Novel Recommendations for the Treatment of Patients With Heart Failure

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Perspectives

Novel Recommendations for the Treatment of Patients With Heart Failure: 2023 Focused Update of the 2021 ESC Heart Failure Guidelines

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The Task Force for the diagnosis and treatment of acute and chronic heart failure (HF) of the European Society of Cardiology (ESC) generally updates their guidelines every 4 years. However, since the presentation of the latest guidelines in 2021, a remarkable number of studies that could potentially change the guidelines have been published. Therefore, the task force decided to provide a focused update of the 2021 guidelines, which includes a few important novel recommendations that are outlined below (Fig. 1).[1]

SGLT2-inhibitors Have Now Received the Strongest Recommendation for the Treatment of Patients With HFmrEF and HFpEF

SGLT2-inhibitors have now received a class I (level of evidence A) recommendation for the treatment of patients with heart failure (HF) and a mildly reduced (HFmrEF) and preserved ejection fraction (HFpEF).[1] This recommendation was based on 2 large randomized, placebo-controlled trials with, respectively, empagliflozin (EMPEROR-Preserved [Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction]) and dapagliflozin (DELIVER [Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure]).[2,3] The task force did not specify NT-proBNP thresholds for treatment, even though both EMPEROR-Preserved and DELIVER included only patients with NT-proBNP levels above 300 pg/mL. Second, patients in the DELIVER and EMPEROR-Preserved trials had to be on (loop) diuretic treatment. Third, patients had to have either left ventricular hypertrophy or left atrial enlargement. Whether the beneficial effects of empagliflozin and dapagliflozin can be extended to patients with fewer symptoms, with lower natriuretic peptide levels and without left ventricular hypertrophy or left atrial enlargement is unknown. Nevertheless, the task force decided to provide a broad recommendation for all patients with HFpEF and HFmrEF. The current recommendation in the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) Guideline for the Management of Heart Failure provides a IIa (level of evidence B) recommendation, because only the data of EMPEROR-Preserved were available at that time, whereas the data of DELIVER were still pending.[4]

Novel Recommendations for Patients With Acute Heart Failure

Two important randomized controlled trials of diuretics in patients who were hospitalized for acute HF have been published recently. First, the CLOROTIC (Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure) trial showed that the addition of 25−100 mg hydrochlorothiazide resulted in 1.4 kg additional body-weight loss, but there was no difference in changes in dyspnea and no reduction in the risk of rehospitalization due to HF, all-cause death or the length of hospital stay.[5] However, worsening renal function and hypokalemia were more commonly observed in the hydrochlorothiazide group. Second, the ADVOR trial (Acetazolamide in Decompensated Heart Failure

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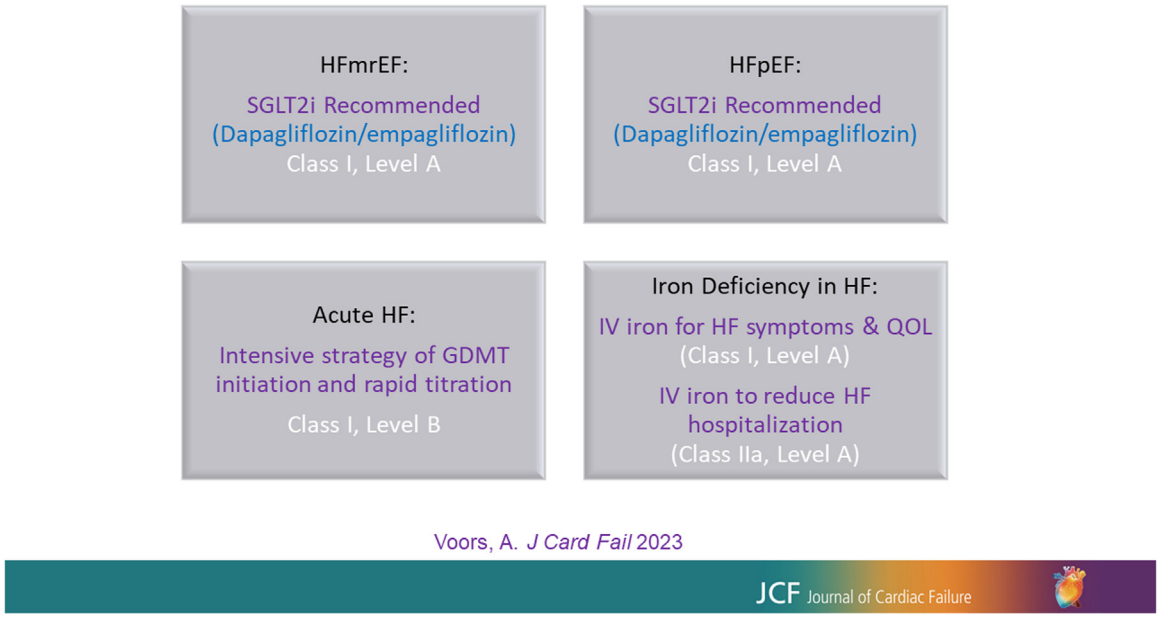

