Evolutions in care, unmet needs, and research priorities in heart failure

Halliday, Brian P; Ahmed, Fozia Z; Beezer, Janine; Fuat, Ahmet; Ludman, Andrew J; Pellicori, Pierpaolo; Oluwasefunmi Savage, Henry ; Taylor, Clare J; Cleland, John G F

DOI:
10.1136/conmed-2024-000010

Document Version
Peer reviewed version

Citation for published version (Harvard):
Halliday, BP, Ahmed, FZ, Beezer, J, Fuat, A, Ludman, AJ, Pellicori, P, Oluwasefunmi Savage, H, Taylor, CJ & Cleland, JGF 2024, 'Evolutions in care, unmet needs, and research priorities in heart failure', *BMJ Considerations in Medicine*, vol. 3, no. 1, e000010. https://doi.org/10.1136/conmed-2024-000010

Evolutions in care, unmet needs, and research priorities in heart failure

Brian P Halliday,[1] Fozia Z Ahmed,[2] Janine Beezer,[3] Ahmet Fuat,[4] Andrew J Ludman,[5] Pierpaolo Pellicori,[6] Henry Oluwasefunmi Savage,[7] Clare J Taylor,[8] John GF Cleland[9]

[1]Royal Brompton Hospital, Guy's and St Thomas' NHS Foundation Trust & National Heart and Lung Institute, Imperial College London

[2] Department of Cardiology, Manchester University NHS Foundation Trust, Manchester, UK

[3]South Tyneside and Sunderland NHS Foundation Trust

[4]Durham University

[5] Royal Devon University Healthcare NHS Foundation Trust

[6]University of Glasgow

[7]Mid and South Essex NHS Foundation Trust

[8]University of Oxford

[9]Royal Brompton and Harefield Hospitals

Correspondence to Brian Halliday, Royal Brompton Hospital, Sydney Street

London SW3 6NP

Email: b.halliday@imperial.ac.uk

Abstract

The current treatment landscape for heart failure is predominantly stratified using ejection fraction. Established drug combinations and devices such as cardiac resynchronisation therapy are available for heart failure with reduced ejection fraction (HFrEF), but medical options for heart failure with preserved ejection fraction (HFpEF) have been lacking.

A major advance in recent years has been the discovery of effective therapies for HFpEF, including sodium-glucose co-transporter 2 (SGLT2) inhibitors and perhaps also the mineralocorticoid receptor antagonist spironolactone. For patients with atrial fibrillation and heart failure, the benefit of rhythm control with either radiofrequency ablation or medical therapy is uncertain. Targeted therapies for the small proportion of patients with transthyretin cardiac amyloidosis are available, while antifibrotics seem promising for a larger proportion of patients.

For patients with HFrEF, additional treatment options have emerged in the past 10 years. The angiotensin receptor–neprilysin inhibitor (ARNI) combination sacubitril–valsartan and SGLT-2 inhibitors reduce mortality and improve life expectancy in symptomatic patients with HFrEF and at least mildly elevated plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP). The oral soluble guanylate cyclase stimulator vericiguat and cardiac myosin activator omecamtiv mecarbil are not yet licensed in the UK but may provide further treatment options, perhaps in more select groups of patients.

Whether all patients with a prior diagnosis of HFrEF who are now in heart failure remission should continue all therapies at maximum tolerated dose indefinitely remains a dilemma.

Evolutions in care

Individualised de-escalation of therapy remains controversial due to the risk of relapse but is occasionally trialled, particularly in patients with a triggering factor such as pregnancy. The ultimate aim is a personalised treatment plan—based on disease phenotype and trajectory—that minimises the risk of relapse and maximises the individual's quality of life.

Background

Current treatment for heart failure is determined predominantly by ejection fraction. While effective treatments have been available for patients with heart failure with reduced ejection fraction (HFrEF) for about 40 years, discovery of therapy that improves the outcome of patients with heart failure with preserved ejection fraction (HFpEF)has been a more recent achievement. Despite these advances, many questions on how best to manage patients with heart failure remain. This article considers the advances in the past 10 years and highlights questions that remain about the best use of available therapies and the hope for more personalised management targeting the underlying disease mechanism. We also outline directions for future research over the next 10–20 years.

