 2 Diabetes.	7437	Finerenone/placebo	Eligible patients had a urinary albumin-to creatinine ratio (with albumin measured in milligrams and	The primary outcome, assessed in a time-to-event analysis, was a	During a median follow-up of 3.4 years, a primary outcome event occurred in 458 of	Met primary endpoint (including HF hospitalization).

		RCT			creatinine measured in grams) of 30 to less than 300 and an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m2 of body-surface area (stage 2 to 4 CKD) or a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of at least 60 ml per minute per 1.73 m2 (stage 1 or 2 CKD). Patients were treated with renin–angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects.	composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The first secondary outcome was a composite of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR, or death from renal causes.	3686 patients (12.4%) in the finerenone group and in 519 of 3666 (14.2%) in the placebo group (hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P = 0.03), with the benefit driven primarily by a lower incidence of hospitalization for heart failure (hazard ratio, 0.71; 95% CI, 0.56 to 0.90). The secondary composite outcome occurred in 350 patients (9.5%) in the finerenone group and in 395 (10.8%) in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 1.01).	
Agarwal, 2022	40	Patients with CKD and type 2 Diabetes.	13026	Finerenone/placebo	Patients included in the FIDELIO-DKD and FIGARO-DKD trials	Main time-to-event efficacy outcomes were a composite of cardiovascular death, non-	The composite cardiovascular outcome occurred in 825 (12.7%) patients receiving finerenone and	Finerenone reduces both CV and renal outcomes, including HF hospitalization

		Patient-level Meta-analysis of 2 RCT				fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, and a composite of kidney failure, a sustained >or=57% decrease in estimated glomerular filtration rate from baseline over > or =4 weeks,or renal death.	939 (14.4%) receiving placebo [hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.78–0.95; P= 0.0018]. The composite kidney outcome occurred in 360 (5.5%) patients receiving finerenone and 465 (7.1%) receiving placebo (HR, 0.77; 95% CI, 0.67–0.88; P= 0.0002). Finerenone also reduced HF hospitalization alone compared with placebo (HR 0.78, 95% CI 0.66–0.92; P = 0.0030)	alone, in patients with CKD and T2DM.
Kalra, 2022	12	Patients with HF, LVEF ≤45% and iron deficiency. RCT	1869	Intravenous ferric derisomaltose/ usual care	Patients with HF, LVEF ≤45% and transferrin saturation <20% or serum ferritin <100 µg/L	The primary outcome was recurrent hospital admissions for heart failure and cardiovascular death, assessed in all	After a median follow-up of 2.7 years, the reduction in the primary endpoint did not reach statistical significance (RR 0.82, 95% CI 0.66–1.02;	Met primary endpoint only after censoring follow-up on September 2020.

						validly randomly assigned patients.	P = 0.070). Hospital admissions for HF were also not significantly reduced (16.7 per 100 patient-years vs. 20.9 per 100 patient-years; HR 0.80, 95% CI 0.62–1.03). 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 = 0.047).	
Graham, 2023	44	Patients with HF and iron deficiency Study-level Meta-analysis including 10 RCT	3373	IV iron/standard care or placebo	RCT comparing IV iron versus standard care/placebo in patients with HF and ID in any clinical setting	The main outcomes of interest were a composite of HHF and cardiovascular death, on HF hospitalization alone and on cardiovascular	IV iron reduced the composite of recurrent HF hospitalization and CV death (rate ratio 0.75, 95% confidence interval [CI] 0.61–0.93; p<0.01) and first HF hospitalization	IV iron reduced HF hospitalization or CV death in patients with HF and iron deficiency, but not mortality.