Fig. 1. Summary of several new recommendations in the 2023 Focused Update of the 2021 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure.[1]

with Volume Overload) showed that the addition of acetazolamide on top of standard of care resulted more often in successful decongestion in 519 patients with acute decompensated HF and in clinical signs of volume overload and elevated natriuretic peptides.[6] In addition, length of hospital stay was reduced by 1 day. However, similar to the CLOROTIC trial, the enhanced decongestion was not accompanied by an improvement in symptoms or a reduction in the risk of hospital readmission due to HF or death. In addition, the median estimated glomerular filtration rate (eGFR) increased in the placebo group from 38 mL/min at baseline to 39 mL/min at 72 hours, whereas the median eGFR dropped from 40 mL/min at baseline to 35 mL/min at 72 hours in the acetazolamide group.[6] It should be noted that the reduction in eGFR in combination with enhanced diuresis is a physiological response of the kidney and is not associated with worse outcomes.[7] However, lower eGFRs might, theoretically, lead to less uptake of chronic HF therapies, such as angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNis), and mineralocorticoid receptor antagonists (MRAs). The task force recognized the enhanced decongestion provided by both therapies, but the lack of impact on clinical outcomes precluded any recommendation in the current guideline update.

Around the same time, the results of STRONG-HF (Safety, Tolerability and Efficacy of Up-titration of Guideline-Directed Medical Therapies for Acute Heart Failure) were presented and published.[8] STRONG-HF was designed to study the effects of rapid uptitration of guideline-directed medical therapies for chronic HF in combination with intensified follow-up in 1078 patients who were hospitalized for acute HF and not already on full dosages of evidence-based HF therapies. The patients who were randomly assigned, before discharge, to high-intensity care received early and rapid intensification of oral HF treatment with ACEis (or ARBs) or ARNIs, beta-blockers, and MRAs, with the aim to be on 50% of recommended dosages of these therapies before discharge and to 100% of the recommended dosages within 2 weeks after discharge. The study was prematurely discontinued due to the large benefit in the patients in the high-intensive-care group, in whom there was a 34% reduction in the risk of cardiovascular death or hospitalization due to HF. It should be noted that the trial was initiated before the beneficial effects of sodium glucose cotransporter-2 inhibitors (SGLT2is) in patients with HF became apparent, and they were, therefore, not mandated in the protocol.

However, the beneficial effects of the initiation of the SGLT2i empagliflozin during hospital admission for acute HF on clinical outcomes were provided by the EMPULSE trial (Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized).[9] A total of 530 patients were randomized in-hospital, when clinically stable, to empagliflozin 10 mg/day or placebo and were treated for up to 90 days. The primary endpoint was a hierarchical composite of mortality, rehospitalizations due to HF or quality of life. Patients treated with empagliflozin had a 36% higher likelihood of obtaining clinical benefits, independent of left ventricular ejection

fraction and diabetes status and whether they were de novo patients or those with decompensated chronic HF. In addition, post hoc analyses showed that the use of empagliflozin resulted in a marked reduction of signs and symptoms of congestion.[10]

