What is in the 2023 Focused Update of the 2021 ESC HF Guidelines?

Ovidiu Chioncel

Emergency Institute for Cardiovascular Diseases C.C.Iliescu, Bucharest

University of Medicine Carol Davila, Bucharest, Romania

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

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

Authors/Task Force Members: Theresa A. McDonagh* (Chairperson) (United Kingdom), Marco Metra * (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Čelutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad195

ESC GUIDELINES

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Methodology of 2023 Focus Updated Guidelines

- All the new recommendations are additive to the recommendations of the 2021 ESC HF Guidelines
- New evidence was considered until *31 March 2023.*
- Only results that would lead to new or *changed class I/IIa recommendations* were selected for inclusion in Recommendation Tables.
- 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. Of course, that does not mean each component is reduced individually.
- 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*.

New evidence

16 RCTs+8 Meta+11 EORP/HFA manuscripts+16 HFA position statements

European Journal of Heart Failure (2016)
doi:10.1002/ejhf.592

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

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16 New RCTs

- **ADVOR** (Acetazolamide in Decompensated Heart Failure with Volume Overload),
- **CLOROTIC** (Combination of Loop Diuretics with Hydrochlorothiazide in Acute Heart Failure),
- **COACH** (Comparison of Outcomes and Access to Care for Heart Failure),
- **DAPA-CKD** (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease),
- **DELIVER** (Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure),
- **EMPA-KIDNEY** (EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease),
- **EMPEROR-Preserved** (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction),
- **EMPULSE** (Empagliflozin in Patients Hospitalized with Acute Heart Failure Who Have Been Stabilized),
- **FIDELIO-DKD** (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease),
- **FIGARO-DKD** (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease),
- **IRONMAN** (Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency),
- **PIVOTAL** (Proactive IV Iron Therapy in Haemodialysis Patients),
- **REVIVED-BCIS2** (Revascularization for Ischemic Ventricular Dysfunction),
- **STRONG-HF** (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies),
- **TRANSFORM-HF** (Torsemide Comparison with Furosemide for Management of Heart Failure),
- **TRILUMINATE** Pivotal (Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System).

Sections with updated recommendations

- **Chronic HF: HFmrEF and HFpEF**
  - **DELIVER** (Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure)
  - **EMPEROR-Preserved** (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction),
  - **TRANSFORM-HF** (Torsemide Comparison with Furosemide for Management of Heart Failure),
- **Acute HF**
  - **ADVOR** (Acetazolamide in Decompensated Heart Failure with Volume Overload),
  - **CLOROTIC** (Combination of Loop Diuretics with Hydrochlorothiazide in Acute Heart Failure),
  - **COACH** (Comparison of Outcomes and Access to Care for Heart Failure)
  - **EMPULSE** (Empagliflozin in Patients Hospitalized with Acute Heart Failure Who Have Been Stabilized)
  - **STRONG-HF** (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies),
- **Comorbidities and prevention of HF**
  - **DAPA-CKD** (Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease),
  - **EMPA-KIDNEY** (EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease)
  - **FIDELIO-DKD** (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease),
  - **FIGARO-DKD** (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease),
  - **IRONMAN** (Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency),
  - **PIVOTAL** (Proactive IV Iron Therapy in Haemodialysis Patients),
  - **REVIVED-BCIS2** (Revascularization for Ischemic Ventricular Dysfunction),
  - **TRILUMINATE** Pivotal (Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System).

3 RCTs with SLGT2 inh in HFrEF

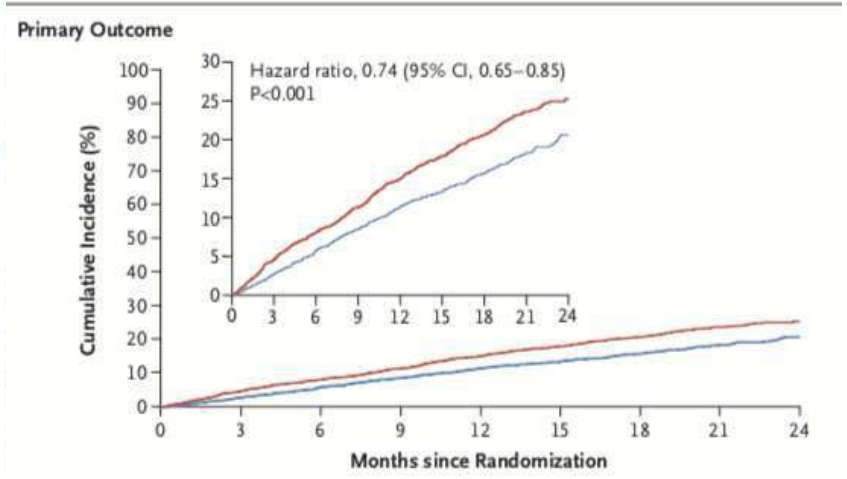
DAPA-HF

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

ABSTRACT



CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

EMPEROR Reduced

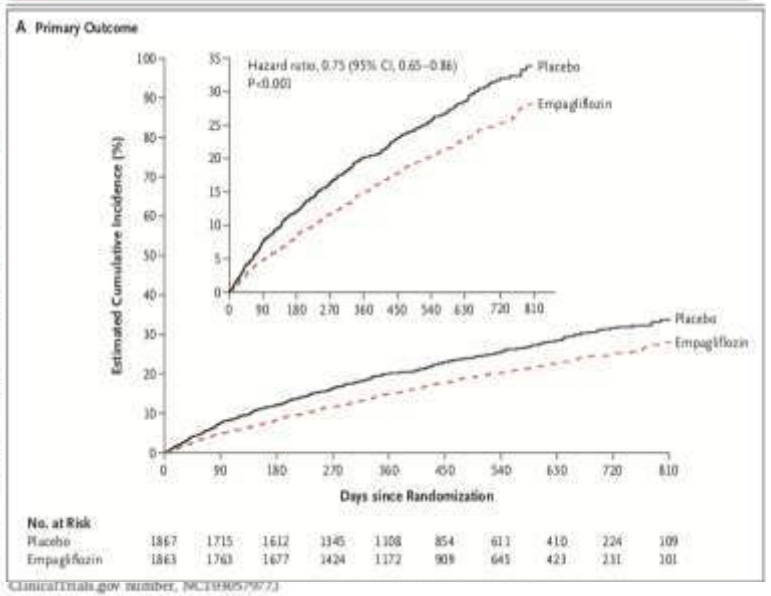
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez-Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

ABSTRACT



ClinicalTrials.gov number, NCT03057977.

SOLOIST-WHF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

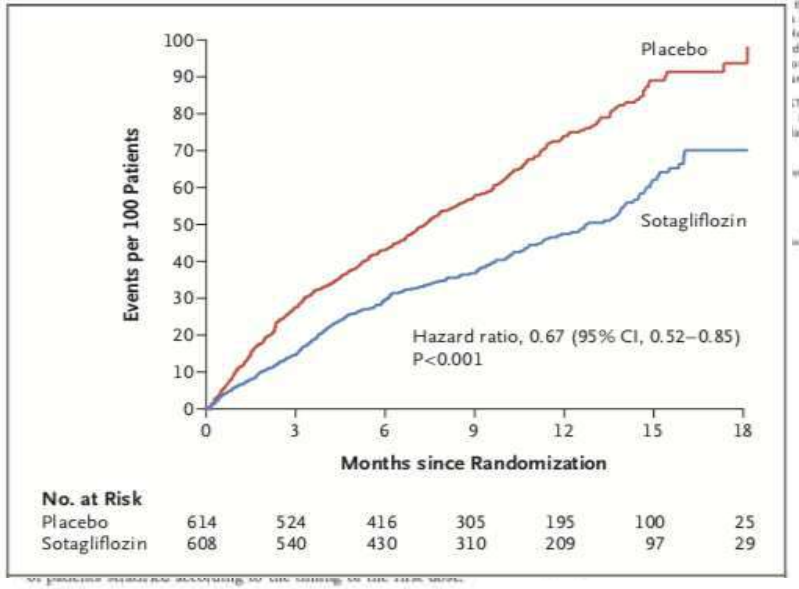
Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

D.L. Bhatt, M. Szarek, P.G. Steg, C.P. Cannon, L.A. Leiter, D.K. McGuire, J.B. Lewis, M.C. Riddle, A.A. Voors, M. Metra, L.H. Lund, M. Komajda, J.M. Testani, C.S. Wilcox, P. Ponikowski, R.D. Lopes, S. Verma, P. Lapuerta, and B. Pitt, for the SOLOIST-WHF Trial Investigators*

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitaliza-



CONCLUSIONS

In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo. (Funded by Sanofi and Lexicon Pharmaceuticals; SOLOIST-WHF ClinicalTrials.gov number, NCT03521934.)

EMPA-Preserved

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner-La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

METHODS

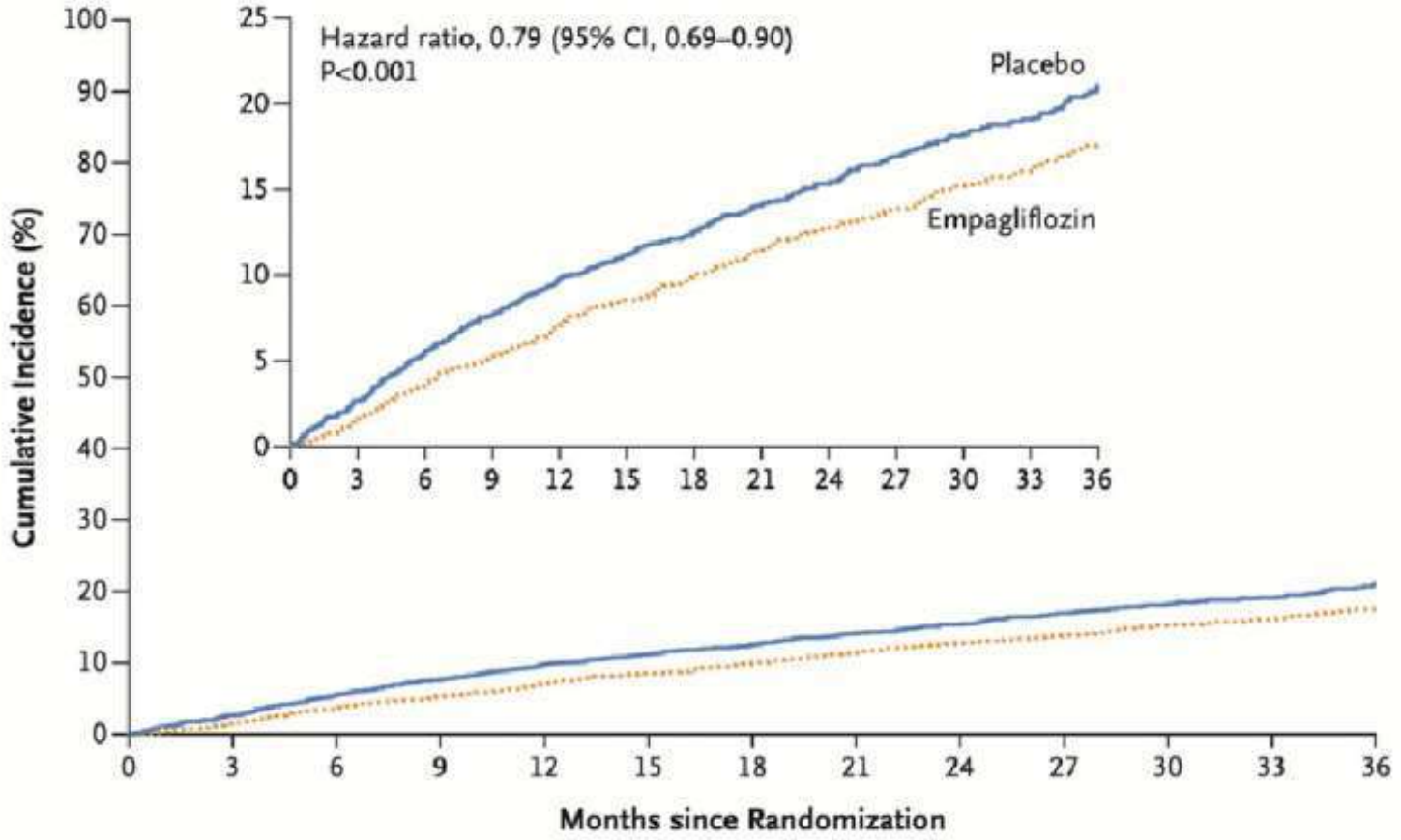
In this double-blind trial, we randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS

Over a median of 26.2 months, a primary outcome event occurred in 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). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

CONCLUSIONS

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).



No. at Risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

A pooled analysis on both the EMPEROR-Reduced and EMPEROR-Preserved trials

(9718 patients; 4860 empagliflozin and 4858 placebo)

ESC European Society of Cardiology

European Heart Journal (2021) 00, 1–11 https://doi.org/10.1093/eurheartj/ehab798

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction

Javed Butler [1*†], Milton Packer[2*†], Gerasimos Filippatos [3], Joao Pedro Ferreira [4], Cordula Zeller [5], Janet Schnee [6], Martina Brueckmann [7], Stuart J. Pocock[8], Faiez Zannad[4], and Stefan D. Anker[9]

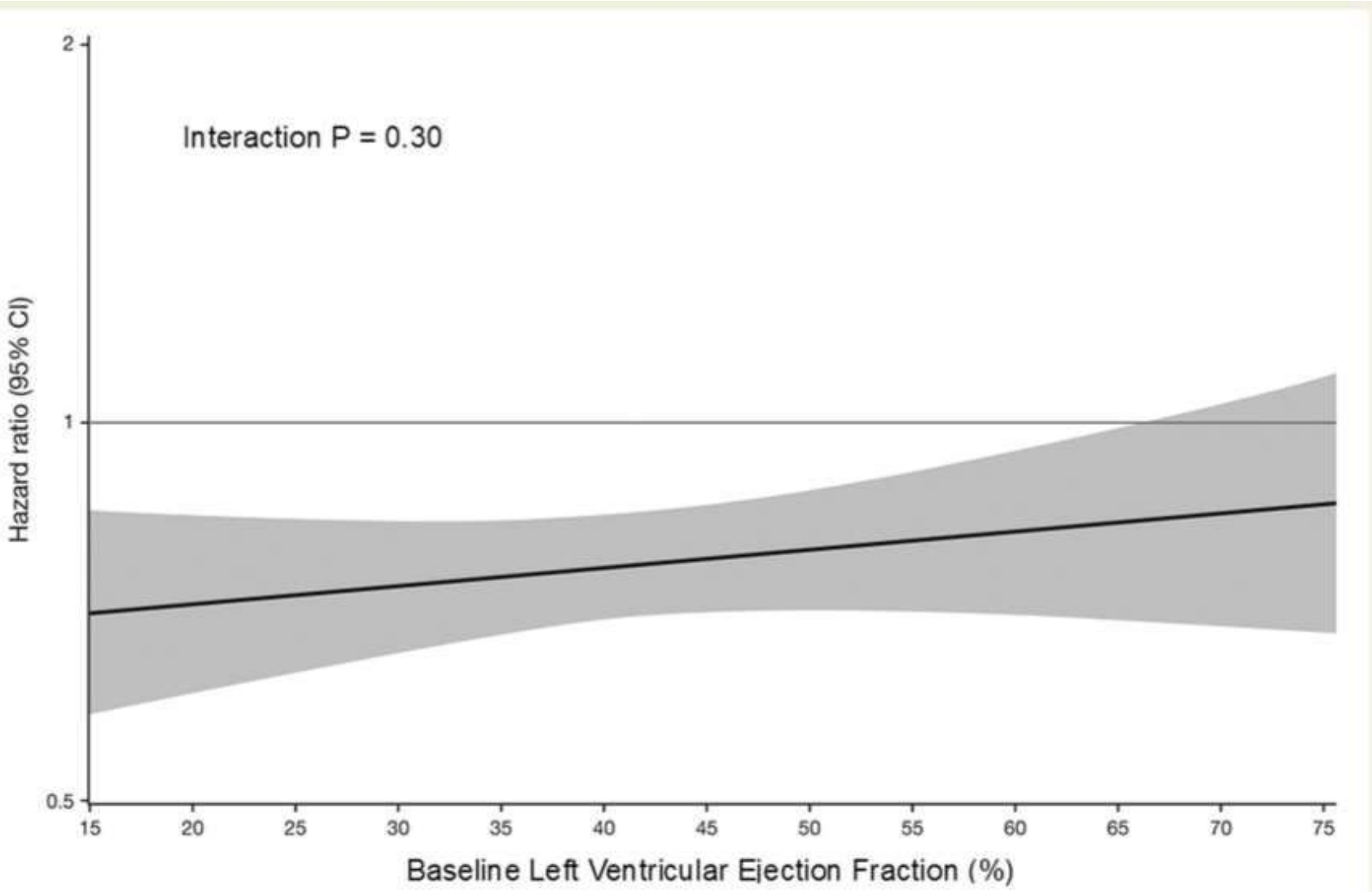
[1]Department of Medicine, University of Mississippi School of Medicine, Jackson, MS, USA; [2]Baylor Heart and Vascular Institute, 621 North Hall Street, Dallas, TX 75226, USA; [3]National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Chaidari, Greece; [4]Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France; [5]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [6]Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA; [7]Boehringer Ingelheim International GmbH, Ingelheim, Germany and Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; [8]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK; and [9]Department of Cardiology (CVK), Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité – Universitätsmedizin Berlin, Berlin, Germany

Received 18 August 2021; revised 22 September 2021; editorial decision 8 November 2021; accepted 23 November 2021

Aims No therapy has shown to reduce the risk of hospitalization for heart failure across the entire range of ejection fractions seen in clinical practice. We assessed the influence of ejection fraction on the effect of the sodium–glucose cotransporter 2 inhibitor empagliflozin on heart failure outcomes.

Methods and results A pooled analysis was performed on both the EMPEROR-Reduced and EMPEROR-Preserved trials (9718 patients; 4860 empagliflozin and 4858 placebo), and patients were grouped based on ejection fraction: <25% (n = 999), 25–34% (n = 2230), 35–44% (n = 1272), 45–54% (n = 2260), 55–64% (n = 2092), and ≥65% (n = 865). Outcomes assessed included (i) time to first hospitalization for heart failure or cardiovascular mortality, (ii) time to first heart failure hospitalization, (iii) total (first and recurrent) hospitalizations for heart failure, and (iv) health status assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ). The risk of cardiovascular death and hospitalization for heart failure declined progressively as ejection fraction increased from <25% to ≥65%. Empagliflozin reduced the risk of cardiovascular death or heart failure hospitalization, mainly by reducing heart failure hospitalizations. Empagliflozin reduced the risk of heart failure hospitalization by ≈30% in all ejection fraction subgroups, with an attenuated effect in patients with an ejection fraction ≥65%. Hazard ratios and 95% confidence intervals were: ejection fraction <25%: 0.73 (0.55–0.96); ejection fraction 25–34%: 0.63 (0.50–0.78); ejection fraction 35–44%: 0.72 (0.52–0.98); ejection fraction 45–54%: 0.66 (0.50–0.86); ejection fraction 55–64%: 0.70 (0.53–0.92); and ejection fraction ≥65%: 1.05 (0.70–1.58). Other heart failure outcomes and measures, including KCCQ, showed a similar response pattern. Sex did not influence the responses to empagliflozin.

Conclusion The magnitude of the effect of empagliflozin on heart failure outcomes was clinically meaningful and similar in patients with ejection fractions <25% to <65%, but was attenuated in patients with an ejection fraction ≥65%.



DELIVER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, B. Claggett, R.A. de Boer, D. DeMets, A.F. Hernandez, S.E. Inzucchi, M.N. Kosiborod, C.S.P. Lam, F. Martinez, S.J. Shah, A.S. Desai, P.S. Jhund, J. Belohlavek, C.-E. Chiang, C.J.W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J.C. Fang, M.A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J.W. Cabrera Honorio, S.P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J.F.K. Saraiva, S.N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V.N. Pham, U. Wilderäng, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, and A.M. Langkilde, for the DELIVER Trial Committees and Investigators*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Solomon can be contacted at csolomon@bwh.harvard.edu or at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

*A complete list of the DELIVER trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 27, 2022, at NEJM.org.

DOI: 10.1056/NEJMoa2206286

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with chronic heart failure and a left ventricular ejection fraction of 40% or less. Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

METHODS

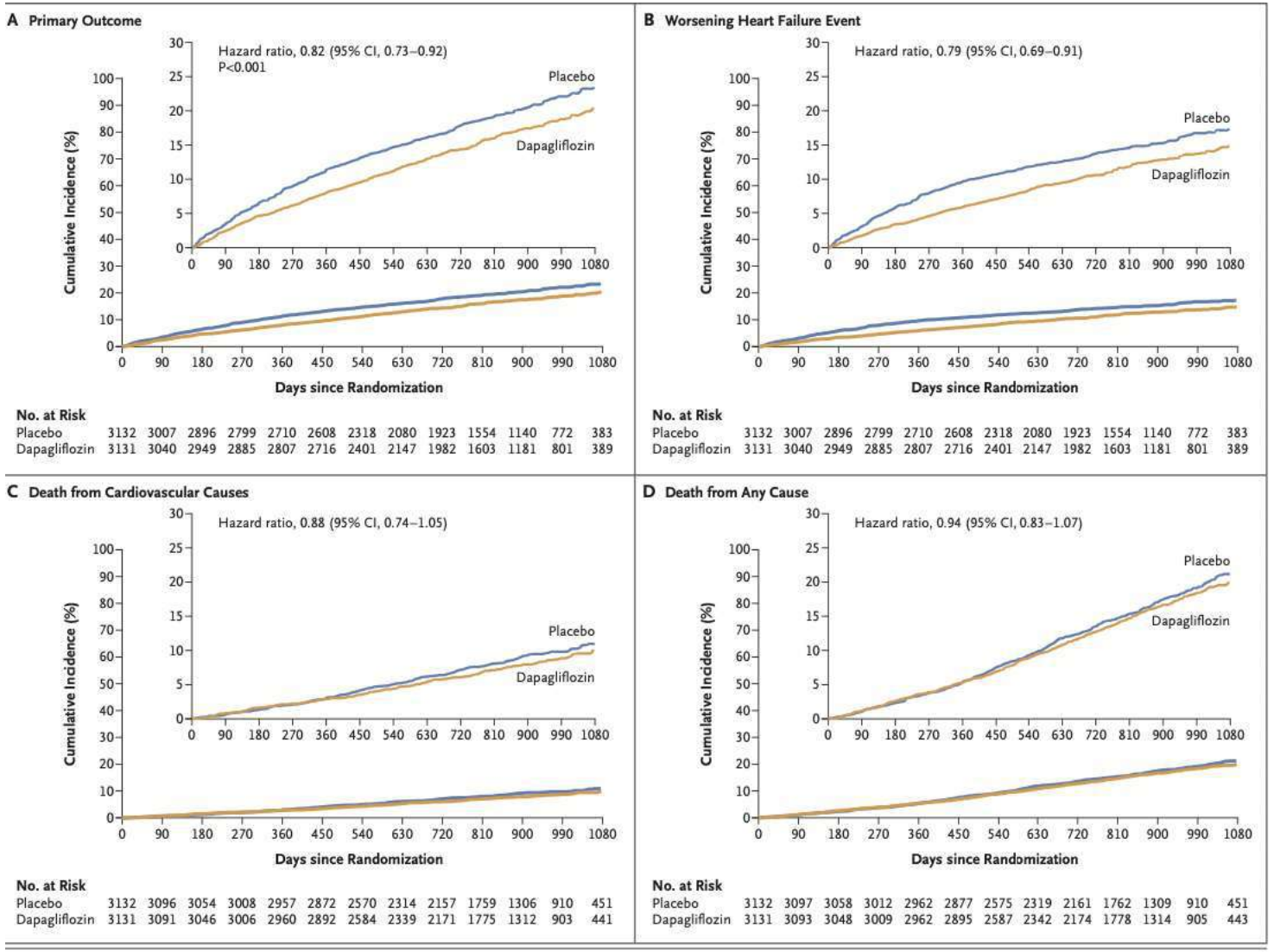
We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death, as assessed in a time-to-event analysis.