Heart failure with preserved ejection fraction

Advances in treatments

One of the greatest advances in heart failure over the past 10 years has been the discovery of medications that improve clinical outcomes for patients with HFpEF, for whom no effective treatment options were previously available.

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) in patients with HFpEF, New York Heart Association (NYHA) class II–IV symptoms, and NT-proBNP >300 ng/l (>900 ng/l for patients with atrial fibrillation) demonstrated a reduction in the primary composite endpoint of cardiovascular mortality and heart failure hospitalisation with the sodium-glucose cotransporter protein-2 (SGLT-2) inhibitor empagliflozin (also discussed by Ahmed *et al* earlier in this issue). This appeared to be predominantly driven by a reduction in heart failure hospitalisation. A post-hoc analysis of

pooled data from EMPEROR-Preserved and EMPEROR-Reduced (which enrolled patients with HFrEF) showed reductions in heart failure hospitalisations that extended up to a left ventricular ejection fraction (LVEF) of ~65% (1). In the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial, which included patients with LVEF >40%, dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death compared with placebo (2). A patient-level, pooled meta-analysis of findings from Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and DELIVER showed that dapagliflozin reduced the risk of death from cardiovascular causes and hospital admissions across the full range of ejection fractions in patients with heart failure (**Figure 1**).(2)

The results of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) study examining the efficacy of the mineralocorticoid receptor antagonist (MRA), spironolactone in patients with NYHA class II–IV symptoms, LVEF >45%, and NT-proBNP >360 ng/l have been debated. This study included 3,445 patients, 51% of whom were enrolled in North and South America and 49% in Russia and Georgia (3). Across the entire population, spironolactone did not reduce the primary endpoint, which was death from cardiovascular causes, aborted cardiac arrest, or hospitalisation for the management of heart failure (hazard ratio [HR] 0.89 [95% confidence interval (CI) 0.77 to 1.04], p=0.14) (**Figure 2**). However, the authors noted differences in population risk profiles and event rates between the two regions and it was suggested that clinical diagnostic criteria may not have been consistently interpreted or applied in Russia and Georgia (4,5). The magnitude of the effects of spironolactone on blood pressure, potassium, and creatinine also raised doubt over whether treatment administration was in line with protocol in Russia and Georgia, despite higher reported treatment adherence.

A subgroup analysis in the population from the Americas found that spironolactone not only reduced the risk of the primary endpoint (HR 0.74 [95% CI 0.57 to 0.97], p=0.03) but also the risk of all-cause mortality (HR 0.82 [95% CI 0.69 to 0.98], p=0.03). Post-hoc analyses of randomised trials should always be interpreted with caution due to the possibility of random error increasing with the number of analyses performed (4). However, no other treatment for HFpEF has been shown to reduce mortality and given the absence of alternative treatment options for patients with HFpEF until recently, some have advocated cautious use of spironolactone in this patient population based on the results of this post-hoc analysis. These findings also emphasise the importance of effective trial monitoring to ensure accurate application of eligibility criteria and highlights some of the flaws in how compliance is assessed during a trial. The heart 'OMics' in AGEing (HOMAGE) randomized clinical trial, however, found that in people with, or at high risk of coronary disease spironolactone reduced systolic blood pressure, NT-proBNP and left atrial volume, suggesting it may potentially delay the onset of heart failure (6).

Unmet needs and future research

Management of atrial fibrillation beyond anticoagulation is a major challenge in the setting of HFpEF, with uncertainty over the benefit of rhythm control and ablation. Some evidence supports the use of ablation for patients with atrial fibrillation and HFrEF; however, the robustness of data from the Catheter Ablation for Atrial Fibrillation with Heart Failure (CASTLE-AF) trial is debated, as ~10% of patients in the ablation arm did not complete follow-up and a further 15% did not receive the intervention (7). Such an approach has therefore not been universally adopted.[8] Similar evidence is lacking for patients with HFpEF, and such a trial would be challenging due to the heterogeneity of the population, as well as those issues

highlighted in CASTLE-AF. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial investigated the use of low-dose rivaroxaban in more than 27,000 patients with stable coronary artery disease. The absolute benefit of the intervention in reducing major adverse cardiovascular events was greatest in around 6000 patients with mild to moderate heart failure, the majority of whom had preserved LVEF, compared with other groups (8).[9] Rivaroxaban could therefore be considered in this patient group, although caution should be paid to this post-hoc sub-group analysis.