Taken together, these studies in patients who were hospitalized for acute HF taught us that enhanced decongestion with thiazides or acetazolamide did not provide additional benefits, whereas treatment with the "foundational 4" (ACEis/ARBs/ARNIs, beta-blockers, MRAs, and SGLT2is) improves clinical outcomes in combination with improvement in the signs and symptoms of congestion. Based on these observations, the task force of the 2023 focused update provided a class I (level of evidence B) recommendation for patients hospitalized due to HF to receive rapidly uptitrated evidence-based treatment before discharge and during frequent and careful follow-up visits during the first 6 weeks following a hospitalization due to HF so as to reduce the risk of rehospitalization or death due to HF. Even though the data from STRONG-HF were not yet available, the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure provides a class I (level of evidence B) recommendation for the initiation or uptitration of guideline-directed medical therapies during hospitalization after clinical stability is achieved.[4]

Upgrade of the Recommendations for the Management of Iron Deficiency in Patients With Heart Failure

Intravenous iron supplementation in symptomatic patients with HFrEF and HFmrEF and iron deficiency, *to alleviate HF symptoms and improve quality of life,* has been upgraded from a class II (level of evidence A) to a class I (level of evidence A) recommendation. In addition, the recommendation to provide intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose in symptomatic patients with HFrEF and HFmrEF and iron deficiency *to reduce the risk of a heart failure hospitalization* has been upgraded from class IIa (level of evidence B) to class IIa (level of evidence A). These upgrades are related to the recent publications of the IRONMAN (Effectiveness of Intravenous Iron Treatment Versus Standard Care in Patients With Heart Failure and Iron Deficiency) trial and the AFFIRM-AHF (Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency) trial.[11,12] The IRONMAN trial showed a nonsignificant reduction of the composite of total (first and recurrent) HF hospitalizations and cardiovascular death in 1137 patients with mainly chronic HFrEF (left ventricular ejection fraction $< 45\%$) who were treated for a mean of 2.7 years with IV ferric derisomaltose.[11] The results of AFFIRM-AHF were already available at the time of the 2021 ESC Guidelines.[12] In addition, it was shown that a prespecified COVID-19 analysis, censoring follow-up in September 2020, resulted in a borderline significant reduction in the risk of the primary endpoint with ferric derisomaltose. Yet, immediately after the presentation and publication of the 2023 focused update of the ESC guidelines, the results of HEART-FID (Ferric Carboxymaltose in Heart Failure With Iron Deficiency) trial were presented and published.[13] This large randomized, placebo-controlled trial randomized 3065 patients with heart failure with reduced ejection fraction (HFrEF) and iron deficiency to ferric carboxymaltose or placebo. The composite primary hierarchical outcome of death or hospitalization due to HF at 1 year or change in results of the 6-minute walk distance at 6 months narrowly missed statistical significance. Fourteen years after the publication of FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) in 2009, a large number of randomized controlled trials of IV iron in patients with HF (mainly HFrEF) have been published. These trials show a consistent modest effect on hard clinical endpoints but a clear effect on symptoms, exercise capacity and quality of life. These findings are well reflected by the current recommendations in the 2023 focused update of the ESC HF guidelines. However, there is a remarkable difference in the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. That provides a class 2a (level of evidence B) for using IV iron in patients with HFrEF to improve functional status and quality of life, and it provides no recommendation for IV iron to improve the risk of cardiovascular mortality or hospitalization due to HF.[4]

SGLT2-inhibitors and Finerenone Receive a IA Recommendations for the Prevention of Heart Failure

Somewhat unexpectedly, this guideline update for the diagnosis and treatment of acute and chronic HF also provides class I (level of evidence A) recommendations for patients without HF. The recommendation is related to the prevention of HF in patients with type 2 diabetes and chronic kidney disease. These patients have an increased risk of developing HF. Specific recommendations are provided for the use of SGLT2is (empagliflozin and dapagliflozin) to prevent HF in patients with chronic kidney disease. This is based on 2 large outcome trials, DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) and EMPA-kidney (Study of Heart and Kidney Protection with Empagliflozin), both showing a reduction in kidney failure and cardiovascular death.[14,15] The