						and all-cause mortality.	or CV death (odds ratio [OR] 0.72, 95% CI 0.53–0.99; P = 0.04). No differences were observed in cardiovascular (OR 0.86, 95% CI 0.70–1.05; P = 0.14) and all-cause mortality (OR 0.93, 95% CI 0.78–1.12; P = 0.47).	
Salah, 2023	43	Patients with HF and iron deficiency Study-level Meta-analysis including 10 RCT	3438	IV iron/standard care or placebo	RCT comparing IV iron versus standard care/placebo in patients with HF and ID in any clinical setting	Outcomes were the composite of CV mortality and first hospitalization for HF; all-cause mortality; CV mortality; first hospitalization for HF; and total hospitalizations for HF.	Intravenous iron resulted in a significant reduction in the composite of CV mortality and first hospitalization for HF [RR 0.0.85; 95% CI (0.77, 0.95)], first hospitalization for HF [RR 0.82; 95% CI (0.67, 0.99)], and total hospitalizations for HF [RR 0.74; 95% CI (0.60, 0.91)] but no statistically significant	IV iron reduced HF hospitalization or CV death in patients with HF and iron deficiency, but not mortality. Also HF hospitalization considered as single outcome was reduced.

							difference in all-cause mortality [RR 0.95; 95% CI. (0.83, 1.09)] or CV mortality [OR 0.89; 95% CI (0.75, 1.05)].	

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726. https://doi.org/10.1093/eurheartj/ehab368
2. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, *et al*.; ADVOR Study Group. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med* 2022;**387**:1185–1195. https://doi.org/10.1056/NEJMoa2203094
3. Trulls JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Snchez-Marteles M, Conde-Martel A, *et al*.; CLOROTIC Trial Investigators. Combining loop with thiazide diuretics for decompensated heart failure: The CLOROTIC trial. *Eur Heart J* 2023;**44**:411–421. https://doi.org/10.1093/eurheartj/ehac689
4. Lee DS, Straus SE, Farkouh ME, Austin PC, Taljaard M, Chong A, *et al*.; COACH Trial Investigators. Trial of an intervention to improve acute heart failure outcomes. *N Engl J Med* 2023;**388**:22–32. https://doi.org/10.1056/NEJMoa2211680
5. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, *et al*.; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–1446. https://doi.org/10.1056/NEJMoa2024816
6. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, *et al*.; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;**387**:1089–1098. https://doi.org/10.1056/NEJMoa2206286
7. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, *et al*. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023;**388**:117–127. https://doi.org/10.1056/NEJMoa2204233
8. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, *et al*.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;**385**:1451–1461. https://doi.org/10.1056/NEJMoa2107038
9. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, *et al*. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med* 2022;**28**:568–574. https://doi.org/10.1038/s41591-021-01659-1
10. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, *et al*.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:2219–2229. https://doi.org/10.1056/NEJMoa2025845
11. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, *et al*.; FIGARO-DKD Investigators. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;**385**:2252–2263. https://doi.org/10.1056/NEJMoa2110956
12. Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, *et al*.; IRONMAN Study Group. Intravenous ferric derisomaltose in patients with heart

failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet* 2022;**400**:2199–2209. https://doi.org/10.1016/S0140-6736(22)02083-9

13. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, *et al*.; PIVOTAL Investigators and Committees. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019;**380**:447–458. https://doi.org/10.1056/NEJMoa1810742
14. Jhund PS, Petrie MC, Robertson M, Mark PB, MacDonald MR, Connolly E, *et al*.; PIVOTAL Investigators and Committees. Heart failure hospitalization in adults receiving hemodialysis and the effect of intravenous iron therapy. *JACC Heart Fail* 2021;**9**:518–527. https://doi.org/10.1016/j.jchf.2021.04.005
15. Perera D, Clayton T, O'Kane PD, Greenwood JP, Weerackody R, Ryan M, *et al*.; REVIVED-BCIS2 Investigators. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med* 2022;**387**:1351–1360. https://doi.org/10.1056/NEJMoa2206606
16. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, *et al*. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet* 2022;**400**:1938–1952. https://doi.org/10.1016/S0140-6736(22)02076-1
17. Mentz RJ, Anstrom KJ, Eisenstein EL, Sapp S, Greene SJ, Morgan S, *et al*.; TRANSFORM-HF Investigators. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: The TRANSFORM-HF Randomized clinical trial. *JAMA* 2023;**329**:214–223. https://doi.org/10.1001/jama.2022.23924
18. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P, *et al*.; TRILUMINATE Pivotal Investigators. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med* 2023;**388**:1833–1842. https://doi.org/10.1056/NEJMoa2300525
19. Anker SD, Butler J, Filippatos G, Shahzeb Khan M, Ferreira JP, Bocchi E, *et al*.; EMPEROR-Preserved Trial Committees and Investigators. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. *Eur J Heart Fail* 2020;**22**:2383-2392. https://doi.org/10.1002/ejhf.2064
20. Solomon SD, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, *et al*. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: Rationale and design of the DELIVER trial. *Eur J Heart Fail* 2021;**23**:1217–1225. https://doi.org/10.1002/ejhf.2249
21. Solomon SD, Vaduganathan M, Claggett BL, de Boer RA, DeMets D, Hernandez AF, *et al*. Baseline characteristics of patients with HF with mildly reduced and preserved ejection fraction: DELIVER trial. *JACC Heart Fail* 2022;**10**:184–197. https://doi.org/10.1016/j.jchf.2021.11.006
22. Vardeny O, Fang JC, Desai AS, Jhund PS, Claggett B, Vaduganathan M, *et al*. Dapagliflozin in heart failure with improved ejection fraction: A prespecified analysis of the DELIVER trial. *Nat Med* 2022;**28**:2504–2511. https://doi.org/10.1038/s41591-022-02102-9
23. Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, *et al*. Dapagliflozin across the range of ejection fraction in patients with heart failure: A patient-level,

pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med* 2022;**28**:1956–1964. https://doi.org/10.1038/s41591-022-01971-4

24. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, *et al*. SGLT-2 inhibitors in patients with heart failure: A comprehensive meta-analysis of five randomised controlled trials. *Lancet* 2022;**400**:757–767. https://doi.org/10.1016/S0140-6736(22)01429-5
25. Masip J, Frank Peacok W, Arrigo M, Rossello X, Platz E, Cullen L, *et al*. Acute heart failure in the 2021 ESC Heart Failure Guidelines: a scientific statement from the Association for Acute CardioVascular Care (ACVC) of the European Society of Cardiology. *Eur Heart J Acute Cardiovasc Care* 2022;**11**:173–185. https://doi.org/10.1093/ehjacc/zuab122
26. Cunningham JW, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, *et al*. Dapagliflozin in patients recently hospitalized with heart failure and mildly reduced or preserved ejection fraction. *J Am Coll Cardiol* 2022;**80**:1302–1310. https://doi.org/10.1016/j.jacc.2022.07.021
27. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, *et al*.; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384**:117–128. https://doi.org/10.1056/NEJMoa2030183
28. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS, *et al*. Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2022;**24**:431–441. https://doi.org/10.1002/ejhf.2397
29. Liu J, Li L, Li S, Wang Y, Qin X, Deng K, *et al*. Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2020;**22**:1619–1627. https://doi.org/10.1111/dom.14075
30. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, *et al*. Improving evidence-based care for heart failure in outpatient cardiology practices: Primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation* 2010;**122**:585–596. https://doi.org/10.1161/CIRCULATIONAHA.109.934471
31. Gheorghiade M, Albert NM, Curtis AB, Thomas Heywood J, McBride ML, Inge PJ, *et al*. Medication dosing in outpatients with heart failure after implementation of a practice-based performance improvement intervention: Findings from IMPROVE HF. *Congest Heart Fail* 2012;**18**:9–17. https://doi.org/10.1111/j.1751-7133.2011.00250.x
32. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, *et al*. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol* 2018;**72**:351–366. https://doi.org/10.1016/j.jacc.2018.04.070
33. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, *et al*. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: A prospective European study. *Eur Heart J* 2017;**38**:1883–1890. https://doi.org/10.1093/eurheartj/ehx026
34. Filippatos G, Pitt B, Agarwal R, Farmakis D, Ruilope LM, Rossing P, *et al*. Finerenone in patients with chronic kidney disease and type 2 diabetes with and without heart