RESULTS

Over a median of 2.3 years, the 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 (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P<0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, NCT03619213.)



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2022

Dapagliflozin in Patients Recently Hospitalized With Heart Failure and Mildly Reduced or Preserved Ejection Fraction

Jonathan W. Cunningham, MD, MPH,[a] Muthiah Vaduganathan, MD, MPH,[a] Brian L. Claggett, PhD,[a] Ian J. Kulac, MS,[a] Akshay S. Desai, MD, MPH,[a] Pardeep S. Jhund, MBChB, PhD,[b] Rudolf A. de Boer, MD,[c] David DeMets, PhD,[d] Adrian F. Hernandez, MD,[e] Silvio E. Inzucchi, MD,[f] Mikhail N. Kosiborod, MD,[g] Carolyn S.P. Lam,[h] Felipe Martinez, MD,[i] Sanjiv J. Shah, MD,[j] Martina M. McGrath, MBBCh,[a] Eileen O'Meara, MD,[k] Ulrica Wilderäng, PhD,[l] Daniel Lindholm, MD, PhD,[l] Magnus Petersson, MD,[l] Anna Maria Langkilde, MD, PhD,[l] John J.V. McMurray, MD,[b] Scott D. Solomon, MD[a]

ABSTRACT

BACKGROUND Patients recently hospitalized for heart failure (HF) are at high risk for rehospitalization and death.

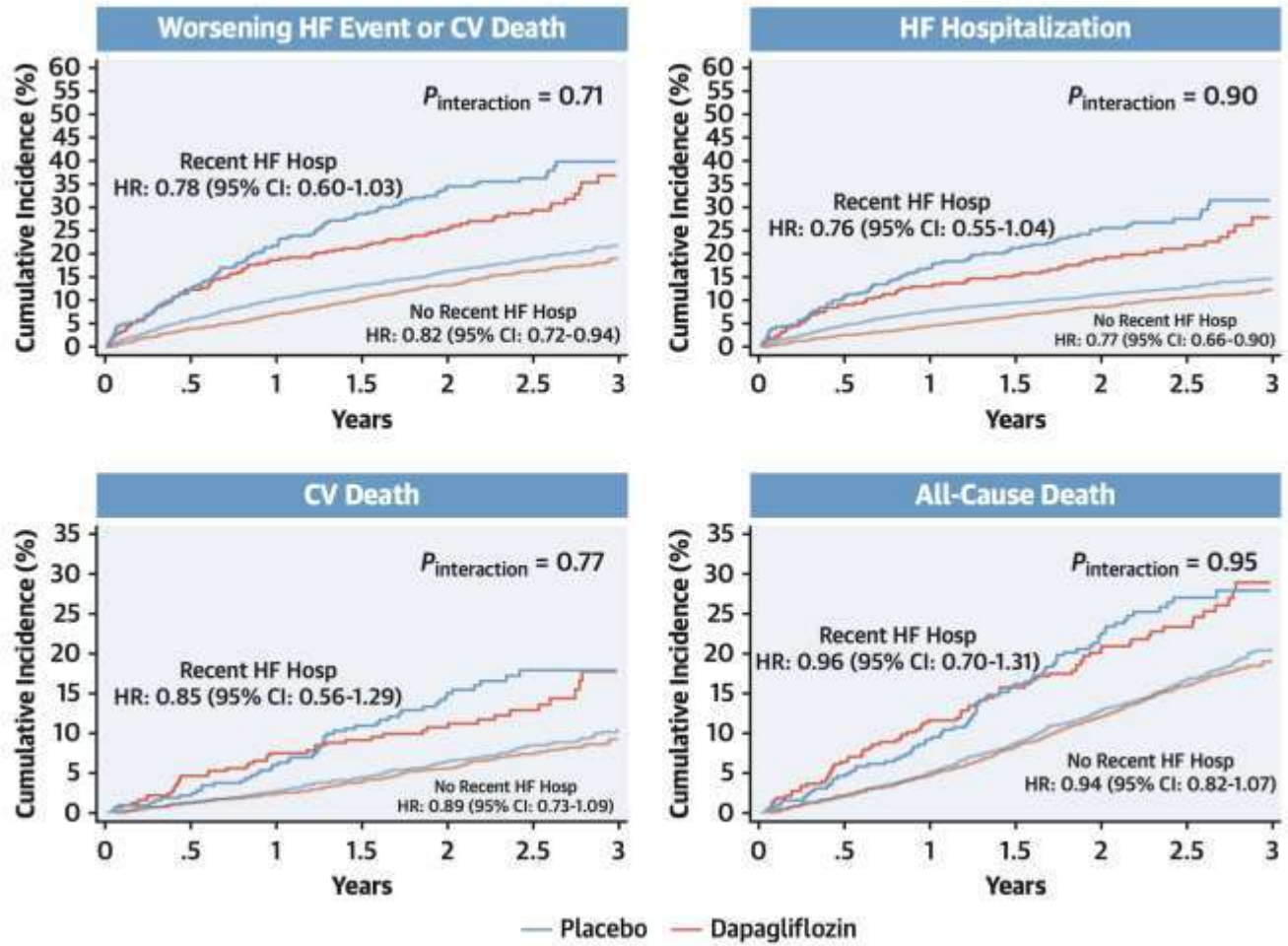
OBJECTIVES The purpose of this study was to investigate clinical outcomes and response to dapagliflozin in patients with HF with mildly reduced or preserved left ventricular ejection fraction (LVEF) who were enrolled during or following hospitalization.

METHODS The DELIVER (Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure) trial randomized patients with HF and LVEF >40% to dapagliflozin or placebo. DELIVER permitted randomization during or shortly after hospitalization for HF in clinically stable patients off intravenous HF therapies. This prespecified analysis investigated whether recent HF hospitalization modified risk of clinical events or response to dapagliflozin. The primary outcome was worsening HF event or cardiovascular death.

RESULTS Of 6,263 patients in DELIVER, 654 (10.4%) were randomized during HF hospitalization or within 30 days of discharge. Recent HF hospitalization was associated with greater risk of the primary outcome after multivariable adjustment (HR: 1.88; 95% CI: 1.60-2.21; $P < 0.001$). Dapagliflozin reduced the primary outcome by 22% in recently hospitalized patients (HR: 0.78; 95% CI: 0.60-1.03) and 18% in patients without recent hospitalization (HR: 0.82; 95% CI: 0.72-0.94; $P_{interaction} = 0.71$). Rates of adverse events, including volume depletion, diabetic ketoacidosis, or renal events, were similar with dapagliflozin and placebo in recently hospitalized patients.

CONCLUSIONS Dapagliflozin safely reduced risk of worsening HF or cardiovascular death similarly in patients with and without history of recent HF hospitalization. Starting dapagliflozin during or shortly after HF hospitalization in patients with mildly reduced or preserved LVEF appears safe and effective. (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213) (J Am Coll Cardiol 2022;■(■):■-■)

CENTRAL ILLUSTRATION Efficacy of Dapagliflozin in Patients With and Without Recent Hospitalization



SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials

Mukesh Vedagandham*, Kieran F Docherty*, Kevin J Claggett, Pardeep S Jhund, Rudolf A de Boer, Adrian F Hernandez, Silvio E Inzucchi, Mikhail N Kosiborod, Carolyn S P Lam, Felipe Martinez, Sanjay J Shah, Akshay S Desai, John J V McMurray†, Scott D Solomon†

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Background SGLT2 inhibitors are strongly recommended in guidelines to treat patients with heart failure with reduced ejection fraction, but their clinical benefits at higher ejection fractions are less well established. Two large-scale trials, DELIVER and EMPEROR-Preserved, in heart failure with mildly reduced or preserved ejection fraction have been done, providing power to examine therapeutic effects on cardiovascular mortality and in patient subgroups when combined with the earlier trials in reduced ejection fraction.

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Interpretation SGLT2 inhibitors reduced the risk of cardiovascular death and hospitalisations for heart failure in a broad range of patients with heart failure, supporting their role as a foundational therapy for heart failure, irrespective of ejection fraction or care setting.

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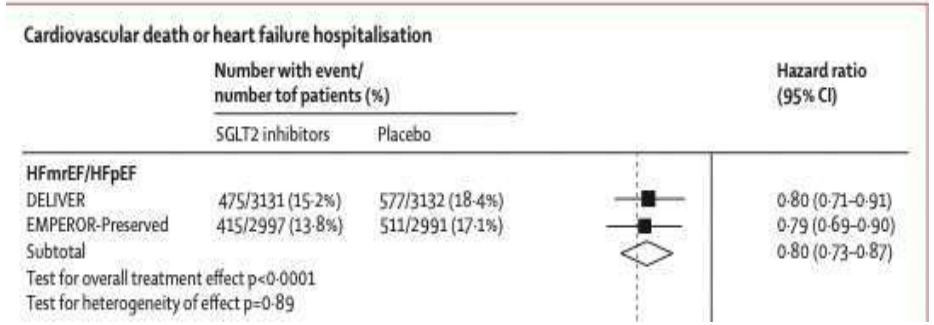
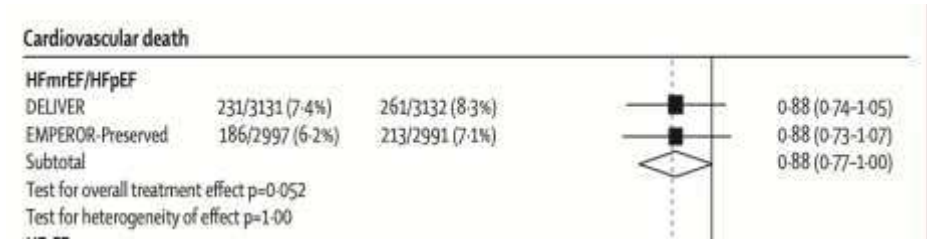
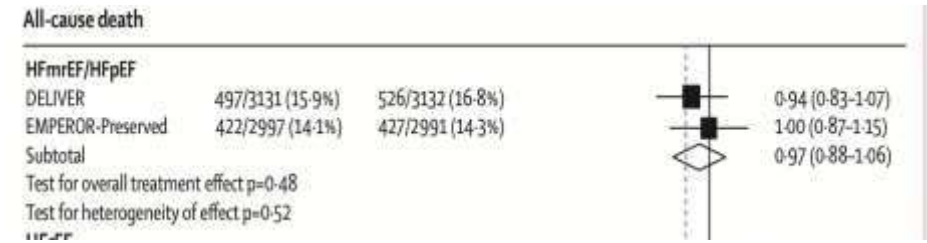
Published Online August 27, 2022 https://doi.org/10.1016/S0140-6736(22)01853-1

*Joint first authors
†Joint senior authors
Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (M Vedagandham MD, K J Claggett PhD, A S Desai MD, Prof S D Solomon MD); British Heart Foundation, University of Glasgow, Glasgow, UK (K F Docherty PhD, Prof P S Jhund PhD, Prof J J V McMurray MD); University of Groningen, Groningen, Netherlands (Prof R A de Boer MD); Duke University Medical Center, Durham, NC, USA (Prof A F Hernandez MD, Prof C S P Lam MBBS); Yale School of Medicine, New Haven, CT, USA (Prof S E Inzucchi MD); Saint Luke's Mid America Heart Institute, Kansas City and University of Missouri-Kansas City, MO, USA (Prof M N Kosiborod MD); National Heart Centre Singapore and Duke-National University of Singapore, Singapore (Prof C S P Lam); Universidad Nacional de Córdoba, Córdoba, Argentina (Prof F Martinez MD); Northwestern University Feinberg School of Medicine, Chicago, IL, USA (Prof S J Shah MD)
Correspondence to: Prof Scott D Solomon, Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
solomon@rics.bwh.harvard.edu







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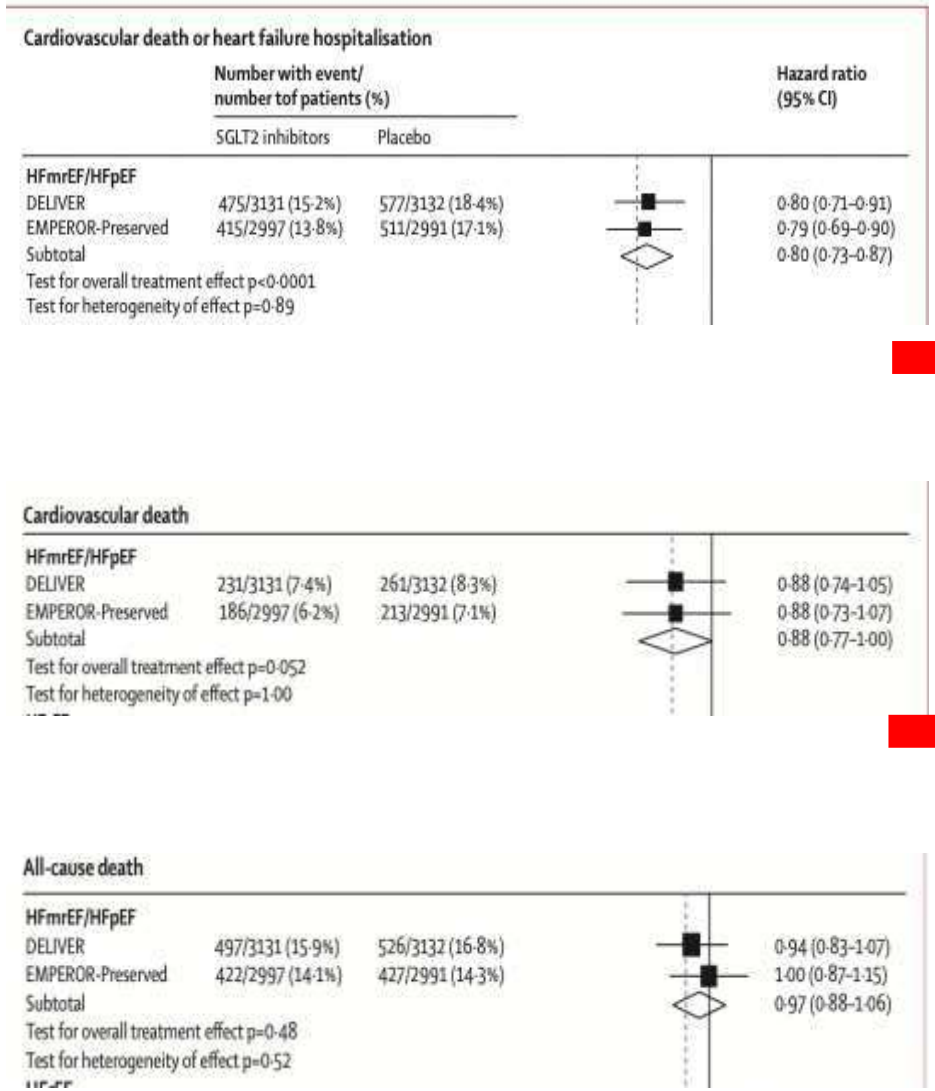

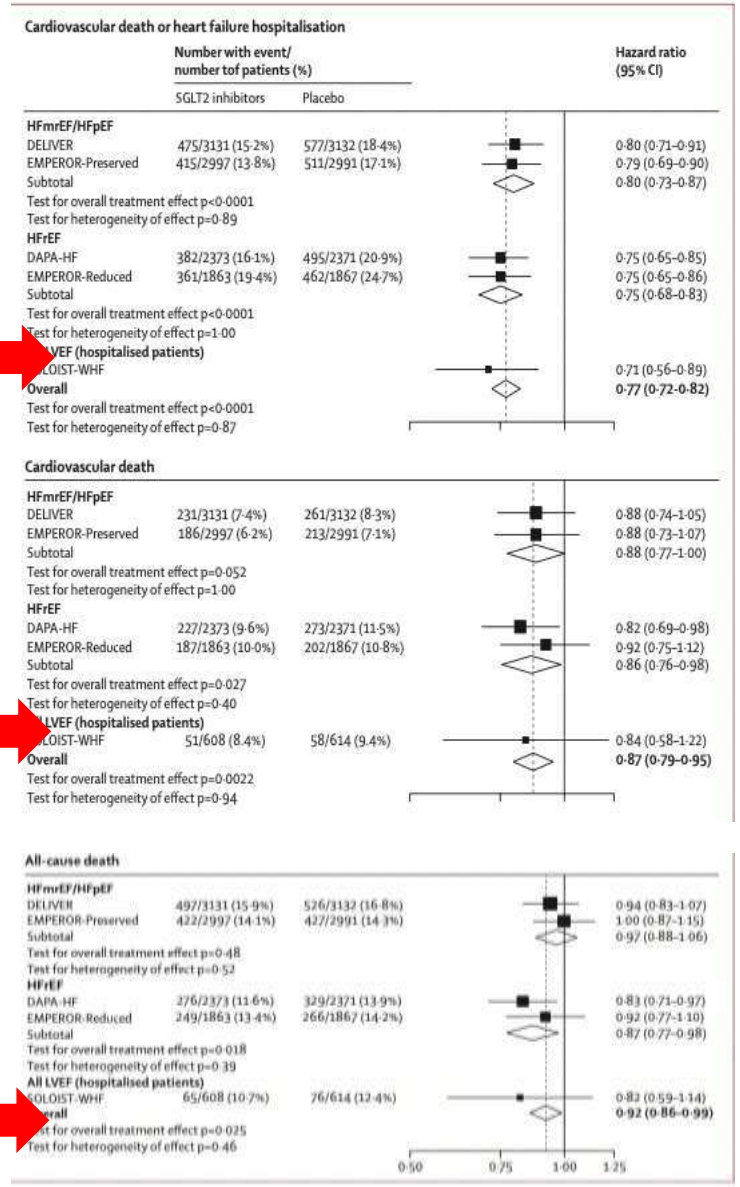

Significant benefit irrespective of covariates

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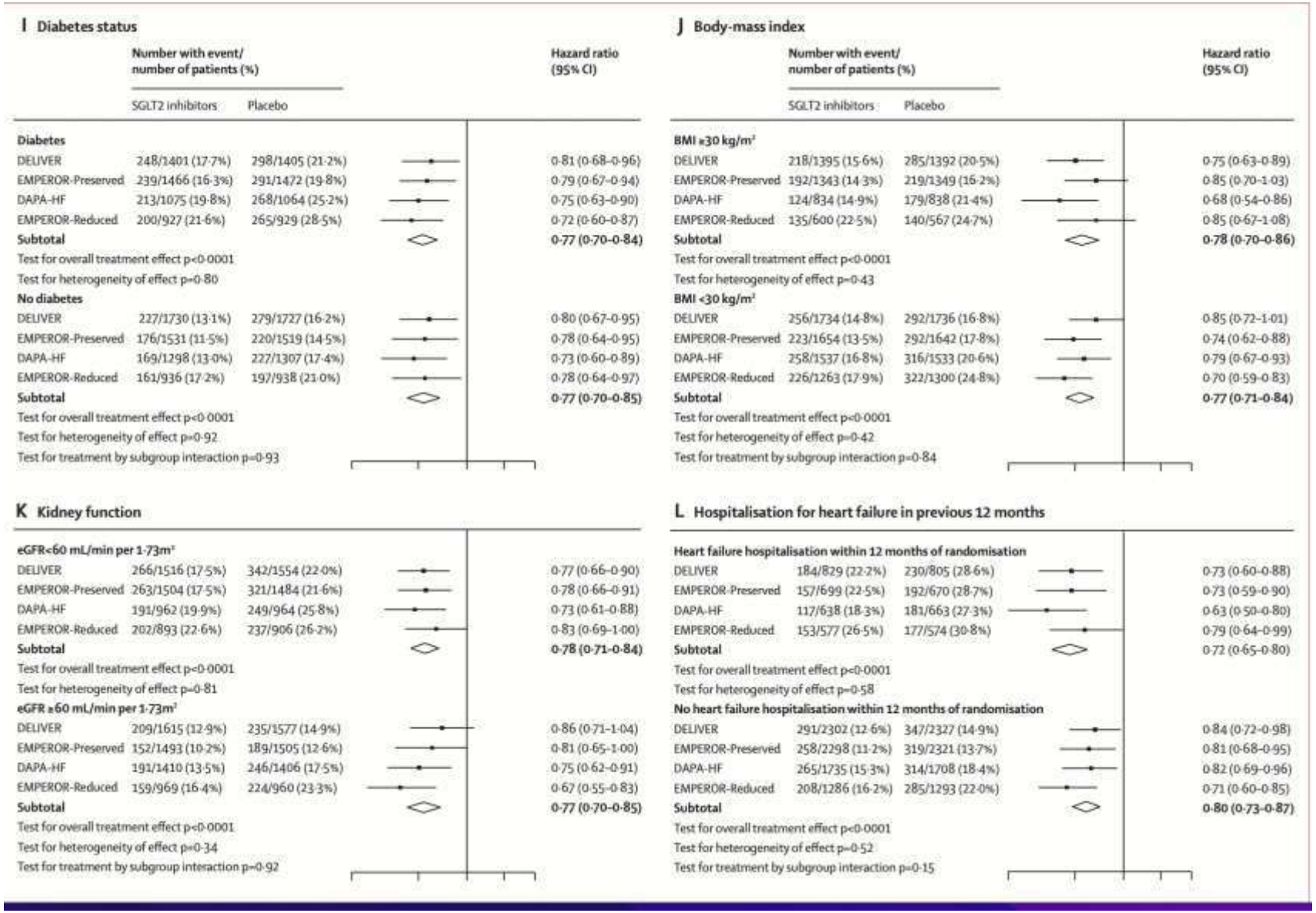