prevention of hospitalizations due to HF was only part of the secondary endpoints, whereas in EMPA-kidney, the risk of cardiovascular death or hospitalization due to HF was not even significantly reduced. The class I (level of evidence A) recommendation to treat patients with type 2 diabetes mellitus and chronic kidney disease with finerenone to reduce the risk of hospitalization due to HF is based on 2 large outcome trials: FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) and FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease).[16,17] FIDELIO-DKD showed a significant reduction in the development of kidney failure and showed no significant reduction in the risk of hospitalizations due to HF. FIGARO enrolled 7436 patients with chronic kidney disease and type 2 diabetes mellitus and showed that after 3.4 years of treatment, finerenone reduced the rate of the primary outcome, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization due to HF. Finerenone significantly reduced the risk of hospitalization due to HF by 29%. None of these trials were designed primarily to study the prevention of incident HF, so one might question the validity of their class I (level of evidence A) recommendations. The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure provides much broader guidance to prevent HF in so-called stage A and B HF, which are stages before symptomatic HF develops.[4] The recommendations of the 2022 AHA/ACC/HFSA Guideline includes the use of SGLT2is and also the treatment of hypertension and cardiovascular disease.

Conclusions

Overall, the task force for the diagnosis and treatment of acute and chronic HF of the ESC provides balanced and well-validated novel recommendations for the treatment of HF, based on novel evidence that has appeared since the presentation of the 2021 ESC HF guidelines.[1,18] Most important, SGLT2is now have a class IA recommendation for the treatment of patients with HFmrEF and HFpEF. After so many years, we finally have an evidence-based treatment for our increasing number of patients with HFmrEF and HFpEF. Second, we have learned a lot about the treatment of acute HF. The addition of hydrochlorothiazide and acetazolamide to standard loop diuretics improves decongestion, but this was not accompanied by a reduction in symptoms and rehospitalizations due to HF. At the same time, there is increasing evidence that initiation and uptitration of guideline-directed chronic HF therapies during a hospitalization for acute HF improves clinical outcomes. Third, the evidence for a beneficial effect of IV iron in patients with HFrEF to improve symptoms and exercise capacity has become stronger, and additional studies have confirmed a potential modest beneficial effect on reducing the risk of hospitalizations due to HF. Finally, appropriate treatment of patients at high risk of HF might reduce the development of HF. HF remains a syndrome that is associated with both disabling symptoms and high morbidity and mortality rates. However, if we apply these recommendations sensibly in clinical practice, we can substantially lower the worldwide burden of HF.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al., ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2023;44:3627–39. https://doi.org/10.1093/eurheartj/ehad195.
2. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089–98. https://doi.org/10.1056/NEJMoa2206286.
3. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–61. https://doi.org/10.1056/NEJMoa2107038.
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Card Fail 202;28:810−30.
5. Trullàs JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Marteles M, Conde-Martel A, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. Eur Heart J 2023;44:411–21. https://doi.org/10.1093/eurheartj/ehac689.
6. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med 2022;387:1185–95. https://doi.org/10.1056/NEJMoa2203094.
7. Emmens JE, Ter Maaten JM, Matsue Y, Figarska SM, Sama IE, Cotter G, et al. Worsening renal function in acute heart failure in the context of diuretic response. Eur J Heart Fail 2022;24:365–74.
8. 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;400:1938–52. https://doi.org/10.1016/S0140-6736(22)02076-1.
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;28:568–74. https://doi.org/10.1038/s41591-021-01659-1.
10. Biegus J, Voors AA, Collins SP, Kosiborod MN, Teerlink JR, Angermann CE, et al. Impact of empagliflozin on

decongestion in acute heart failure: the EMPULSE trial. Eur Heart J 2023;44:41–50.
11. Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, et al. 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;400:2199–209. https://doi.org/10.1016/S0140-6736(22)02083-9.
12. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet 2020;396:1895–904. https://doi.org/10.1016/S0140-6736(20)32339-4.
13. Mentz RJ, Garg J, Rockhold FW, Butler J, De Pasquale CG, Ezekowitz JA, et al., HEART-FID Investigators. Ferric carboxymaltose in heart failure with iron deficiency. N Engl J Med 2023;389:975–86. https://doi.org/10.1056/NEJMoa2304968.
14. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436–46. https://doi.org/10.1056/NEJMoa2024816.
15. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388:117–27. https://doi.org/10.1056/NEJMoa2204233.
16. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219–29. https://doi.org/10.1056/NEJMoa2025845.
17. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 2021;385:2252–63. https://doi.org/10.1056/NEJMoa2110956.
18. 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;42:3599–726. https://doi.org/10.1093/eurheartj/ehab368.