failure: A prespecified subgroup analysis of the FIDELIO-DKD trial. *Eur J Heart Fail* 2022;**24**:996–1005. https://doi.org/10.1002/ejhf.2469

35. Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: Collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022;**400**:1788–1801. https://doi.org/10.1016/S0140-6736(22)02074-8
36. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, *et al*.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–869. https://doi.org/10.1056/NEJMoa011161
37. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, *et al*.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–860. https://doi.org/10.1056/NEJMoa011303
38. de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, *et al*. Diabetes management in chronic kidney disease: A consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care* 2022;**45**:3075–3090. https://doi.org/10.2337/dci22-0027
39. House AA, Wanner C, Sarnak MJ, Pina IL, McIntyre CW, Komenda P, *et al*. Heart failure in chronic kidney disease: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019;**95**:1304–1317. https://doi.org/10.1016/j.kint.2019.02.022
40. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, *et al*.; FIDELIO-DKD and FIGARO-DKD Investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: The FIDELITY pooled analysis. *Eur Heart J* 2022;**43**:474–484. https://doi.org/10.1093/eurheartj/ehab777
41. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, *et al*.; AFFIRM-AHF Investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: A multicentre, double-blind, randomised, controlled trial. *Lancet* 2020;**396**:1895–1904. https://doi.org/10.1016/S0140-6736(20)32339-4
42. Pocock SJ, Rossello X, Owen R, Collier TJ, Stone GW, Rockhold FW. Primary and secondary outcome reporting in randomized trials: JACC state-of-the-art review. *J Am Coll Cardiol* 2021;**78**:827–839. https://doi.org/10.1016/j.jacc.2021.06.024
43. Salah HM, Savarese G, Rosano GMC, Ambrosy AP, Mentz RJ, Fudim M. Intravenous iron infusion in patients with heart failure: A systematic review and study-level meta-analysis. *ESC Heart Fail* 2023;**10**:1473–1480. https://doi.org/10.1002/ehf2.14310
44. Graham FJ, Pellicori P, Kalra PR, Ford I, Bruzzese D, Cleland JGF. Intravenous iron in patients with heart failure and iron deficiency: An updated meta-analysis. *Eur J Heart Fail* 2023;**25**:528–537. https://doi.org/10.1002/ejhf.2810
45. Vukadinovic D, Abdin A, Emrich I, Schulze PC, von Haehling S, Bohm M. Efficacy and safety of intravenous iron repletion in patients with heart failure: A systematic review and meta-analysis. *Clin Res Cardiol* 2023. https://doi.org/10.1007/s00392-023-02207-2.

46. Anker SD, Khan MS, Butler J, von Haehling S, Jankowska EA, Ponikowski P, *et al*. Effect of intravenous iron replacement on recurrent heart failure hospitalizations and cardiovascular mortality in patients with heart failure and iron deficiency: A Bayesian meta-analysis. *Eur J Heart Fail* 2023. https://doi.org/10.1002/ejhf.2860.

47. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, *et al*.; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;**361**:2436–2448. https://doi.org/10.1056/NEJMoa0908355

48. Comin-Colet J, Lainscak M, Dickstein K, Filippatos GS, Johnson P, Luscher TF, *et al*. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: A subanalysis of the FAIR-HF study. *Eur Heart J* 2013;**34**:30–38. https://doi.org/10.1093/eurheartj/ehr504

49. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, *et al*.; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015;**36**:657–668. https://doi.org/10.1093/eurheartj/ehu385