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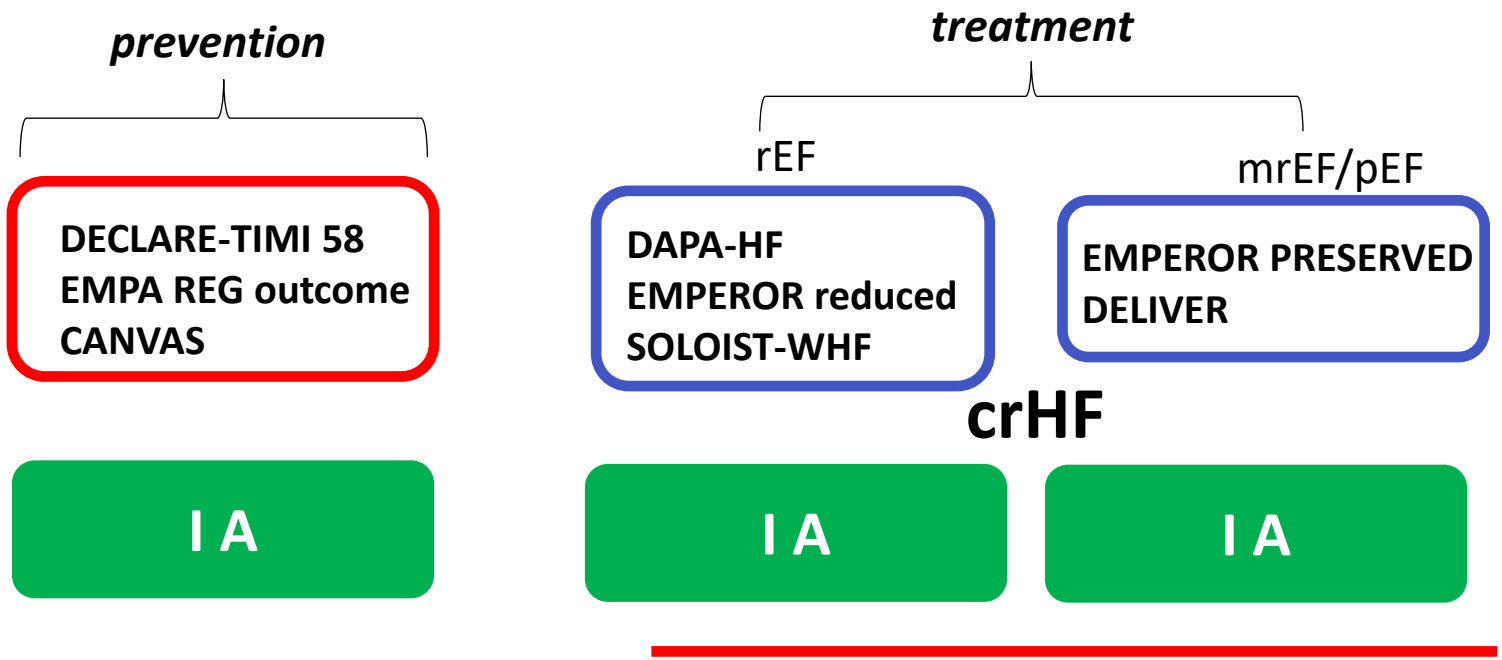
prevention
treatment
rEF
mrEF/pEF
DECLARE-TIMI 58
EMPA REG outcome
CANVAS
DAPA-HF
EMPEROR reduced
SOLOIST-WHF
EMPEROR PRESERVED
DELIVER
crHF
I A
I A
I A

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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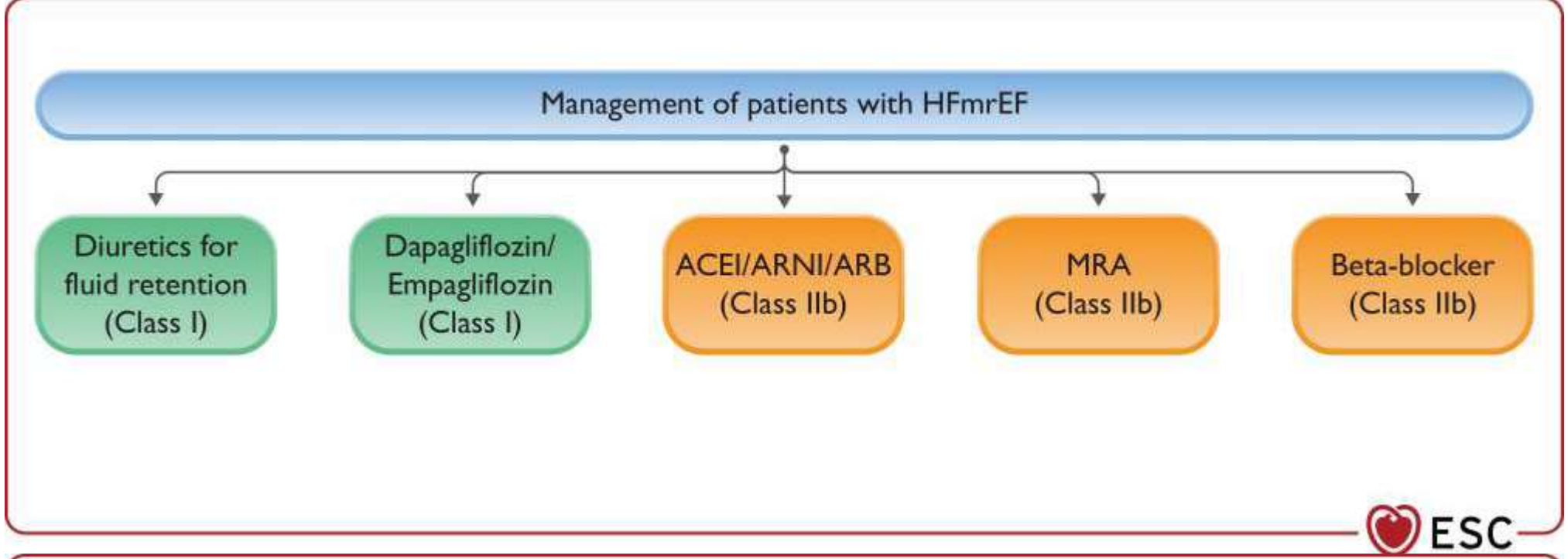
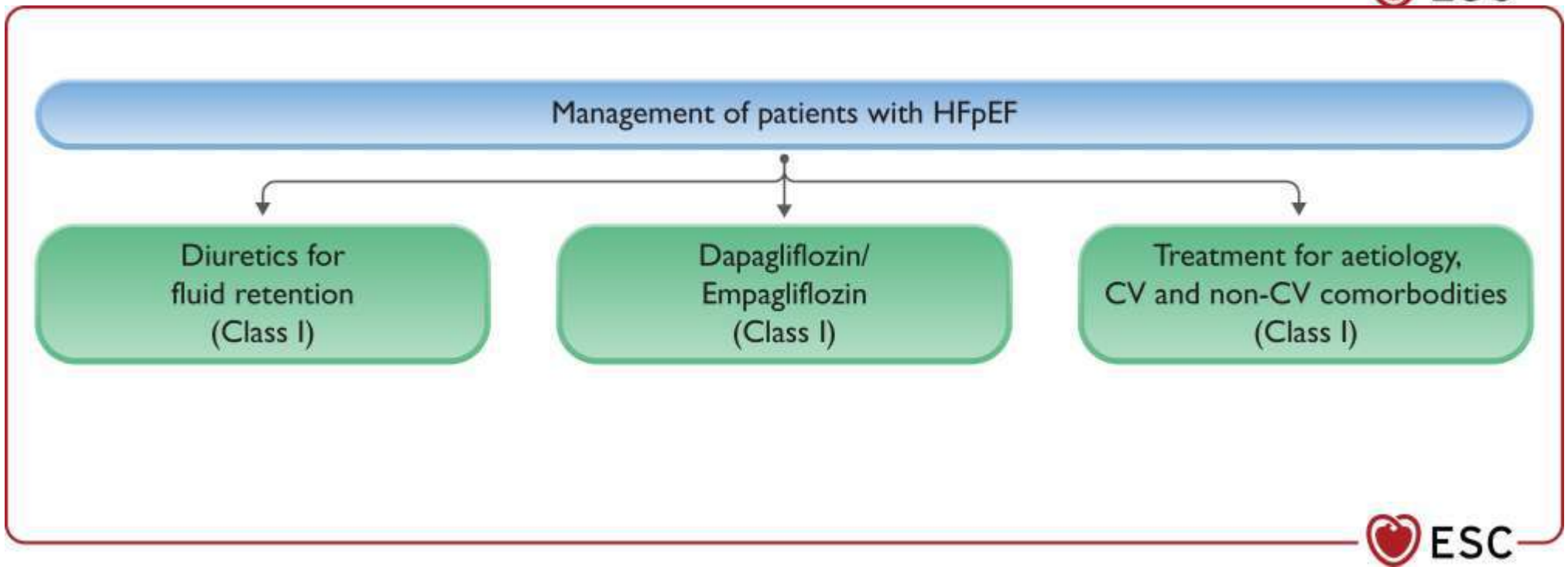

Management of patients with HFmrEF
Diuretics for fluid retention (Class I)
Dapagliflozin/ Empagliflozin (Class I)
ACEI/ARNI/ARB (Class IIb)
MRA (Class IIb)
Beta-blocker (Class IIb)
ESC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Diuretics for fluid retention (Class I)
Dapagliflozin/ Empagliflozin (Class I)
Treatment for aetiology, CV and non-CV comorbodities (Class I)
ESC

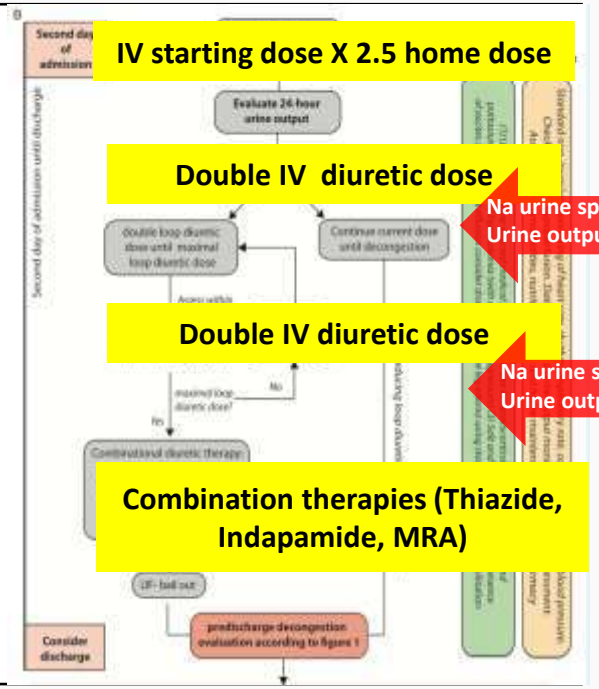
Acute Heart Failure

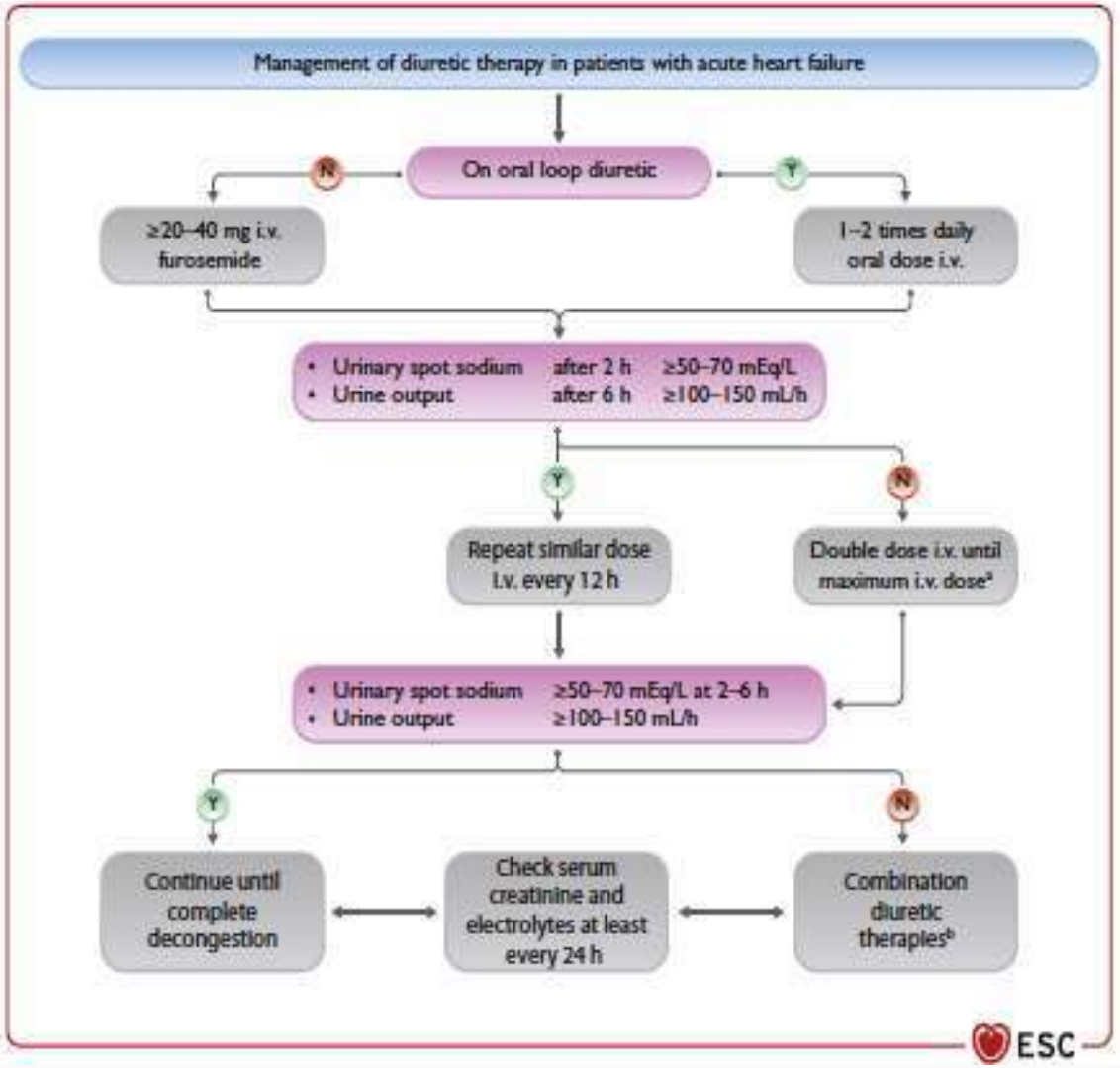
Diuretics in AHF: 2021 Guidelines

Diuretics		
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.[150]	I	C
Combination of a loop diuretic with thiazide-type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretic doses.[150]	IIa	B


ESC POSITION PAPER

The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology





A satisfactory diuretic response can be defined as a urine sodium content >50mEq/L at two-hours and/or a urine output >100mL/hour during the first 6 hours.

Sequential nephron blockade: CLOROTIC

ESC European Society of Cardiology
European Heart Journal (2023) 44, 411–421 https://doi.org/10.1093/eurheartj/ehac689
CLINICAL RESEARCH
Heart failure and cardiomyopathies

Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial

Joan Carles Trullàs[1,2]*, José Luis Morales-Rull[3], Jesús Casado[4], Margarita Carrera-Izquierdo[5], Marta Sánchez-Marteles[6], Alicia Conde-Martel[7], Melitón Francisco Dávila-Ramos[8], Pau Llácer[9], Prado Salamanca-Bautista[10], José Pérez-Silvestre[11], Miguel Ángel Plasín[12], José Manuel Cerqueiro[13], Paloma Gil[14], Francesc Formiga[15], Luis Manzano[16], and CLOROTIC trial investigators

See the editorial comment for this article 'Time to revisit combination loop and thiazide diuretic therapy for patients with acute heart failure', by R. Zakeri et al., https://doi.org/10.1093/eurheartj/ehac784.

Abstract

Aims To evaluate whether the addition of hydrochlorothiazide (HCTZ) to intravenous furosemide is a safe and effective strategy for improving diuretic response in acute heart failure (AHF).

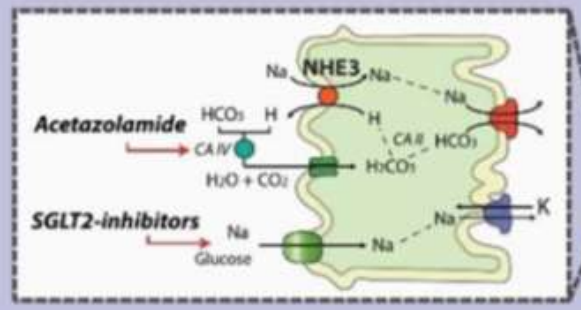
Methods and results A prospective, double-blind, placebo-controlled trial, including patients with AHF randomized to receive HCTZ or placebo in addition to an intravenous furosemide regimen. The coprimary endpoints were changes in body weight and patient-reported dyspnoea 72 h after randomization. Secondary outcomes included metrics of diuretic response and mortality/rehospitalizations at 30 and 90 days. Safety outcomes (changes in renal function and/or electrolytes) were also assessed. Two hundred and thirty patients (48% women, 83 years) were randomized. Patients assigned to HCTZ were more likely to lose weight at 72 h than those assigned to placebo [−2.3 vs. −1.5 kg; adjusted estimated difference (notionally 95% confidence interval) −1.14 (−1.84 to −0.42); $P = 0.002$], but there were no significant differences in patient-reported dyspnoea (area under the curve for visual analogue scale: 960 vs. 720; $P = 0.497$). These results were similar 96 h after randomization. Patients allocated to HCTZ showed greater 24 h diuresis (1775 vs. 1400 mL; $P = 0.05$) and weight loss for each 40 mg of furosemide (at 72 and at 96 h) ($P < 0.001$). Patients assigned to HCTZ more frequently presented impaired renal function (increase in creatinine >26.5 μmol/L or decrease in eGFR >50%; 46.5 vs. 17.2%; $P < 0.001$), but hypokalaemia and hypokalaemia were similar between groups. There were no differences in mortality or rehospitalizations.

Conclusion The addition of HCTZ to loop diuretic therapy improved diuretic response in patients with AHF.

Tubulo-glomerular feed-back in HF

HF induces a state of increased proximal renal sodium reabsorption, but loop diuretics, thiazides, MRA work distal at loop of Henle

Proximal nephron inhibition as add-on to loops



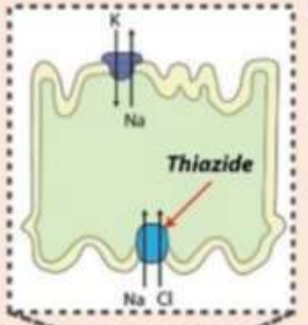
Arguments for proximal nephron inhibition

* Proximal nephron reabsorbs +/- 75% of filtered sodium inhibition here will boost loop diuretic efficacy.
* Presenting more Na and Cl to the macula densa might lead to decongestion whith less severe metabolic perpetuations

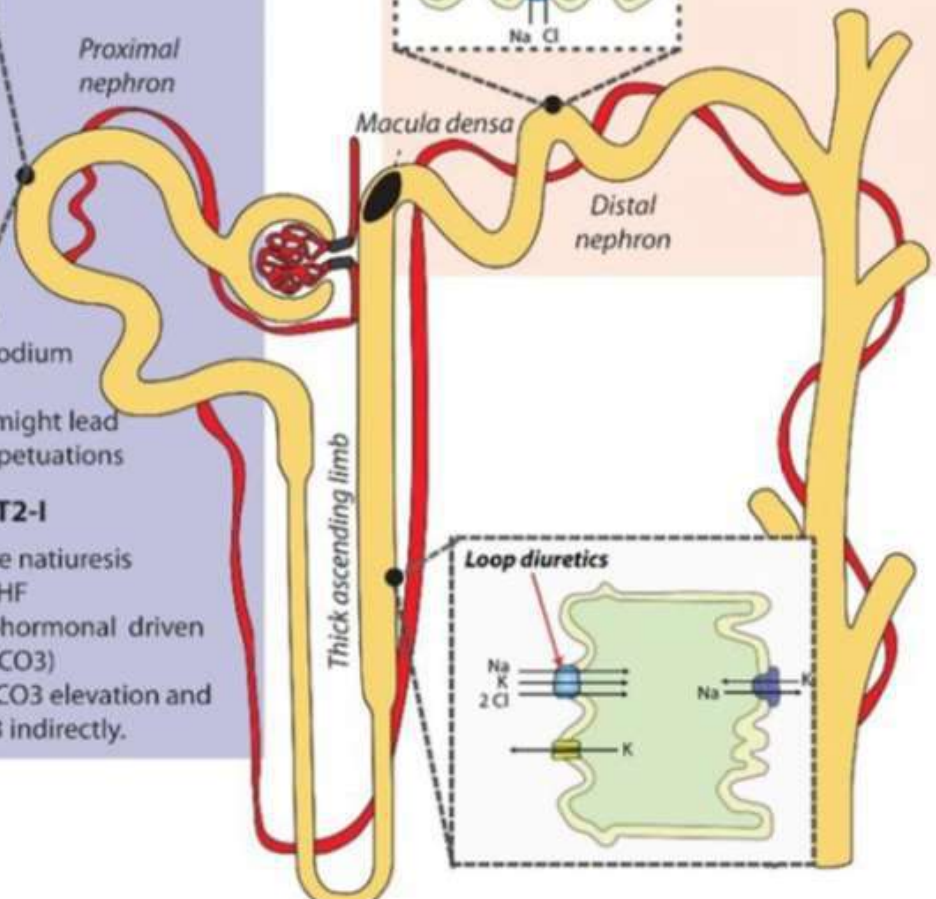
Difference between acetazolamide and SGLT2-I

* SGLT2-I = more aquauresis, acetazolamide = more natiuresis
* SGLT2-I preferrably continued as GDMT during AHF
* Acetazolamide works better in situation of neurohormonal driven stimulation of NHE3 (Eg illustrated by elevated HCO3)
* Acetazolamide prevents loop diuretic induced HCO3 elevation and the associated resistance through targeting NHE3 indirectly.

Distal nephron inhibition as add-on to loops



* Distal nephron reabsorbs +/- 5% of filtered sodium In settings of chronic loop exposure the distal nephron reabsorbs proportionally more sodium
* Downsides of thiazides might include more alterations in creatinine, BUN, potassium and sodium
* Thiazides also block some proximal sodium transport although the significance in HF is unknown.



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

W. Mullens, J. Dauw, P. Martens, F.H. Verbrugge, P. Nijst, E. Meekers, K. Tartaglia, F. Chenot, S. Moubayed, R. Dierckx, P. Blouard, P. Troisfontaines, D. Derthoo, W. Smolders, L. Bruckers, W. Droogne, J.M. Ter Maaten, K. Damman, J. Lassus, A. Mebazaa, G. Filippatos, F. Ruschitzka, and M. Dupont, for the ADVOR Study Group*

ABSTRACT

BACKGROUND

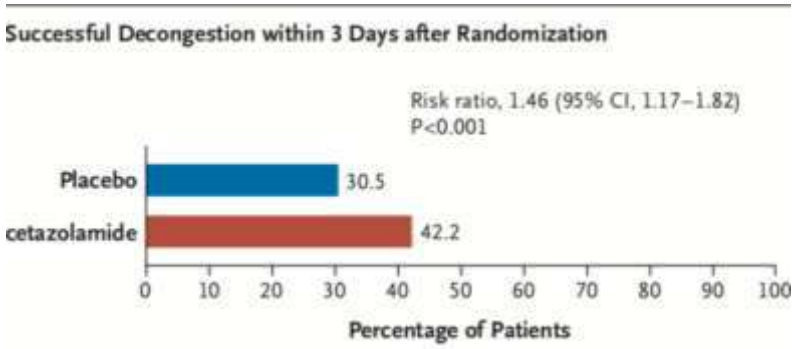
Whether acetazolamide, a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption, can improve the efficiency of loop diuretics, potentially leading to more and faster decongestion in patients with acute decompensated heart failure with volume overload, is unclear.

METHODS

In this multicenter, parallel-group, double-blind, randomized, placebo-controlled

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Mullens can be contacted at wilfried.mullens@zol.be or at Ziekenhuis Oost-Limburg, Schiepse Bos 6, Genk 3600, Belgium.

*A list of the principal investigators in the ADVOR Study Group is provided in



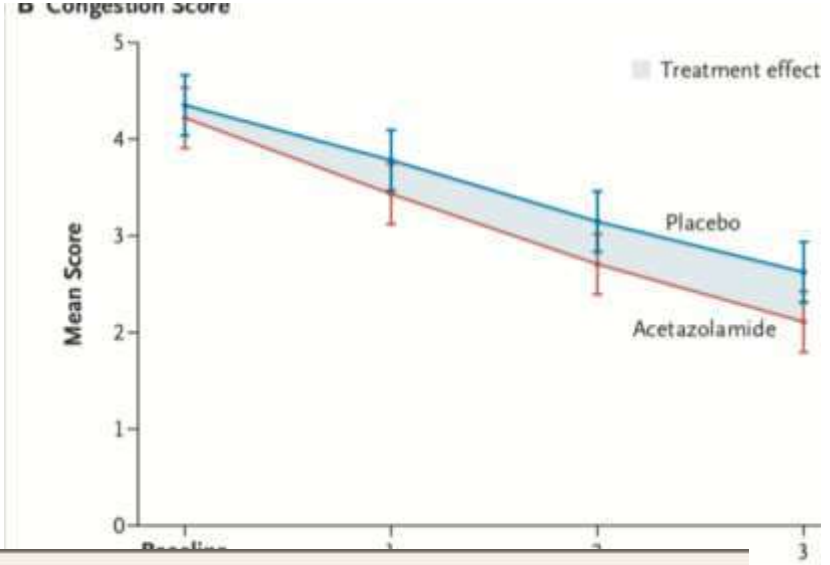


Table 2. Primary and Secondary End Points, Sensitivity and Exploratory Analyses, and Adverse Events.*

Variable	Placebo (N=259)	Acetazolamide (N=256)	Treatment Effect (95% CI)	P Value
Primary end point				
Successful decongestion within 3 days after randomization — no. (%)†	79 (30.5)	108 (42.2)	Risk ratio, 1.46 (1.17–1.82)	<0.001
Secondary end points				
Duration of hospital stay (95% CI) — days‡	9.9 (9.1–10.8)	8.8 (8.0–9.5)	0.89 (0.81–0.98)	
Death from any cause or rehospitalization for heart failure during 3 mo of follow-up — no. (%)	72 (27.8)	76 (29.7)	Hazard ratio, 1.07 (0.78–1.48)	

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ORIGINAL ARTICLE

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W. Mullens, J. Dauw, P. Martens, F.H. Verbrugge, P. Nijst, E. Meekers,
for the ADVOR Study Group*

ESC European Society of Cardiology
European Heart Journal (2023) 44, 411–421
https://doi.org/10.1093/eurheartj/ehac689

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial

José Pérez-Silvestre[11], Miguel Ángel Plasín[12], José Manuel Cerqueiro[13], Paloma Gil[14],

IV Furosemide

Natriuresis

Blocking proximal Na reabsorption

IV acetazolamide 500 mg/daily

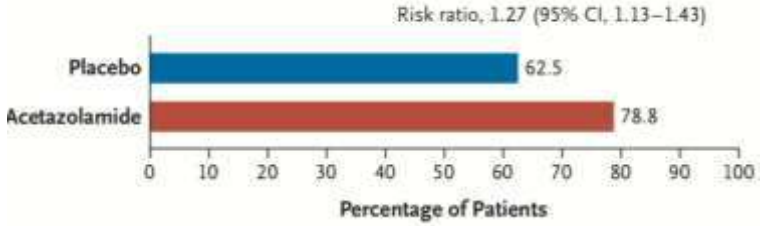
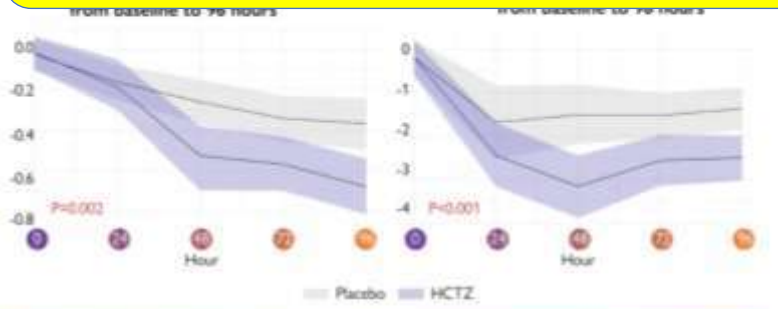


Table 2. Primary and Secondary End Points, Sensitivity and Exploratory Analyses, and Adverse

Variable	Placebo (N = 259)	Acetazolamide (N = 256)
Primary end point		
Successful decongestion within 3 days after randomization — no. (%)†	79 (30.5)	108 (42.2)
Secondary end points		
Duration of hospital stay (95% CI) — days‡	9.9 (9.1–10.8)	8.8 (8.0–9.5)
Death from any cause or rehospitalization for heart failure during 3 mo of follow-up — no. (%)	72 (27.8)	76 (29.7)

Sequential nephron blockade

HCT 25- 100 mg/daily according to eGFR



Safety	Placebo	HCTZ	p-value
All-cause mortality at 90 days	19 (16.4%)	23 (20.2%)	0.566
All-cause rehospitalizations at 90 days	40 (34.5%)	43 (37.7%)	0.709
Impaired renal function (serum creatinine and eGFR)	20 (17.2%)	53 (46.5%)	<0.001
Hyponatraemia (Na+ ≤ 130 mmol/L) - (Na+ ≤ 125 mmol/L)	6 (5.2%)–2 (1.7%)	10 (8.8%)–3 (2.6%)	0.416–0.682
Hypokalaemia (K+ ≤ 3.0 mmol/L) - (K+ ≤ 2.5 mmol/L)	18 (16.1%)–0 (0.0%)	43 (40.6%)–2 (1.8%)	<0.001–0.245
Serious adverse events	27 (23.3%)	26 (22.8%)	0.93

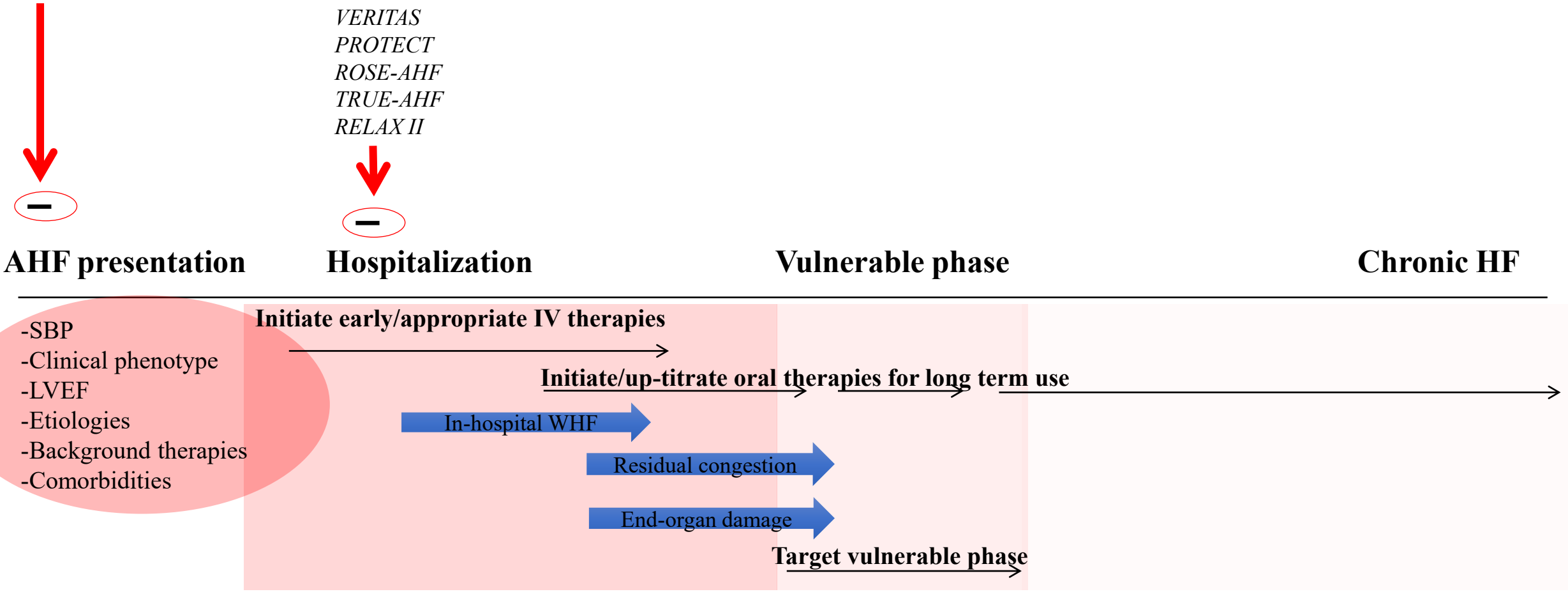
Two decades of negative RCTs

"Time is muscle" strategies

GALACTIC-AHF
ELISABETH
FAST and FURO

Short-term infusions

REVIVE
SURVIVE
RITZ
ASCEND-HF
ATOMIC-HF
BLAST-AHF
VERITAS
PROTECT
ROSE-AHF
TRUE-AHF
RELAX II



Lessons from RCTs

"moving to the left"

European Heart Journal Supplements (2016) 18(Supplement G), G19-G32
The Heart of the Matter
doi:10.1093/eurheartj/suw045

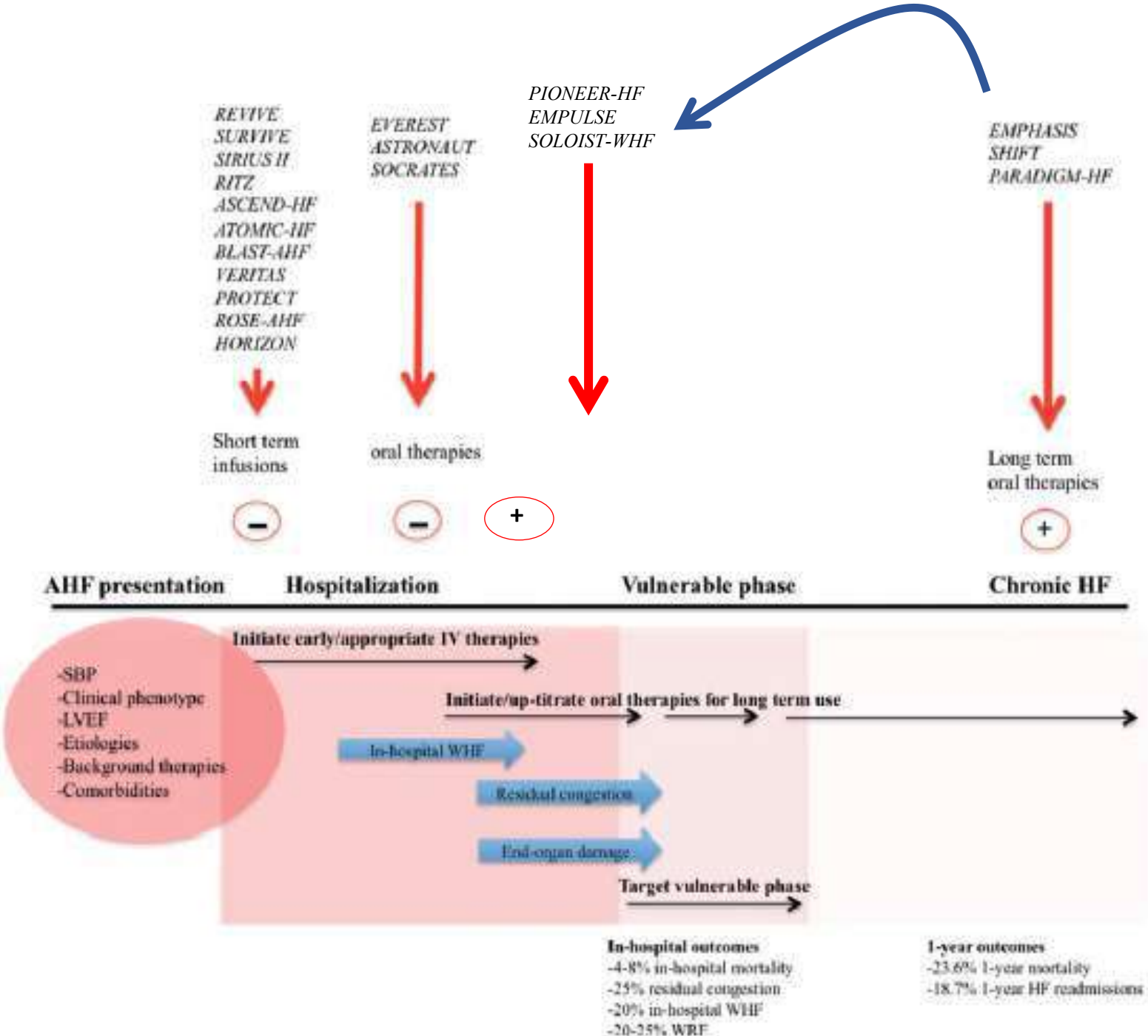
The bumpy road to drug development for acute heart failure

Carine E. Hamo[1], Javed Butler[1], Mihai Gheorghiade[2], and Ovidiu Chioncel[3]*

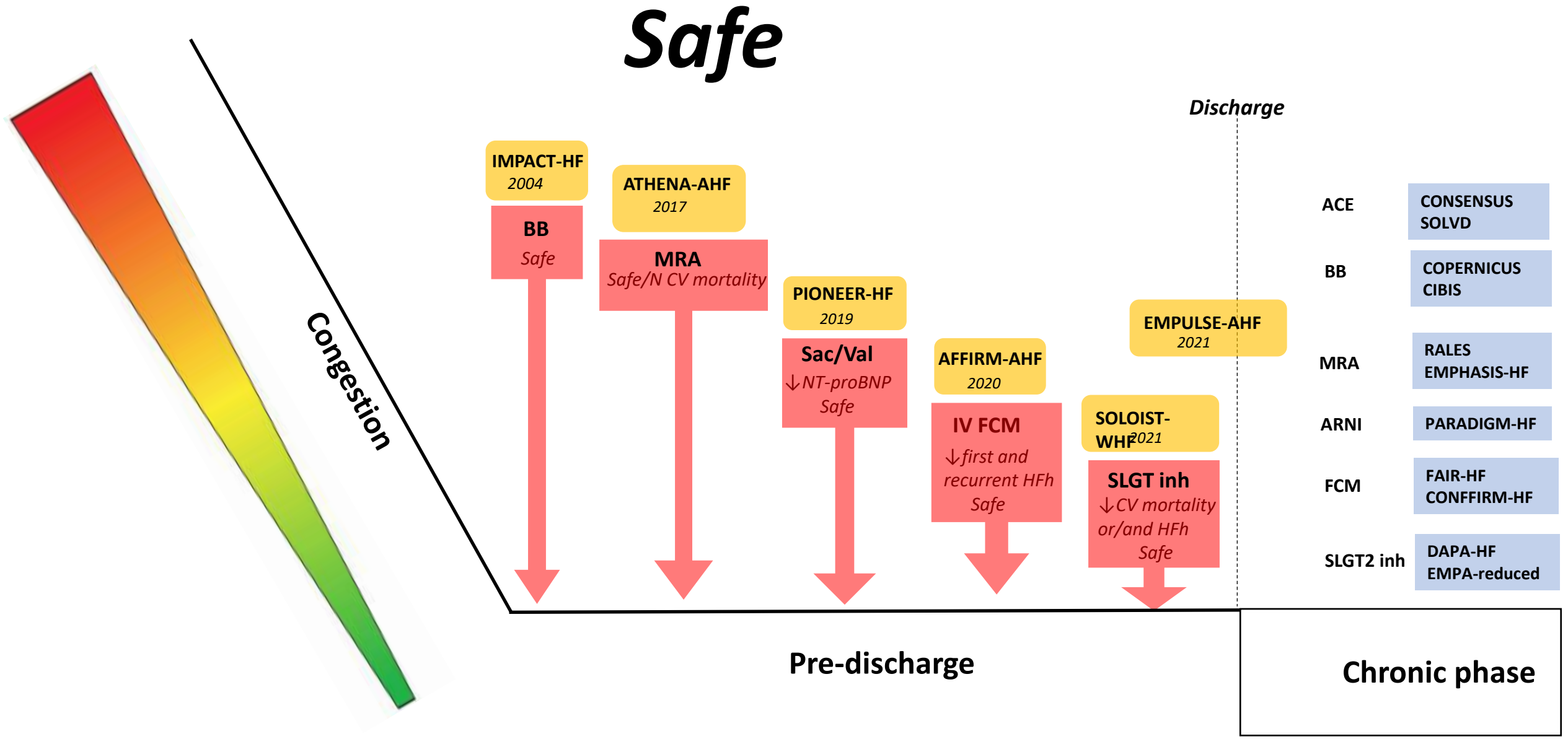
[1]Department of Medicine, Stony Brook University, Stony Brook, NY 11794, USA
[2]Center for Cardiovascular Innovation, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA
[3]Institute of Emergency for Cardiovascular Diseases 'Professor C.C. Iliescu', University of Medicine and Pharmacy Carol Davila, Bucuresti 950474, Romania

KEYWORDS
Worsening chronic heart failure;
Clinical trials;
Drug development

The prevalence of heart failure (HF) continues to grow, in large part attributed to the aging population. Parallel to this trend is the increasing burden of hospitalization for worsening HF, which accounts for the majority of the very high societal burden of costs of care for these patients. These hospitalizations represent a change in the trajectory of the disease process and are associated with a significantly higher risk of adverse outcomes, a trend that has not changed over the past two decades. Although short-term readmissions are due to haemodynamic congestion, long-term prognosis and mortality are the result of the continuous deterioration of cardiac substrate, worsening of comorbidities, and progression of HF. Thus, when planning a new therapeutic intervention in acute HF, it is essential to have insight into the mechanism and temporal distribution of adverse outcomes. Furthermore, as acute HF patients die or are readmitted due to multiple reasons it is important to match the mechanism of action of the intervention to the mechanism of the adverse event. Despite many clinical trials to date in these patients, there currently is not a single agent that is known to improve post-discharge mortality risk in these patients. A variety of reasons have been offered to account for the lack of success in these clinical trials. A careful review of these previous experiences offers some significant insights into lessons learned and provides guidance for future novel intervention development for this growing patient population.



Initiation of oral therapies during hospitalization

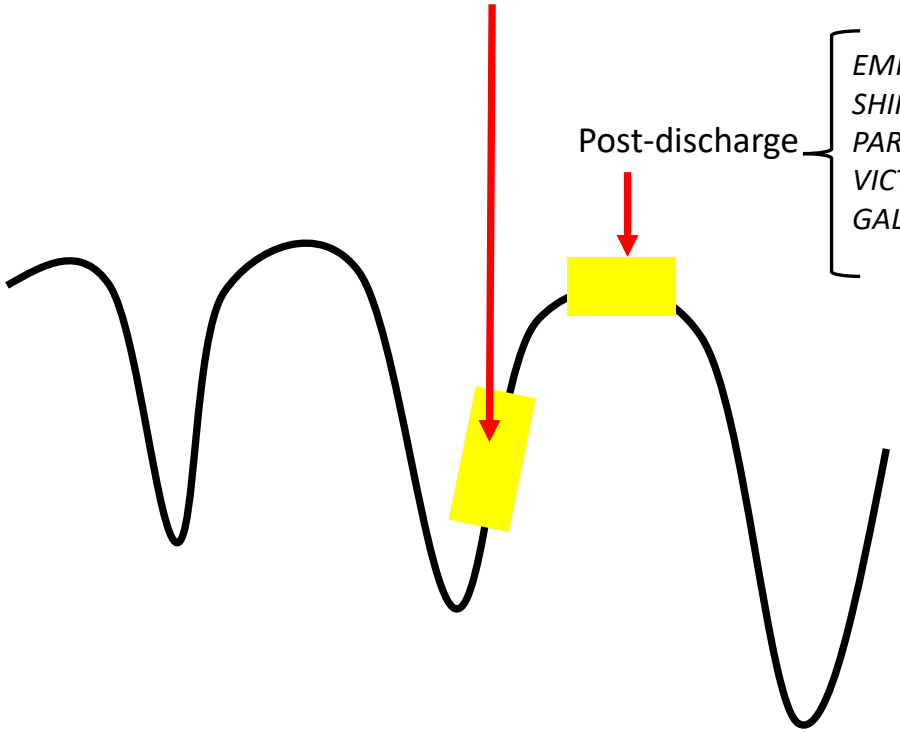


During hospitalization
After stabilization

PIONEERR-HF
EMPULSE
SOLOIST-WHF

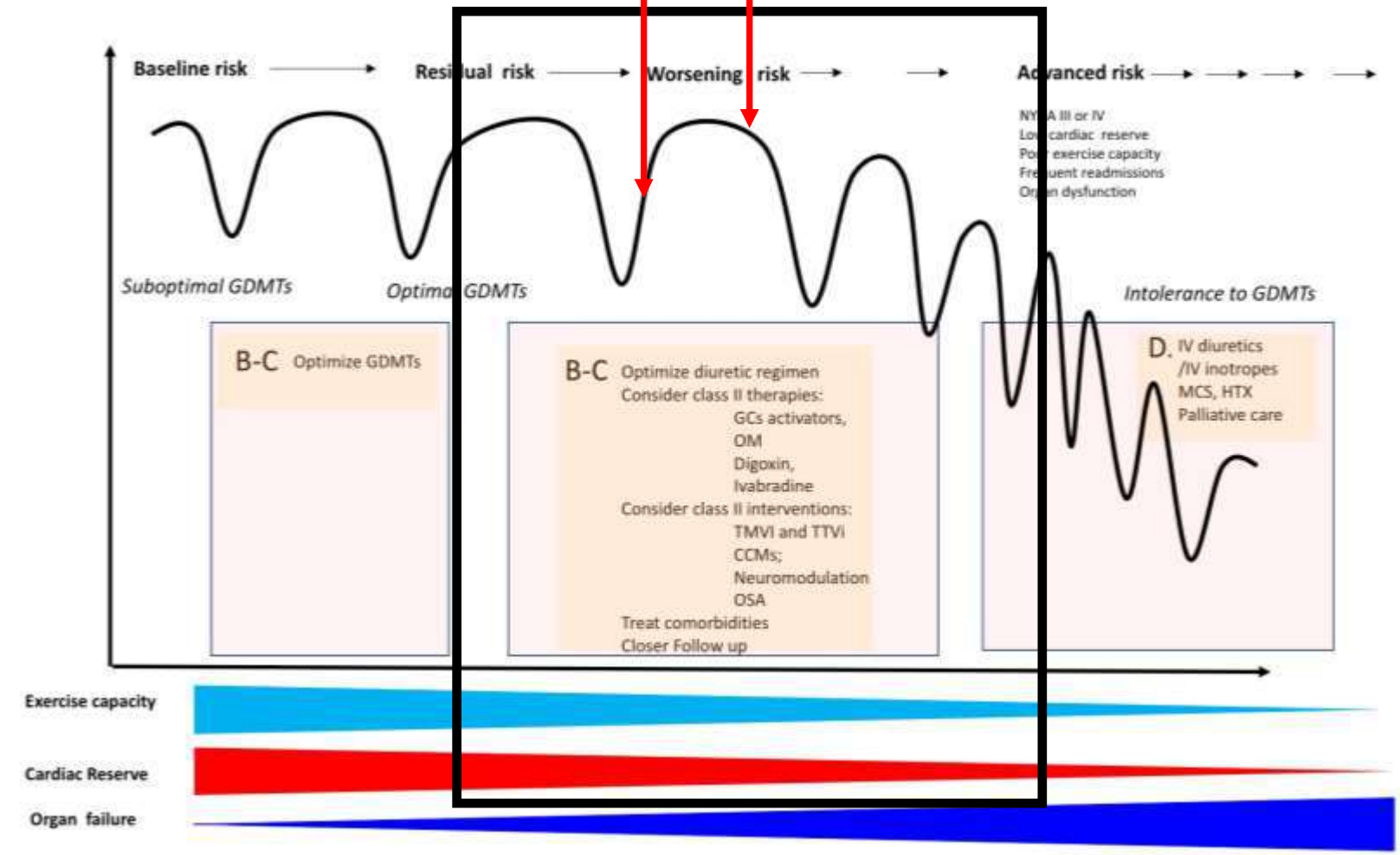
Post-discharge

EMPHASIS
SHIFT
PARADIGM-HF
VICTORIA
GALACTIC



During hospitalization
After stabilization

Post-discharge

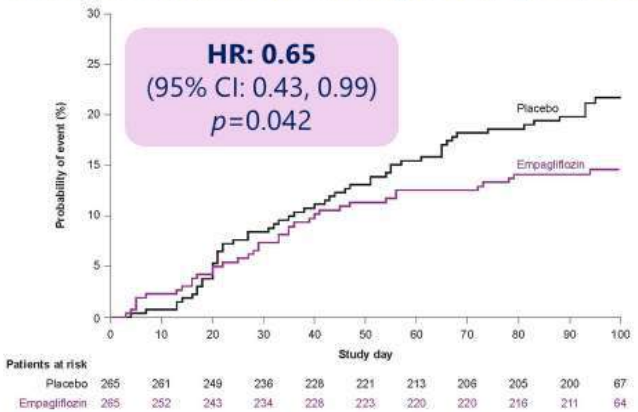


NATURE MEDICINE

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

Lower Risk of HF Events or All-Cause Mortality

35% lower risk in the empagliflozin group than in the placebo group



Number-needed-to-treat:
15 patients treated for
90 days to prevent an event

HFSA 2022 ANNUAL SCIENTIFIC MEETING
September 30 – October 3, 2022

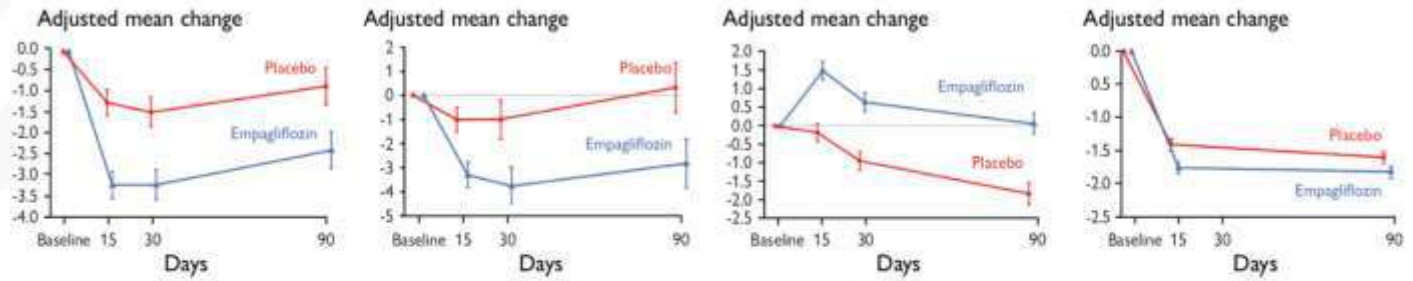
ESC European Society of Cardiology
European Heart Journal (2023) 44, 41–50
https://doi.org/10.1093/eurheartj/ehac530

CLINICAL RESEARCH
Clinical trials

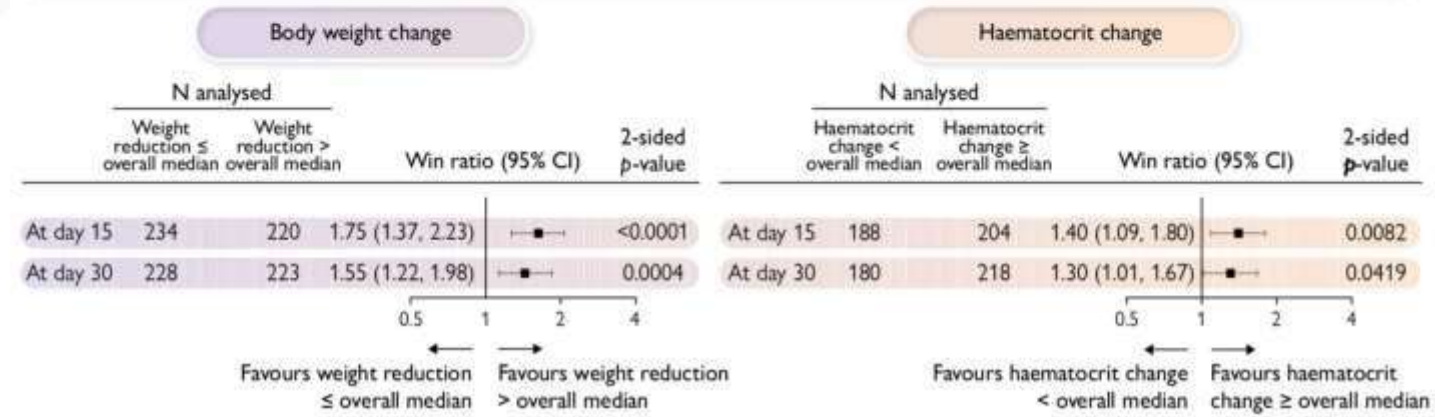
Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial

Jan Biegus[1*], Adriaan A. Voors[2], Sean P. Collins[3,4], Mikhail N. Kosiborod[5,6], John R. Teerlink[7], Christiane E. Angermann[8], Jasper Tromp[9], Joao Pedro Ferreira[10,11], Michael E. Nassif[12], Mitchell A. Psotka[13], Martina Brueckmann[14,15], Afshin Salsali[16,17], Jonathan P. Blatchford[18], and Piotr Ponikowski[1]

Treatment effect



Clinical benefit at day 90§



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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CLINICAL RESEARCH
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Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial

NATURE MEDICINE

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

Mitchell A. Psotka[1], Jasper Tromp[2], C. Jan Willem Borleffs[3], Changsheng Ma[4],

IV Furosemide

Natriuresis

Glucosuria/other cardiac

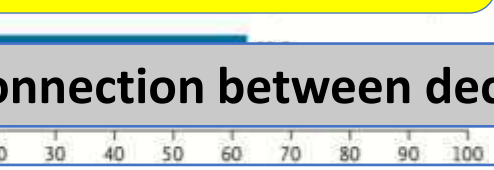
Blocking proximal Na reabsorption
IV acetazolamide 500 mg/daily

Sequential nephron blockade
HCT 25- 100 mg/daily according to eGFR

SGLT2 inhibition
Empaglifozin 10 mg/daily

Disconnection between decongestion and 90-day outcomes

Outcome' benefit



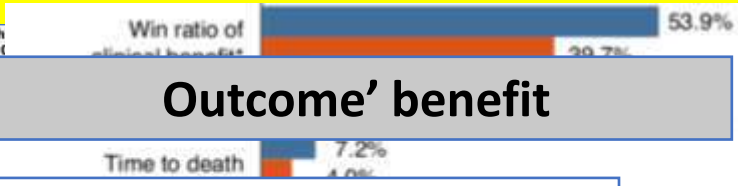


Table 2. Primary and Sec

Variable

Primary end point

Successful decongestion
ization — no.

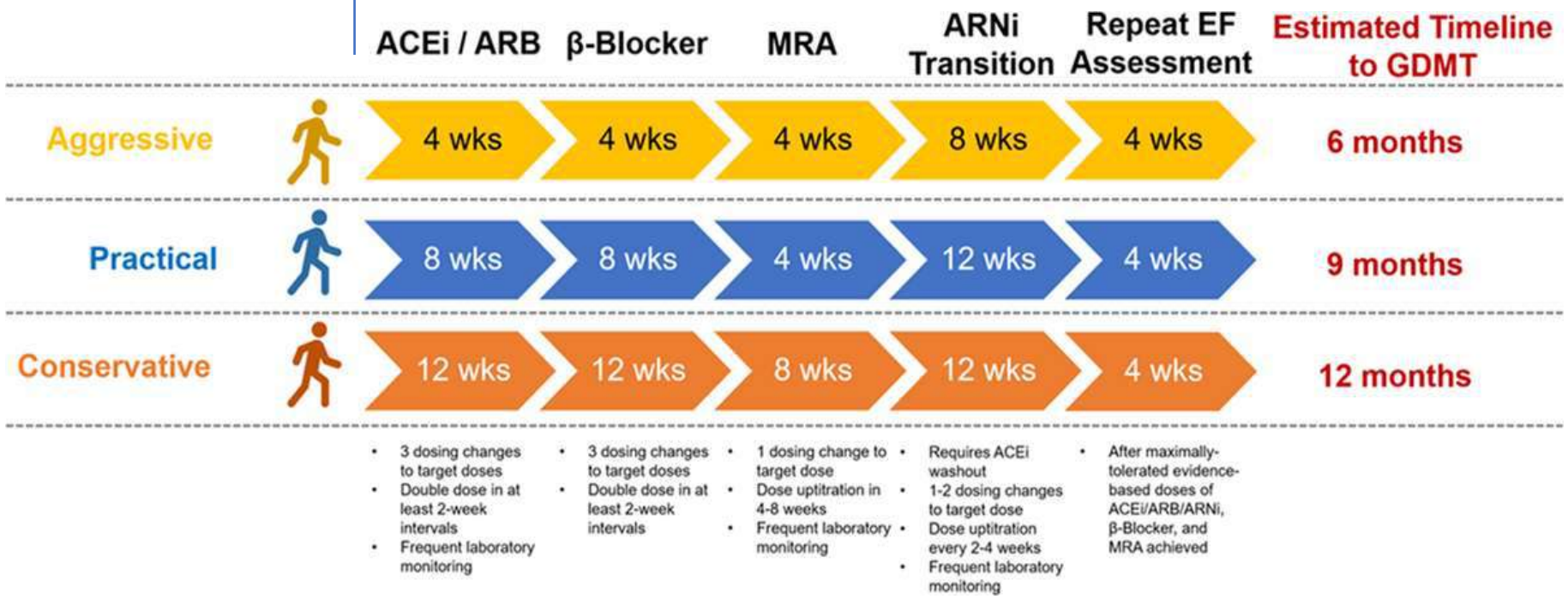
Secondary end points

Duration of hospital stay

Death from any cause o
failure during

Ties

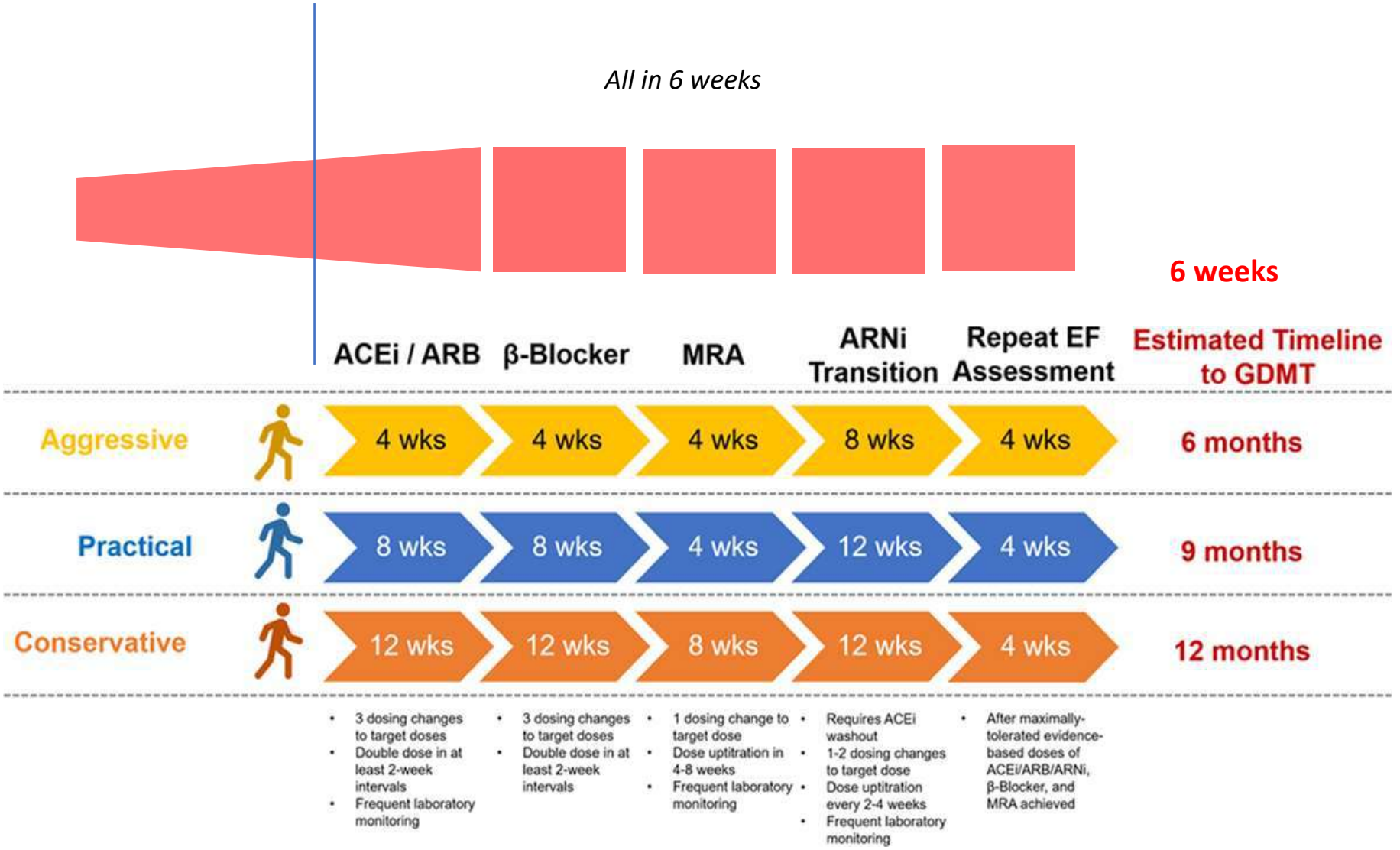
GDMTs Uptitration



Timely Management of New-Onset Heart Failure-The Other Vulnerable Phase. Circulation. 2019;140:621–623

Uptitration

STRONG



Timely Management of New-Onset Heart Failure-The Other Vulnerable Phase. Circulation. 2019;140:621–623

ESC European Society of Cardiology

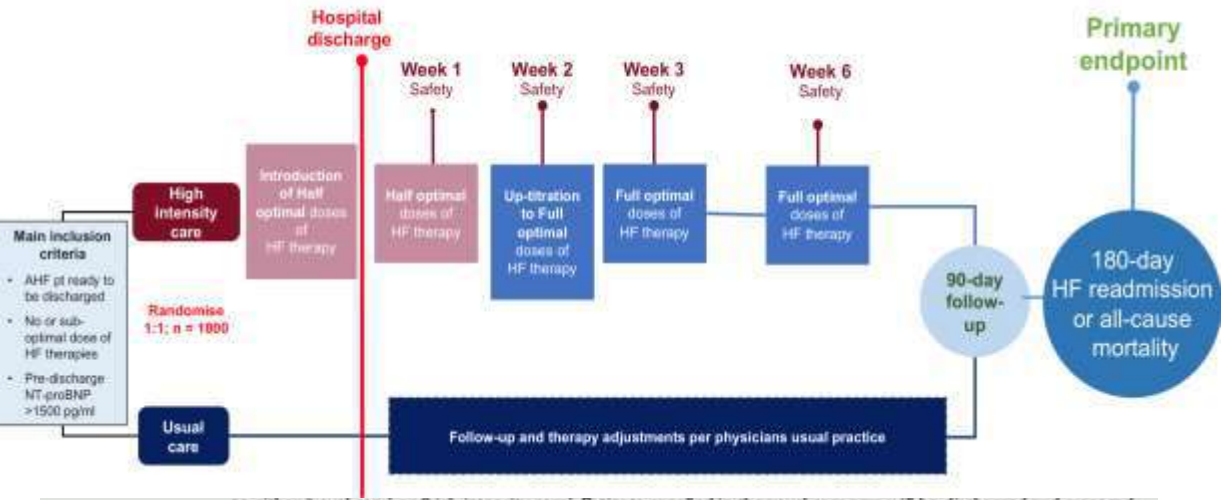
European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1575

STUDY DESIGN

Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of Heart Failure therapies (STRONG-HF): rationale and design for a multicentre, randomized, parallel-group study

Antoine Kimmoun[1], Gad Cotter[2], Beth Davison[2], Koji Takagi[1], Faouzi Addad[3], Jelena Celutkiene[4], Ovidiu Chioncel[5], Alain Cohen Solal[1,6], Rafael Diaz[7], Albertino Damasceno[8], Hans-Dirk Duengen[9], Gerasimos Filippatos[10], Eva Goncalvesova[11], Imad Merai[12], Marco Metra[13], Piotr Ponikowski[14], Dmitry Privalov[15], Karen Sliwa[16], Mahmoud Umar Sani[17], Adriaan A. Voors[18], Zaur Shogenov[19], and Alexandre Mebazaa[1,20]*

[1]INSERM UMR-S 942, St. Louis and Lariboisère University Hospitals, Paris University, Paris, France; [2]Momentum Research Inc., Durham, NC, USA; [3]Department of Cardiology,



to either 'usual care' or 'high-intensity care'. Patients enrolled in the usual care arm will be discharged and managed according to usual clinical practice at the site. In the high-intensity care arm, doses of oral HF medications – including a BB, ACEi or ARB, and MRA – will be up-titrated to 50% of recommended doses before discharge and to 100% of recommended doses within 2 weeks of discharge. Up-titration will be delayed if the patients develop worsening

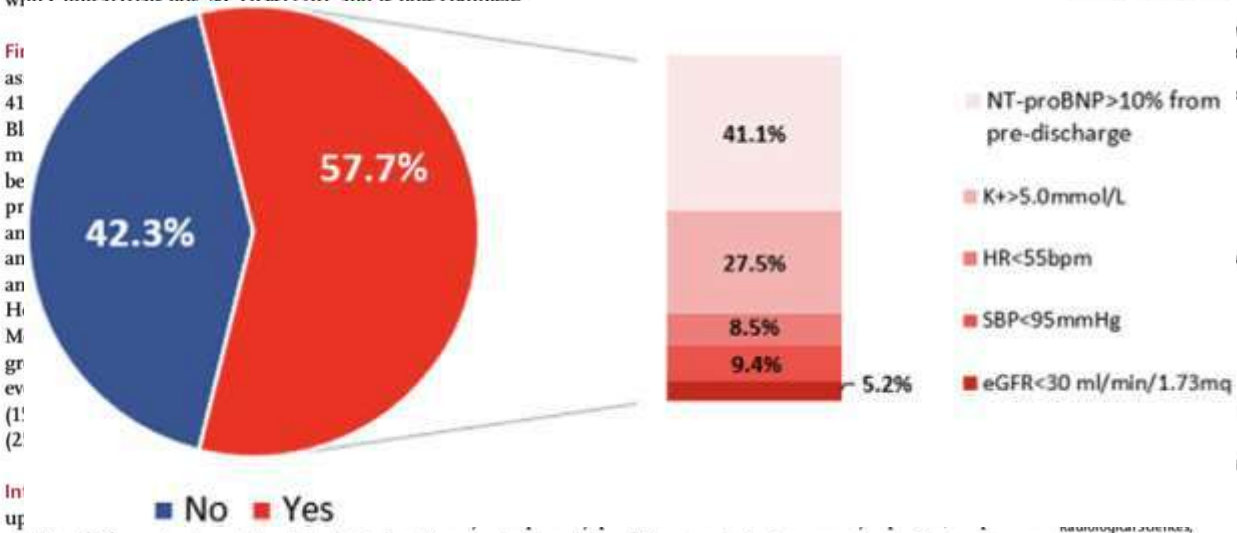
Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

Alexandre Mebazaa, Beth Davison, Ovidiu Chioncel, Alain Cohen-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski, Karen Sliwa, Adriaan A Voors, Christopher Edwards, Maria Novosadova, Koji Takagi, Albertino Damasceno, Hadiza Saidu, Etienne Gayat, Peter S Pang, Jelena Celutkiene, Gad Cotter

Summary

Background There is a paucity of evidence for dose and pace of up-titration of guideline-directed medical therapies after admission to hospital for acute heart failure.

Methods In this multinational, open-label, randomised, parallel-group trial (STRONG-HF), patients aged 18–85 years admitted to hospital with acute heart failure, not treated with full doses of guideline-directed drug treatment, were recruited from 87 hospitals in 14 countries. Before discharge, eligible patients were randomly assigned (1:1), stratified by left ventricular ejection fraction (≤40% *vs* >40%) and country, with blocks of size 30 within strata and randomly ordered sub-blocks of 2, 4, and 6, to either usual care or high-intensity care. Usual care followed usual local practice, and high-intensity care 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 after discharge that closely monitored clinical status, laboratory values, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations. The primary endpoint was 180-day readmission to hospital due to heart failure or all-cause death. Efficacy and safety were assessed in the intention-to-treat (ITT) population (ie, all patients validly randomly assigned to treatment). The primary endpoint was assessed in all patients enrolled at hospitals that followed up patients to day 180. Because of a protocol amendment to the primary endpoint, the results of patients enrolled on or before this amendment were down-weighted. This study is registered with ClinicalTrials.gov, NCT03412201, and is now complete.



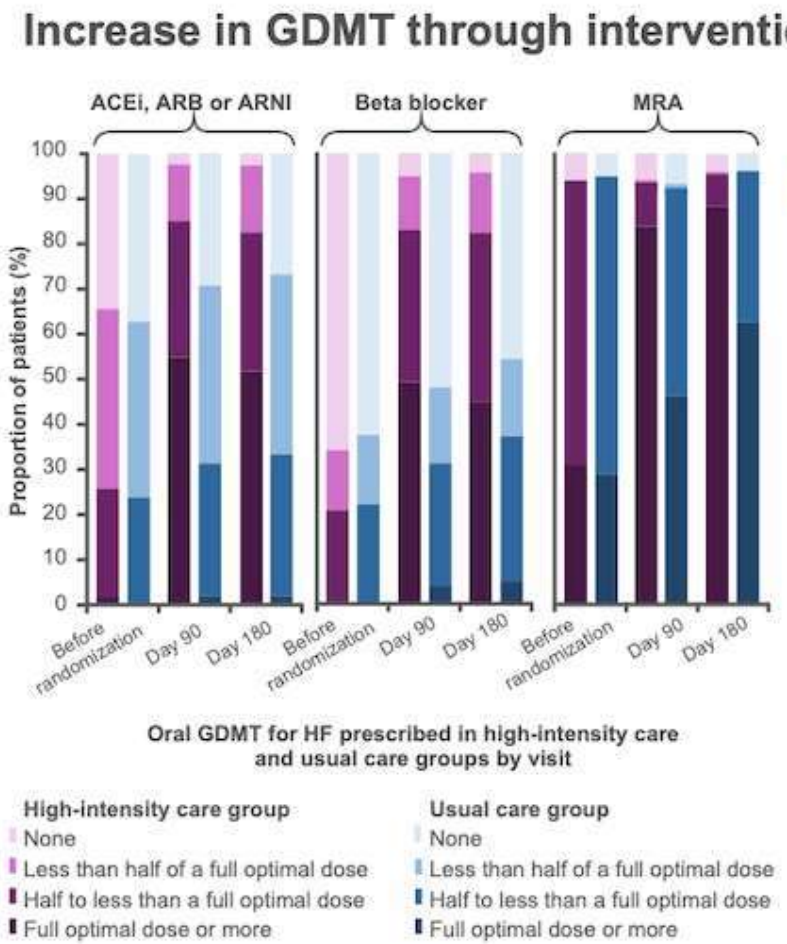
quality of life, and reduced the risk of 180-day all-cause death or heart failure readmission compared with usual care.

Published Online November 7, 2022 https://doi.org/10.1016/S0140-6736(22)02076-1

Université Paris Cité, INSERM UMR-S 942 (MASCOT), Paris, France (Prof A Mebazaa MD, B Davison PhD, Prof A Cohen-Solal MD, Prof E Gayat MD, G Cotter MD); Department of Anesthesiology and Critical Care and Burn Unit, Saint-Louis and Lariboisière Hospitals, FHU PROMICE, DMU Parabol, APHP Nord, Paris, France (Prof A Mebazaa, Prof E Gayat); Momentum Research, Durham, NC, USA

and Public Health, University of Brescia, Brescia, Italy

Significant benefit of rapid up-titration

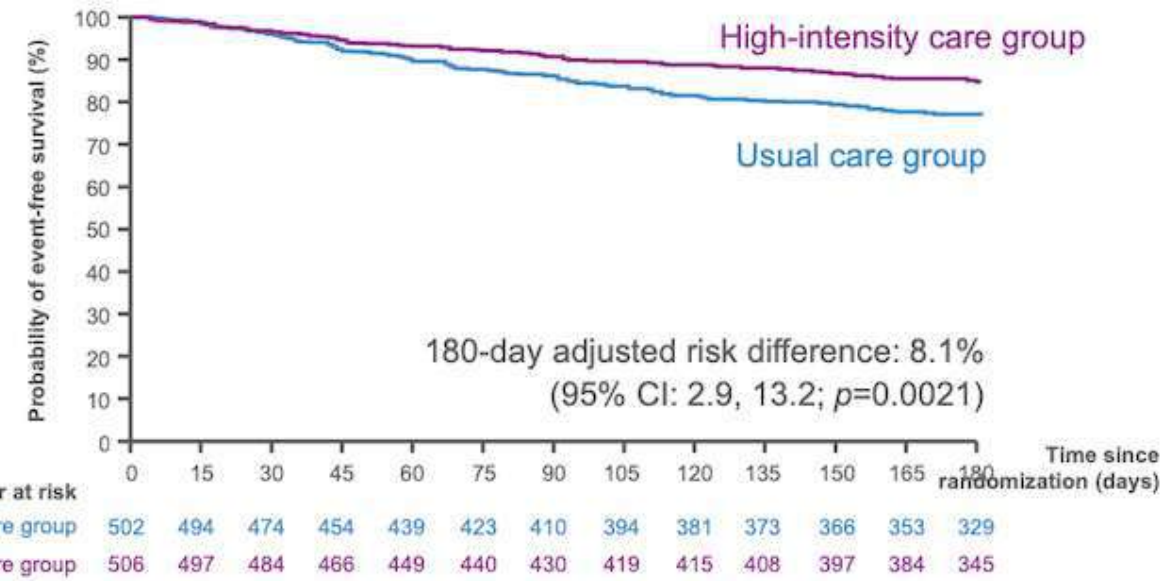


Greater reduction in NT-proBNP

Translating into better outcomes

Figure shows KM survival curve for all-cause death or HF readmission†

	High-intensity care group (n=542)	Usual care group (n=536)	Adjusted treatment effect (95% CI)	*p*- value
NT-proBNP (pg/mL)*				
Baseline	3258.4 (3087.5, 3438.8)	3159.2 (2995.4, 3332.0)	–	–
Day 90	1356.6 (1223.1, 1504.6)	1729.5 (1559.6, 1917.9)	–	–
Adjusted ratio of geometric means	0.436	0.564	0.77 (0.67, 0.89)	0.0003



Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

Alexandre Mebazaa, Beth Davison, Ovidiu Chioncel, Alain Cohen-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski, Karen Sliwa, Adriaan A Voors, Christopher Edwards, Maria Novosadova, Koji Takagi, Albertino Damasceno, Hadiza Saidu, Etienne Gayat, Peter S Pang, Jelena Celutkiene, Gad Cotter

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Published Online November 7, 2022 https://doi.org/10.1016/

- Irrespective of age, sex
- Irrespective of LVEF
- Irrespective of NT-pro-BNP
- Irrespective of SBP
- Irrespective of NCCs
- Irrespective of S-creatinine
- Irrespective of risk

Based on RCT inclusion and exclusion criteria

Real Life
??

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

Comorbidities

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

ABSTRACT

BACKGROUND

Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an 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 to receive dapagliflozin (10 mg once daily) or placebo. 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.

RESULTS

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 a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P=0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

CONCLUSIONS

Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of 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 was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Heerspink at the Department of Clinical Pharmacy and Pharmacology, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, the Netherlands, or at h.j.lambers.heerspink@umcg.nl.

*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 24, 2020, at NEJM.org.

N Engl J Med 2020;383:1436-46.
DOI: 10.1056/NEJMoa2024816

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

ABSTRACT

BACKGROUND

The effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression are not well understood. The EMPA-KIDNEY trial was designed to assess the effects of treatment with empagliflozin in a broad range of such patients.

METHODS

We enrolled patients with chronic kidney disease who had an 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. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or matching placebo. 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.

RESULTS

A total of 6609 patients underwent randomization. During a median of 2.0 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 and across subgroups defined according to eGFR ranges. The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P=0.003), but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or death from cardiovascular causes (which occurred in 4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1%, respectively). The rates of serious adverse events were similar in the two groups.

CONCLUSIONS

Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.)

The members of the writing committee (W.G. Herrington, N. Staplin, C. Wanner, J.B. Green, S.J. Hauske, J.R. Emberson, D. Preiss, P. Judge, K.J. Mayne, S.Y.A. Ng, E. Sammons, D. Zhu, M. Hill, W. Stevens, K. Wallendszus, S. Brenner, A.K. Cheung, Z.-H. Liu, J. Li, L.S. Hooi, W. Liu, T. Kadowaki, M. Nangaku, A. Levin, D. Cherney, A.P. Maggioni, R. Pontremoli, R. Deo, S. Goto, X. Rossello, K.R. Tuttle, D. Steubl, M. Petrini, D. Massey, J. Eilbracht, M. Brueckmann, M.J. Landray, C. Baigent, and R. Haynes) assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the writing committee are listed in the Appendix. Dr. Herrington can be contacted at cco.empakidney@ndph.ox.ac.uk or at the EMPA-KIDNEY Central Coordinating Office, Richard Doll Building, Old Road Campus, Roosevelt Dr., Oxford OX3 7LF, United Kingdom.

*A complete list of members of the EMPA-KIDNEY Collaborative Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Herrington and Staplin and Drs. Landray, Baigent, and Haynes contributed equally to this article.

This article was published on November 4, 2022, at NEJM.org.

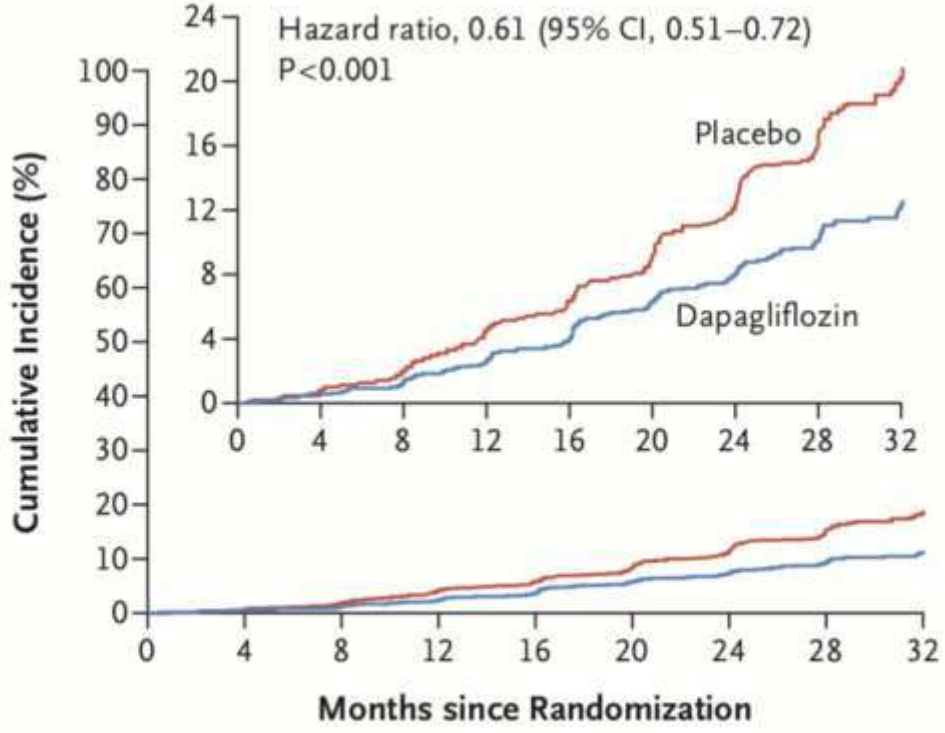
N Engl J Med 2023;388:117-27.
DOI: 10.1056/NEJMoa2204233

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

A Primary Composite Outcome



No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

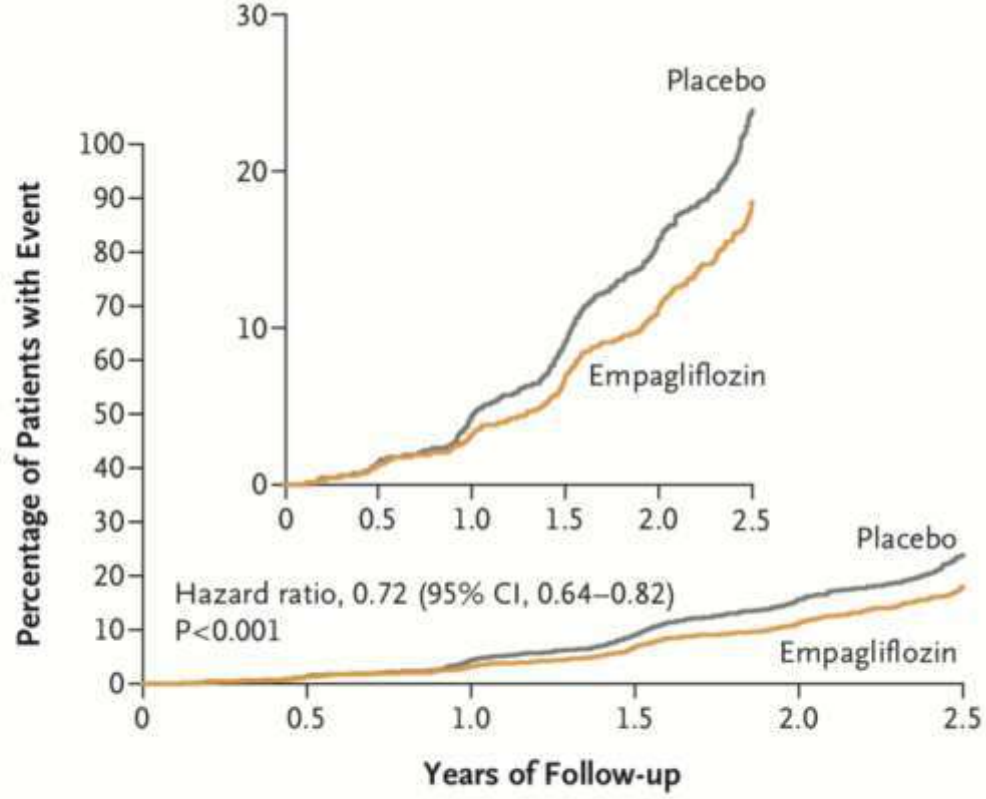
The EMPA-KIDNEY Collaborative Group*

ABSTRACT

BACKGROUND

The effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression are not well understood. The EMPA-KIDNEY trial was

The members of the writing committee (W.G. Herrington, N. Staplin, C. Wanner,



No. at Risk

Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death.[5,7,35]	I	A

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

ABSTRACT

BACKGROUND

Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced albuminuria in short-term trials involving patients with chronic kidney disease (CKD) and type 2 diabetes. However, its long-term effects on kidney and cardiovascular outcomes are unknown.

METHODS

In this double-blind trial, we randomly assigned 5734 patients with CKD and type 2 diabetes in a 1:1 ratio to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in 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 m^2 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 m^2. 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. The primary composite outcome, assessed in a time-to-event analysis, was kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes. The key secondary composite outcome, also assessed in a time-to-event analysis, was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

RESULTS

During a median follow-up of 2.6 years, a primary outcome event 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). Overall, the frequency of adverse events was similar in the two groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than with placebo (2.3% and 0.9%, respectively).

CONCLUSIONS

In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. (Funded by Bayer; FIDELIO-DKD ClinicalTrials.gov number, NCT02540993.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bakris at the Department of Medicine, University of Chicago, 5841 S. Maryland Ave., MC 1027, Chicago, IL 60637, or at gbakris@gmail.com.

*A complete list of the FIDELIO-DKD investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 23, 2020, at NEJM.org.

N Engl J Med 2020;383:2219-29.
DOI: 10.1056/NEJMoa2025845

ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*

ABSTRACT

BACKGROUND

Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has favorable effects on cardiorenal outcomes in patients with predominantly stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. The use of finerenone in patients with type 2 diabetes and a wider range of CKD is unclear.

METHODS

In this double-blind trial, we randomly assigned patients with CKD and type 2 diabetes to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and 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 m^2 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 m^2 (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. The primary outcome, assessed in a time-to-event analysis, was a 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. Safety was assessed as investigator-reported adverse events.

RESULTS

A total of 7437 patients underwent randomization. Among the patients included in the analysis, during a median follow-up of 3.4 years, a primary outcome event occurred in 458 of 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). The overall frequency of adverse events did not differ substantially between groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (1.2%) than with placebo (0.4%).

CONCLUSIONS

Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared with placebo. (Funded by Bayer; FIGARO-DKD ClinicalTrials.gov number, NCT02545049.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Pitt at the Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI 48109, or at bpitt@med.umich.edu.

*A complete list of the FIGARO-DKD investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Pitt and Filippatos contributed equally to this article.

This article was published on August 28, 2021, at NEJM.org.

N Engl J Med 2021;385:2252-63.
DOI: 10.1056/NEJMoa2110956

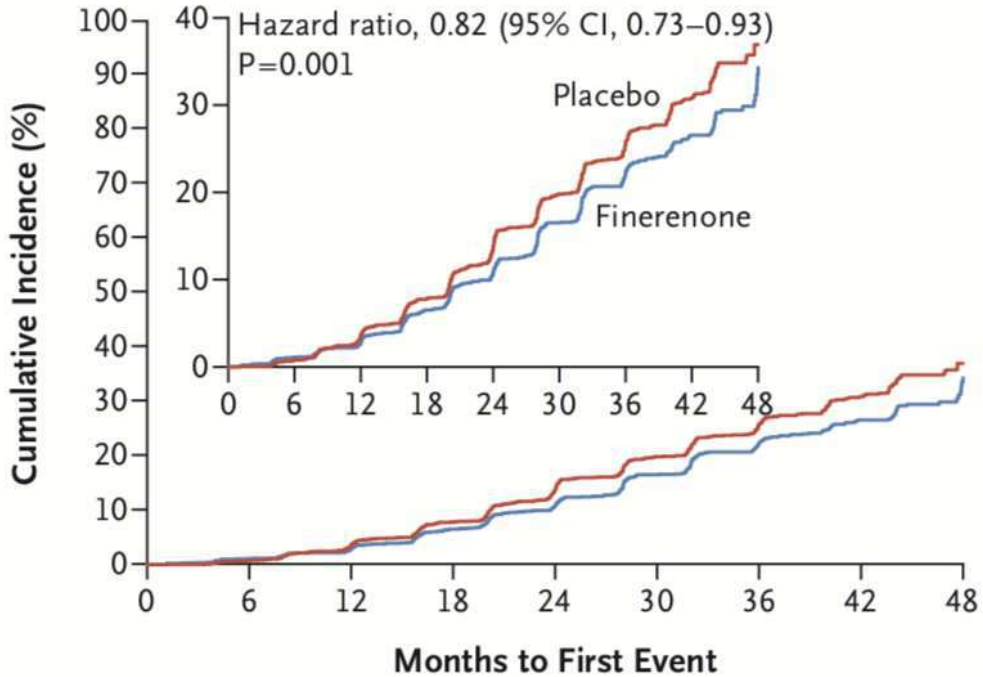
ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

ABSTRACT

A Primary Composite Outcome



No. at Risk

Placebo	2841	2724	2586	2379	1758	1248	792	453	82
Finerenone	2833	2705	2607	2397	1808	1274	787	441	83

by Bayer; FIDELIO-DKD ClinicalTrials.gov number, NCT02540993.)

ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Pitt at the Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI 48109, or at bpitt@med.umich.edu.

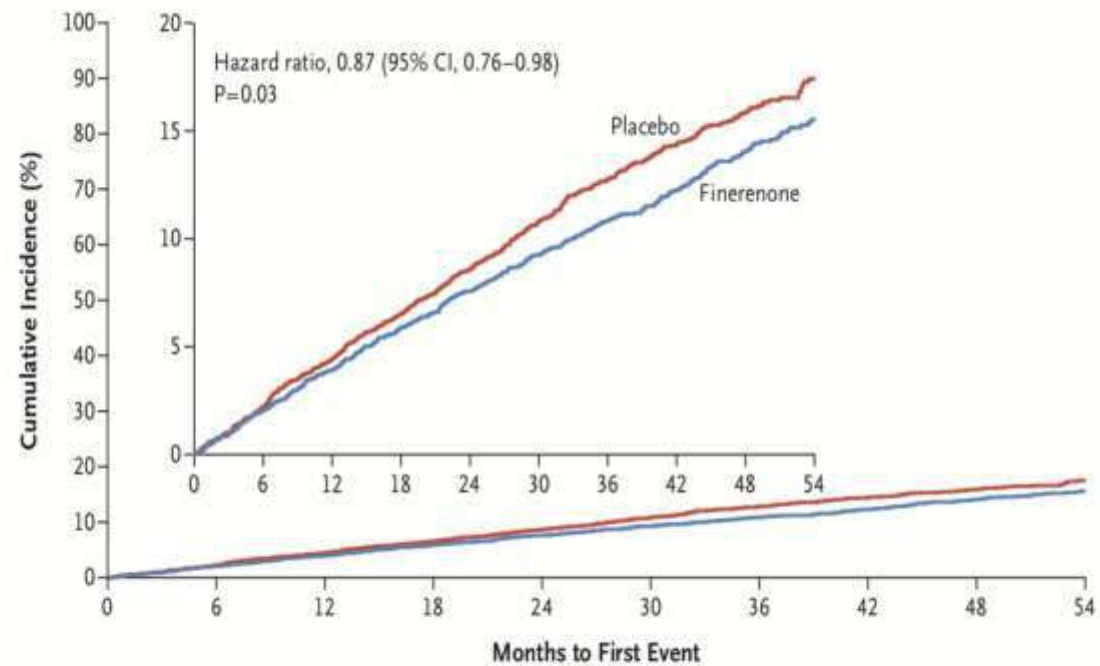
ABSTRACT

BACKGROUND

Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has favorable effects on cardiorenal outcomes in patients with predominantly stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. The use of finerenone in patients with type 2 diabetes and a wider range of CKD is unclear.

METHODS

Primary Composite Outcome



No. at Risk

Placebo	3666	3577	3479	3389	3267	2730	2125	1657	1076	585
Finerenone	3686	3600	3517	3427	3320	2781	2184	1712	1093	598

(Funded by Bayer; FIGARO-DKD ClinicalTrials.gov number, NCT02545049.)

Circulation

ORIGINAL RESEARCH ARTICLE

Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial

Gerasimos Filippatos, MD; Stefan D. Anker, MD, PhD; Rajiv Agarwal, MD, MS; Luis M. Ruilope, MD; Peter Rossing, MD; George L. Bakris, MD; Christoph Tasto, PhD; Amer Joseph, MBBS; Peter Kolkhof, PhD; Andrea Lage, MD; Bertram Pitt, MD; on behalf of the FIGARO-DKD Investigators

BACKGROUND: Chronic kidney disease and type 2 diabetes are independently associated with heart failure (HF), a leading cause of morbidity and mortality. In the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trials, finerenone (a selective, nonsteroidal mineralocorticoid receptor antagonist) improved cardiovascular outcomes in patients with albuminuric chronic kidney disease and type 2 diabetes. These prespecified analyses from FIGARO-DKD assessed the effect of finerenone on clinically important HF outcomes.

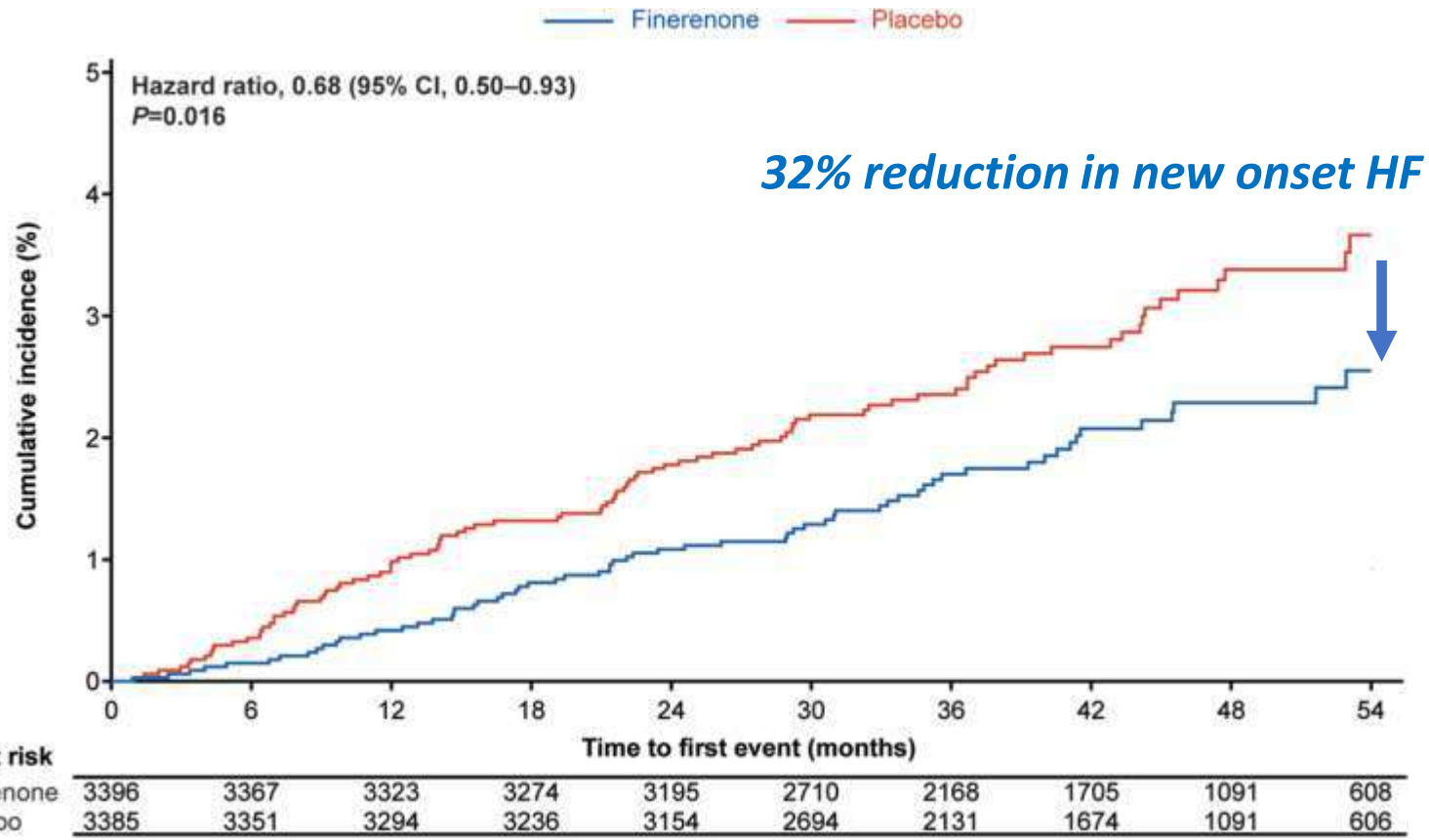
METHODS: Patients with type 2 diabetes and albuminuric chronic kidney disease (urine albumin-to-creatinine ratio ≥30 to <300 mg/g and estimated glomerular filtration rate ≥25 to ≤90 mL per min per 1.73 m², or urine albumin-to-creatinine ratio ≥300 to ≤5000 mg/g and estimated glomerular filtration rate ≥60 mL per min per 1.73 m²), without symptomatic HF with reduced ejection fraction, were randomized to finerenone or placebo. Time-to-first-event outcomes included new-onset HF (first hospitalization for HF [HHF] in patients without a history of HF at baseline); cardiovascular death or first HHF; HF-related death or first HHF; first HHF; cardiovascular death or total (first or recurrent) HHF; HF-related death or total HHF; and total HHF. Outcomes were evaluated in the overall population and in prespecified subgroups categorized by baseline HF history (as reported by the investigators).

RESULTS: Overall, 7352 patients were included in these analyses; 571 (7.8%) had a history of HF at baseline. New-onset HF was significantly reduced with finerenone versus placebo (1.9% versus 2.8%; hazard ratio [HR], 0.68 [95% CI, 0.50–0.93]; *P*=0.0162). In the overall population, the incidences of all HF outcomes analyzed were significantly lower with finerenone than placebo, including an 18% lower risk of cardiovascular death or first HHF (HR, 0.82 [95% CI, 0.70–0.95]; *P*=0.011), a 29% lower risk of first HHF (HR, 0.71 [95% CI, 0.56–0.90]; *P*=0.0043) and a 30% lower rate of total HHF (rate ratio, 0.70 [95% CI, 0.52–0.94]). The effects of finerenone on improving HF outcomes were not modified by a history of HF. The incidence of treatment-emergent adverse events was balanced between treatment groups.

CONCLUSIONS: The results from these FIGARO-DKD analyses demonstrate that finerenone reduces new-onset HF and improves other HF outcomes in patients with chronic kidney disease and type 2 diabetes, irrespective of a history of HF.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02545049.

Key Words: aldosterone ■ chronic kidney disease ■ type 2 diabetes ■ finerenone ■ heart failure ■ mineralocorticoid receptor antagonist



32% reduction in new onset HF

ESC European Society of Cardiology
European Heart Journal (2022) 43, 474–484
https://doi.org/10.1093/eurheartj/ehab777

FASTTRACK CLINICAL RESEARCH
Diabetes and metabolic disorders

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis

Rajiv Agarwal [1*†], Gerasimos Filippatos [2*†], Bertram Pitt [3], Stefan D. Anker [4], Peter Rossing [5,6], Amer Joseph [7], Peter Kolkhof [8], Christina Nowack [9], Martin Gebel [10], Luis M. Ruilope [11,12,13], and George L. Bakris [14]; on behalf of the FIDELIO-DKD and FIGARO-DKD investigators [‡]

[1]Indiana University School of Medicine and Richard L. Roudebush VA Medical Center, 1481 W. 10th St, Indianapolis, IN 46202, USA; [2]Department of Cardiology, Attikon University Hospital, Rimini 1, Chaidari 124 62, Athens, Greece; [3]Department of Medicine, University of Michigan School of Medicine, 1500 E. Medical Centre Dr #6303, Ann Arbor, MI 48109, USA; [4]Department of Cardiology (CVK) and Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research Partner Site Berlin, CharitéUniversitätsmedizin, Charitépl. 1, 10117 Berlin, Germany; [5]Steno Diabetes Center Copenhagen, Niels Steensens Vej 2-4, 2820 Gentofte, Denmark; [6]Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3b 315, DK-2200 Copenhagen, Denmark; [7]Cardiology and Nephrology Clinical Development, Bayer AG, Müllerstraße 178, 13353 Berlin, Germany; [8]Research and Development, Preclinical Research Cardiovascular, Bayer AG, Friedrich-Ebert-Straße 217-333, 42117, Wuppertal, Germany; [9]Research and Development, Clinical Development Operations, Bayer AG, Friedrich-Ebert-Straße 217-333, 42117, Wuppertal, Germany; [10]Research and Development, Integrated Analysis Statistics, Bayer AG, Friedrich-Ebert-Straße 217-333, 42117, Wuppertal, Germany; [11]Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Instituto de Investigación Hospital 12 de OctubreCentro de ActividadesAmbulatorias, 6ª Planta Bloque DAvda. de Córdoba, s/n28041 Madrid, Spain; [12]CIBER-CV, Hospital Universitario 12 de Octubre, Av. de Córdoba, s/n, 28041, Madrid, Spain; [13]Faculty of Sport Sciences, European University of Madrid, C. Tajo, s/n, 28670 Villaviciosa de Odón, Madrid, Spain; and [14]Department of Medicine, University of Chicago Medicine, 5841 South Maryland Avenue, MC 6092, 60637 Chicago, IL, USA

Received 27 August 2021; revised 23 September 2021; editorial decision 26 October 2021; accepted 1 November 2021; online publish-ahead-of-print 22 November 2021

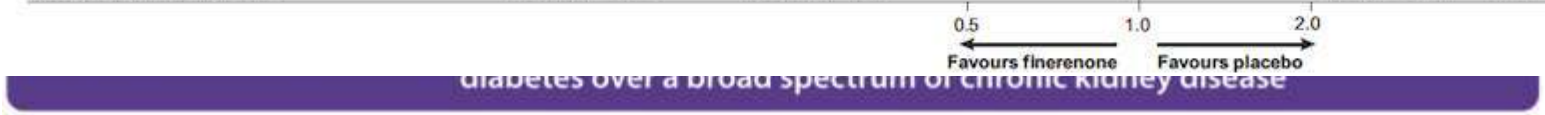
See the editorial comment for this article 'Bringing FIDELITY to the estimate of treatment effects of finerenone in chronic kidney disease due to type 2 diabetes', by Carly Adamson and Pardeep S. Jhund, https://doi.org/10.1093/eurheartj/ehab827.

Aims The complementary studies FIDELIO-DKD and FIGARO-DKD in patients with type 2 diabetes and chronic kidney disease (CKD) examined cardiovascular and kidney outcomes in different, overlapping stages of CKD. The purpose of the FIDELITY analysis was to perform an individual patient-level prespecified pooled efficacy and safety analysis across a broad spectrum of CKD to provide more robust estimates of safety and efficacy of finerenone compared with placebo.

Methods and results For this prespecified analysis, two phase III, multicentre, double-blind trials involving patients with CKD and type 2 diabetes, randomized 1:1 to finerenone or placebo, were combined. Main time-to-event efficacy outcomes were a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, and a composite of kidney failure, a sustained ≥57% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death. Among 13 026 patients with a median follow-up of 3.0 years (interquartile range 2.3–3.8 years), the composite cardiovascular outcome occurred in 825 (12.7%) patients receiving finerenone and 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; $P = 0.0002$). Overall safety outcomes were generally similar between treatment arms. Hyperkalaemia leading to permanent treatment discontinuation occurred more frequently in patients receiving finerenone (1.7%) than placebo (0.6%).

Conclusion Finerenone reduced the risk of clinically important cardiovascular and kidney outcomes vs. placebo across the spectrum of CKD in patients with type 2 diabetes.

Outcome	Finerenone (n = 6519)		Placebo (n = 6507)		Hazard ratio (95% CI)	*P*-value[a]
	Number of patients with event (%)	Number of patients with event per 100 patient-years	Number of patients with event (%)	Number of patients with event per 100 patient-years		
Composite cardiovascular outcome[b]	825 (12.7)	4.34	939 (14.4)	5.01	0.86 (0.78–0.95)	0.0018
Death from cardiovascular causes	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
Non-fatal myocardial infarction	173 (2.7)	0.88	189 (2.9)	0.97	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	1.01	198 (3.0)	1.02	0.99 (0.82–1.21)	0.95
Hospitalization for heart failure	256 (3.9)	1.31	325 (5.0)	1.68	0.78 (0.66–0.92)	0.0030
eGFR ≥57% composite kidney outcome[c]	360 (5.5)	1.96	465 (7.1)	2.55	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	1.38	297 (4.6)	1.62	0.84 (0.71–0.99)	0.039
End-stage kidney disease[d]	151 (2.3)	0.76	188 (2.9)	0.96	0.80 (0.64–0.99)	0.040[e]
Sustained decrease in eGFR to <15 mL/min/1.73 m²	195 (3.0)	1.06	237 (3.6)	1.29	0.81 (0.67–0.98)	0.026[e]
Sustained ≥57% decrease in eGFR from baseline	257 (3.9)	1.40	361 (5.5)	4.03	0.70 (0.60–0.83)	< 0.0001
Renal death	2 (<0.1)	0.01	4 (<0.1)	0.02	0.53 (0.10–2.91)	0.46[e]
eGFR ≥40% composite kidney outcome[f]	854 (13.1)	4.81	995 (15.3)	5.64	0.85 (0.77–0.93)	0.0004
Sustained ≥40% decrease in eGFR from baseline	817 (12.5)	4.60	962 (14.8)	5.45	0.84 (0.76–0.92)	0.0002
Death from any cause	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–>1.00[g])	0.051[e]
Hospitalization for any cause	2836 (43.5)	19.04	2926 (45.0)	19.91	0.96 (0.91–1.01)	0.087[e]



diabetes over a broad spectrum of chronic kidney disease

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

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

*Paul R Kalra, John G F Cleland, Mark C Petrie, Elizabeth A Thomson, Philip A Kalra, Iain B Squire, Faiza Z Ahmed, Abdallah Al-Mohammad, Peter J Cowburn, Paul W X Foley, Fraser J Graham, Alan G Japp, Rebecca E Lane, Ninian N Lang, Andrew J Ludman, Iain C Macdougall, Pierpaolo Pellicori, Robin Ray, Michele Robertson, Alison Seed, Ian Ford, for the IRONMAN Study Group**

Summary

Background For patients with heart failure, reduced left ventricular ejection fraction and iron deficiency, intravenous ferric carboxymaltose administration improves quality of life and exercise capacity in the short-term and reduces hospital admissions for heart failure up to 1 year. We aimed to evaluate the longer-term effects of intravenous ferric derisomaltose on cardiovascular events in patients with heart failure.

Methods IRONMAN was a prospective, randomised, open-label, blinded-endpoint trial done at 70 hospitals in the UK. Patients aged 18 years or older with heart failure (left ventricular ejection fraction ≤45%) and transferrin saturation less than 20% or serum ferritin less than 100 µg/L were eligible. Participants were randomly assigned (1:1) using a web-based system to intravenous ferric derisomaltose or usual care, stratified by recruitment context and trial site. The trial was open label, with masked adjudication of the outcomes. Intravenous ferric derisomaltose dose was determined by patient bodyweight and haemoglobin concentration. The primary outcome was recurrent hospital admissions for heart failure and cardiovascular death, assessed in all validly randomly assigned patients. Safety was assessed in all patients assigned to ferric derisomaltose who received at least one infusion and all patients assigned to usual care. A COVID-19 sensitivity analysis censoring follow-up on Sept 30, 2020, was prespecified. IRONMAN is registered with ClinicalTrials.gov, NCT02642562.

Findings Between Aug 25, 2016, and Oct 15, 2021, 1869 patients were screened for eligibility, of whom 1137 were randomly assigned to receive intravenous ferric derisomaltose (n=569) or usual care (n=568). Median follow-up was 2·7 years (IQR 1·8–3·6). 336 primary endpoints (22·4 per 100 patient-years) occurred in the ferric derisomaltose group and 411 (27·5 per 100 patient-years) occurred in the usual care group (rate ratio [RR] 0·82 [95% CI 0·66 to 1·02]; p=0·070). In the COVID-19 analysis, 210 primary endpoints (22·3 per 100 patient-years) occurred in the ferric derisomaltose group compared with 280 (29·3 per 100 patient-years) in the usual care group (RR 0·76 [95% CI 0·58 to 1·00]; p=0·047). No between-group differences in deaths or hospitalisations due to infections were observed. Fewer patients in the ferric derisomaltose group had cardiac serious adverse events (200 [36%]) than in the usual care group (243 [43%]; difference −7·00% [95% CI −12·69 to −1·32]; p=0·016).

Interpretation For a broad range of patients with heart failure, reduced left ventricular ejection fraction and iron deficiency, intravenous ferric derisomaltose administration was associated with a lower risk of hospital admissions for heart failure and cardiovascular death, further supporting the benefit of iron repletion in this population.

Funding British Heart Foundation and Pharmacosmos.

Lancet 2022; 400: 2199–209

Published Online November 5, 2022 https://doi.org/10.1016/S0140-6736(22)02078-5

See Comment page 2158

*Members listed in the appendix (pp 3–7)

Department of Cardiology, Portsmouth Hospitals University NHS Trust, Portsmouth, UK (Prof P R Kalra MD); College of Medical, Veterinary and Life Sciences (Prof P R Kalra), School of Cardiovascular and Metabolic Health (Prof) G F Cleland MD, Prof M C Petrie MBChB, N N Lang PhD, P Pellicori MD), and Robertson Centre for Biostatistics (E A Thomson MA, F J Graham MRCP, M Robertson BSc, Prof I Ford PhD) University of Glasgow, Glasgow, UK; Faculty of Science and Health, University of Portsmouth, Portsmouth, UK (Prof P R Kalra); Department of Renal Medicine, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK (Prof P A Kalra MD); Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK (Prof P A Kalra); Department of Cardiovascular Sciences, University of Leicester, Leicester, UK (Prof I B Squire MD); Department of Cardiology, Manchester University NHS Foundation Trust, Manchester, UK (F Z Ahmed MD); Department of Cardiology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (Prof A Al-Mohammad MD); Department of Infection, Immunity and Cardiovascular Disease, The University of

Introduction

Iron deficiency is common in patients with chronic heart failure, irrespective of left ventricular ejection fraction or haemoglobin concentrations, and is independently associated with more severe symptoms, poorer exercise capacity, and an increased risk of hospitalisation and death.[1–4] Motivated by placebo-controlled trials reporting that intravenous ferric carboxymaltose can improve quality of life and exercise capacity assessed at 24 weeks for ambulatory patients with heart failure and a reduced ejection fraction,[5,6] we conducted the Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency (IRONMAN) trial. We aimed to investigate the long-term effects of repeated doses of intravenous ferric derisomaltose on hospital admission due to heart failure and cardiovascular death in a broad range of patients with heart failure and iron deficiency. Given that there are theoretical risks of repeated doses of intravenous iron, including a potential increase in

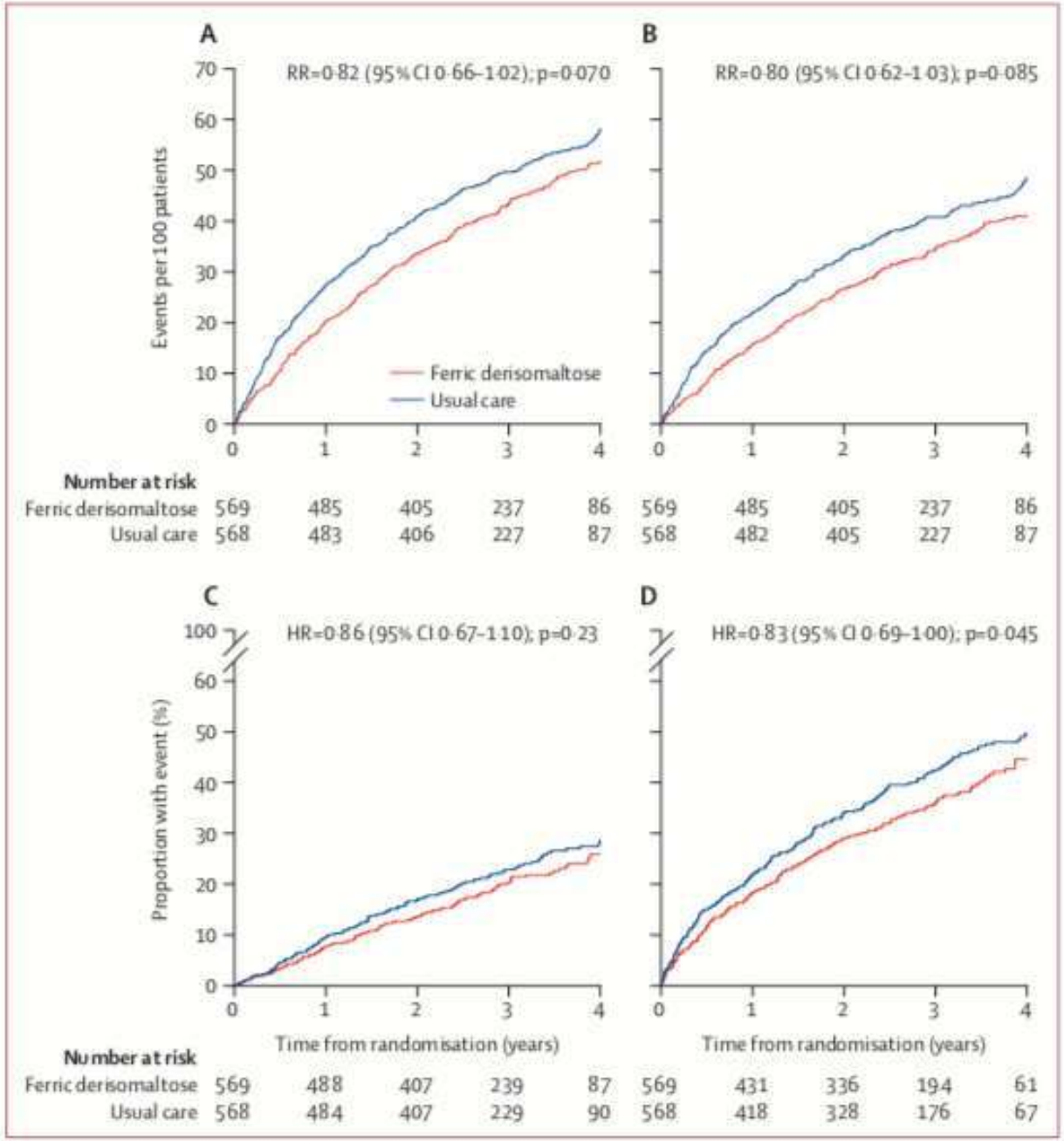


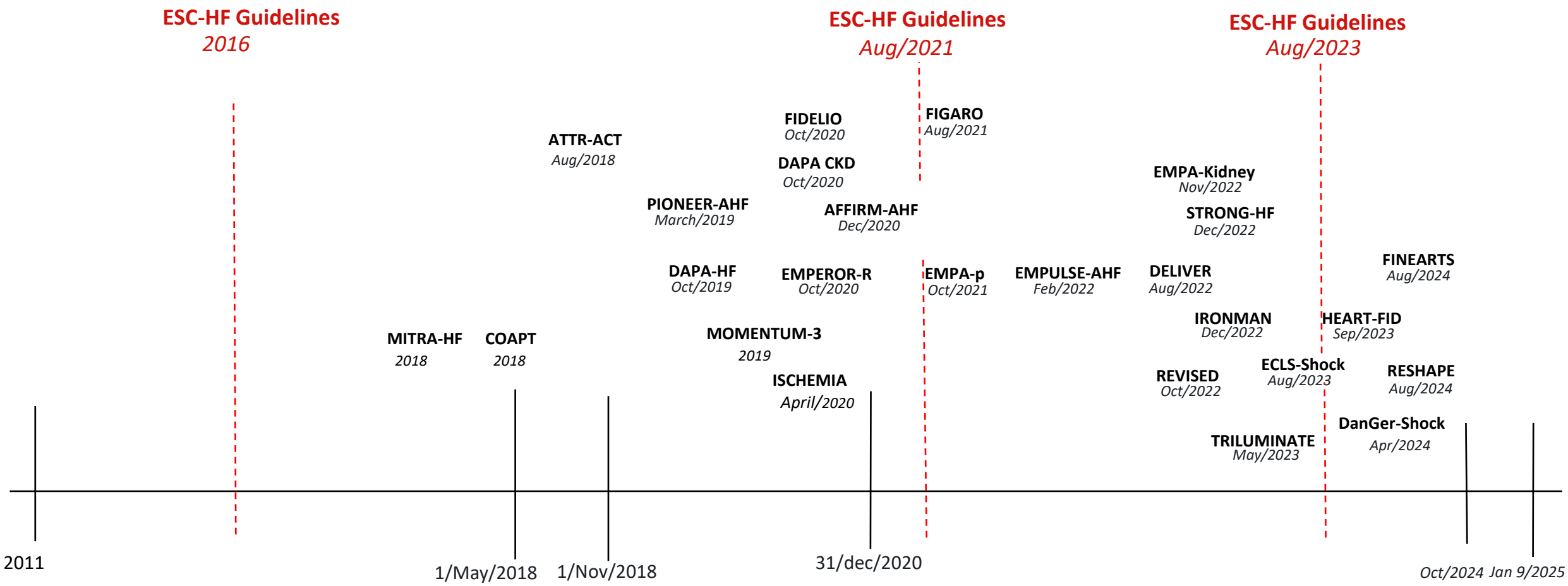
Figure 2: Estimated mean frequency functions and cumulative incidence curves for key cardiovascular

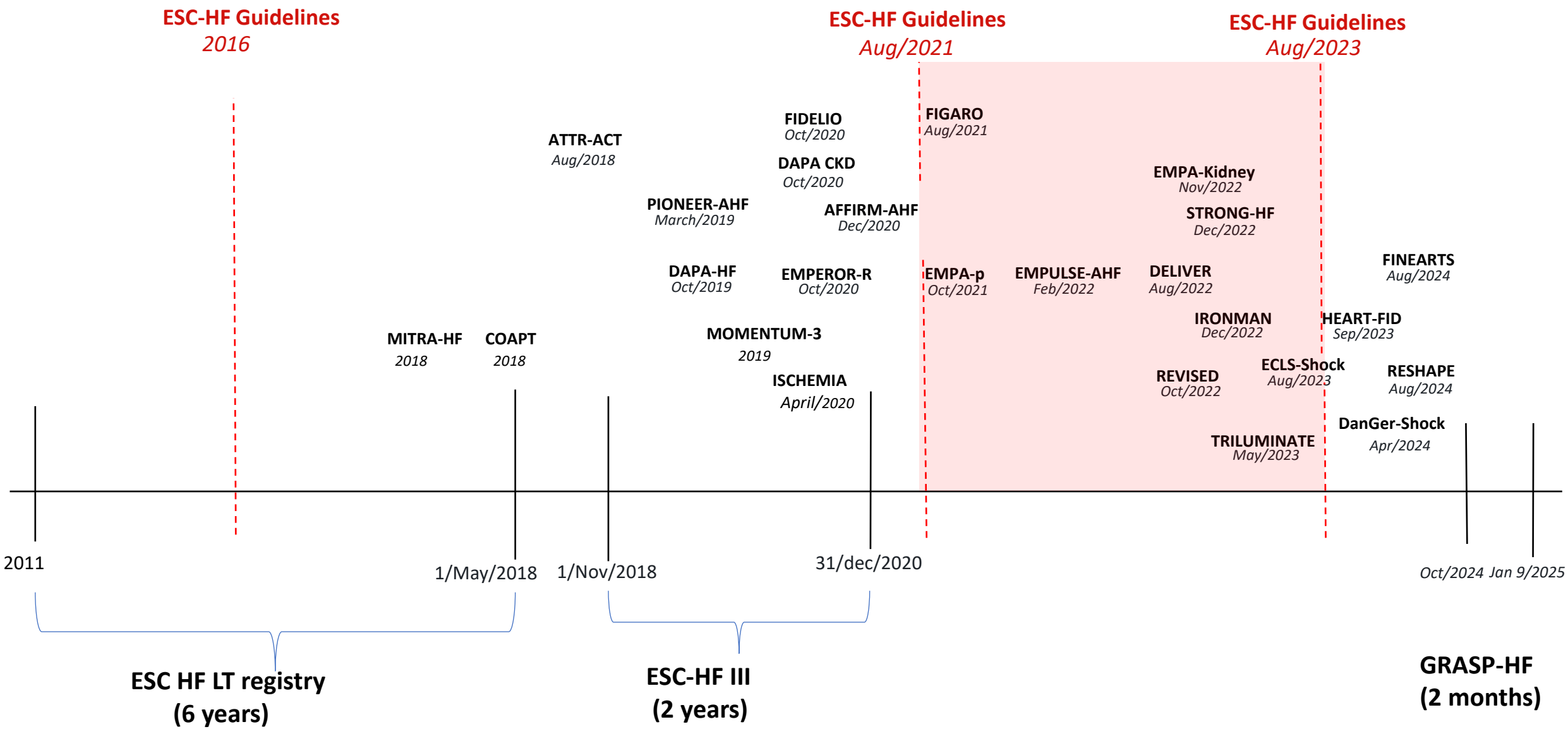
Recommendations	Class[a]	Level[b]
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.[c] [12,41,47–49]	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose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

Other RCTs not included

- **COACH** (Comparison of Outcomes and Access to Care for Heart Failure),
- **PIVOTAL** (Proactive IV Iron Therapy in Haemodialysis Patients),
- **REVIVED-BCIS2** (Revascularization for Ischemic Ventricular Dysfunction)
- **TRANSFORM-HF** (Torsemide Comparison with Furosemide for Management of Heart Failure),
- **TRILUMINATE** Pivotal (Clinical Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System).

- **PUSH-AHF**
- **HEART-FID**


ESC-HF Guidelines
2016
ESC-HF Guidelines
Aug/2021
ESC-HF Guidelines
Aug/2023
ATTR-ACT
Aug/2018
FIDELIO
Oct/2020
FIGARO
Aug/2021
DAPA CKD
Oct/2020
EMPA-Kidney
Nov/2022
PIONEER-AHF
March/2019
AFFIRM-AHF
Dec/2020
STRONG-HF
Dec/2022
DAPA-HF
Oct/2019
EMPEROR-R
Oct/2020
EMPA-p
Oct/2021
EMPULSE-AHF
Feb/2022
DELIVER
Aug/2022
FINEARTS
Aug/2024
IRONMAN
Dec/2022
HEART-FID
Sep/2023
MITRA-HF
2018
COAPT
2018
MOMENTUM-3
2019
ISCHEMIA
April/2020
REVISED
Oct/2022
ECLS-Shock
Aug/2023
RESHAPE
Aug/2024
DanGer-Shock
Apr/2024
TRILUMINATE
May/2023
2011
1/May/2018
1/Nov/2018
31/dec/2020
Oct/2024
Jan 9/2025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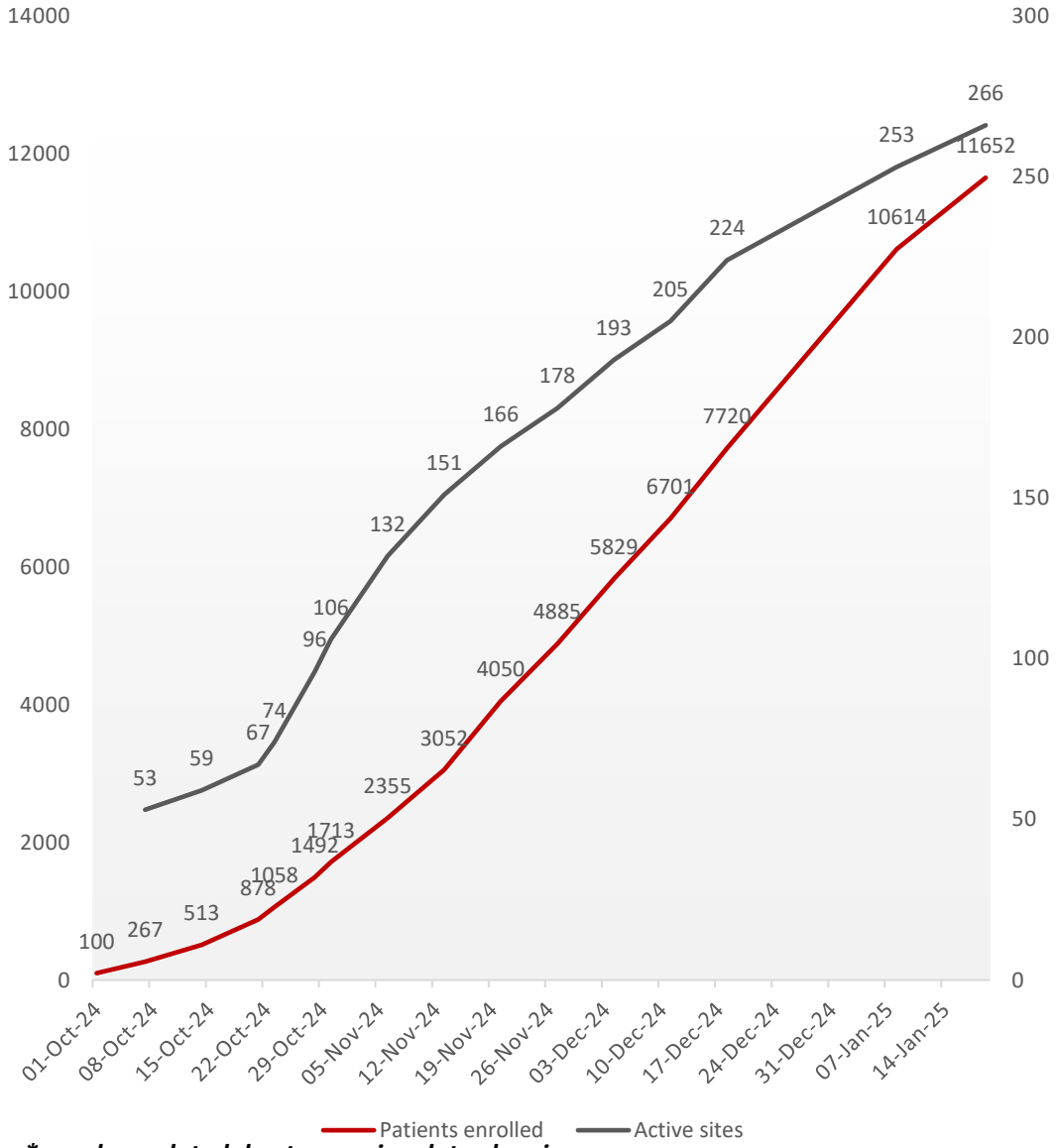
TRILUMINATE
May/2023
2011
1/May/2018
1/Nov/2018
31/dec/2020
Oct/2024
Jan 9/2025
ESC HF LT registry
(6 years)
ESC-HF III
(2 years)
GRASP-HF
(2 months)

GRASP-HF



**may be updated due to ongoing data cleaning*

11.652 recruited patients

(in the shortest time period as compared to other registries)

Enrolment start date: 27-SEP-2024

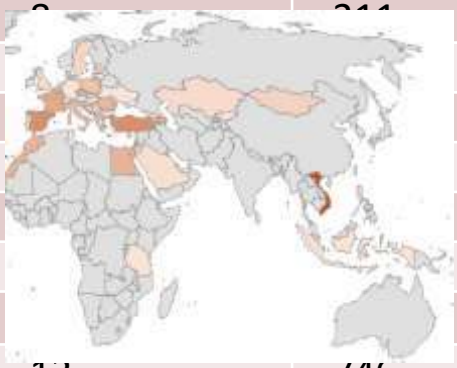
Enrolment end date: 09-JAN-2025

2 months consecutive enrollment/center

Activation of centers based on:

- **Ethics approval**
- **Fully executed agreement with ESC**

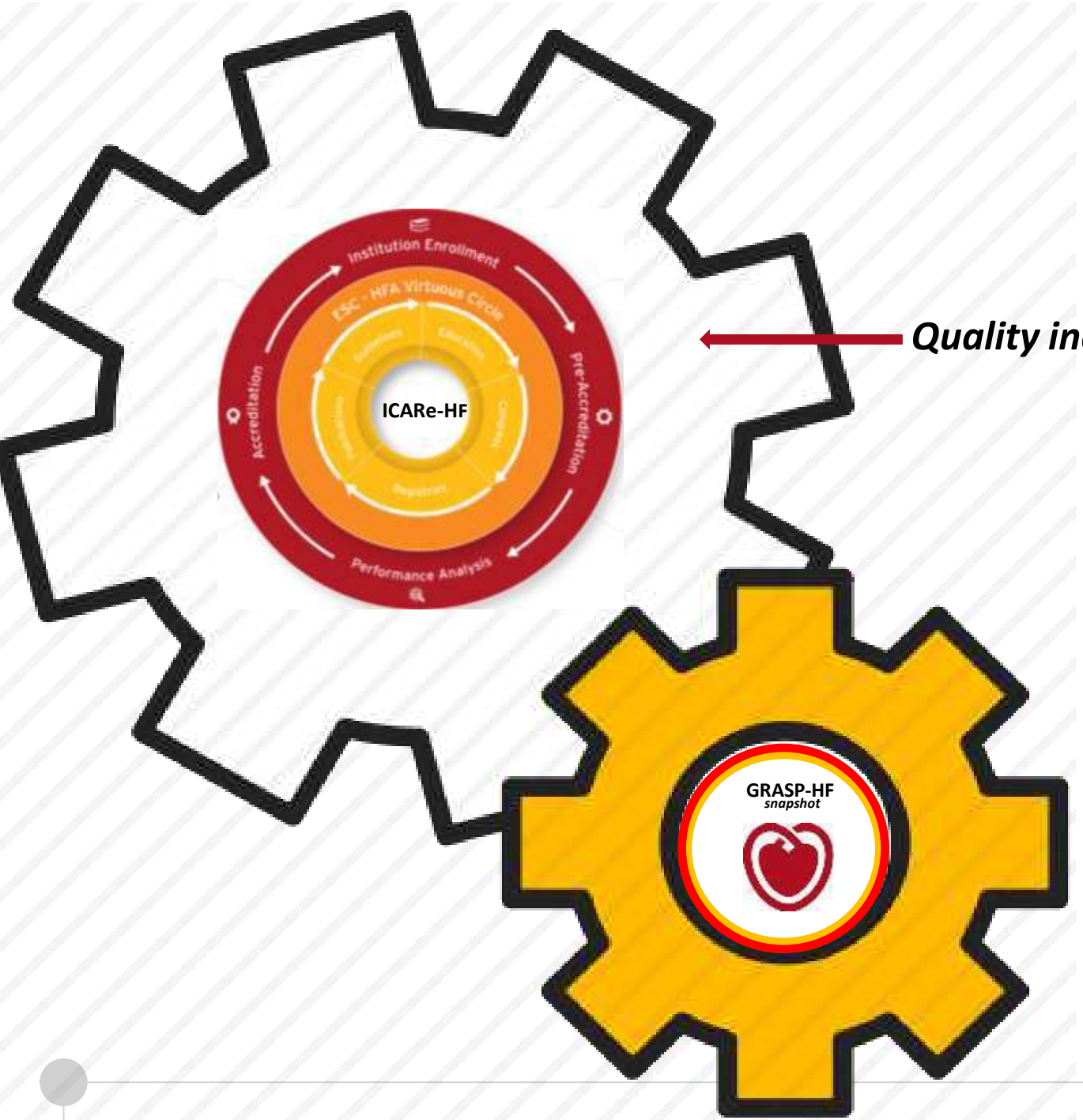
Country	Centers per country	Patients per country
Armenia	**3**	**429**
Azerbaijan	**16**	**206**
Belgium		
Bhutan		
Bosnia & Herzegovina		
Bulgaria		
Croatia		
Cyprus		
Czech Republic		
Egypt	13	746
Estonia	3	66
France	16	342
Georgia	2	68
Germany	1	387
Greece	4	88
Hungary	3	50
Indonesia	1	50
Israel	1	102
Italy	11	277
Jordan		
Kazakhstan		
Kosovo		
Kyrgyzstan	1	238



Country	Centers per country	Patients per country
Latvia	2	31
Lithuania	2	177
Malta	1	32
Mongolia	5	65
Morocco	13	683
North Macedonia	4	78
Poland	9	289
Portugal	4	481
Romania	12	617
Saudi Arabia	2	225
Serbia	4	249
Singapore	1	32
Slovakia	4	82
Spain	**22**	**650**
Sweden	4	92
Switzerland	1	102
Tanzania	1	0
Tunisia	1	151
Türkiye	22	559
		115
		100
		73
Vietnam	39	1811

Big Thank You to Azerbaijan

ESC-HF Guidelines



Quality indicators

ESC
Educational programs

NHFSs