Questions also remain about the efficacy of medical therapies, particularly beta blockers among patients with atrial fibrillation and heart failure. The optimal heart rate for patients with atrial fibrillation and heart failure is debated and whether there is any benefit beyond rate control is unclear(9).[10]

One explanation provided for the lack of effective therapies in HFpEF is the heterogeneity of the disease within this cohort. It is recognised that there may be several different phenogroups of disease, each driven by different mechanisms that may be responsive to different treatments. Improved phenotyping of disease may lead to better and more targeted therapy (10). A small proportion of patients, but perhaps greater than previously appreciated, will have cardiac amyloidosis, particularly transthyretin forms of the disease. Therapies that target this disease process, slowing progression and improving outcomes, have emerged(11). Diagnosing patients early in the disease course by identifying red flags, such as unexplained cardiac hypertrophy or carpal tunnel syndrome and using non-invasive imaging methods such as ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or magnetic resonance

imaging (MRI), will be key to improving outcomes in patients for whom such treatments are available.

Therapies targeting fibrosis, a ubiquitous component of HFpEF and an important driver of disease (12), may be more relevant for a larger proportion of the HFpEF population. A double-blind, placebo-controlled trial of pirfenidone—a targeted antifibrotic medication previously used in interstitial lung disease—in patients with HFpEF with markers of interstitial fibrosis on cardiovascular MRI demonstrated reductions in fibrosis over follow-up (13). The findings of this study require validation in a larger cohort. Spironolactone has seldom been used in the HFpEF population on account of the initial results of TOPCAT (4),[4] but it is now being used more widely with the results of the post-hoc analysis[7] and ESC guidance supporting its use in the mEF range (14).

Heart failure with reduced ejection fraction

Advances in treatments

For patients with HFrEF, two of the biggest advances over the past 10 years have been the introduction of the ARNi combination sacubitril–valsartan and SGLT2 inhibitors. When combined with beta blockers and MRAs in quadruple therapy, these new treatments have produced large reductions in mortality and improved quality of life for patients with symptomatic heart failure and elevated NT-proBNP (15), as described by Ahmed *et al* earlier in this issue. Whether asymptomatic patients or those with lower plasma concentrations of natriuretic peptides who have milder forms of the disease gain similar relative risk reductions in adverse outcome remains unclear. Even if the relative benefit will be the same, absolute risk reduction might be small in this cohort, perhaps not justifying the costs of additional

treatments. With greater emphasis being appropriately placed on prevention of heart failure and identification of larger number of patients at risk of developing heart failure, these are important questions to pursue.

Heart failure in remission

Whether patients who experience resolution of symptoms and improvement in LVEF continue to gain benefit from all four therapies at maximum tolerated doses is unclear. This is relevant to a growing group of individuals and is considered important by many. Examples include a 30-year-old woman with a previous diagnosis of peripartum cardiomyopathy who has resolution of symptoms and wishes to become pregnant or, alternatively, an elderly patient with multiple comorbidities who is experiencing fatigue and light-headedness and attributes these symptoms to therapies for heart failure. The Therapy withdrawal in REcovered Dilated cardiomyopathy (TRED-HF) trial found that at least half of patients with heart failure and improved ejection fraction relapsed when all pharmacological therapy was discontinued (**Figure 3**)(16,17). This confirms that complete cessation of all therapies should generally not be performed. However, whether individualised de-escalation of therapy is safe and improves quality of life is uncertain. Given the increasing number of medications available, ways of tailoring therapy to the individual to minimise side effects and reduce the risk of relapse are becoming a growing priority.

Indeed, the rising number of drug options available to manage heart failure makes de-escalation strategies increasingly attractive, given that many patients with heart failure experience polypharmacy. A systematic review found the prevalence of polypharmacy, typically

defined as ≥5 medications, ranged from 17.2% to 99% (18). One study in patients with heart failure hospitalisations found that 84% of patients at admission and 95% at discharge took ≥5 medications and 42% at admission and 55% at discharge took ≥10 medications, with non-cardiovascular drugs accounting for most medications taken by older adults with heart failure (19). Polypharmacy presents challenges, such as increased adverse events and reduced concordance. It is good practice to review medications regularly and stop those that are either unnecessary or contraindicated in heart failure.

Methods

A group of experts gathered for an in-depth consideration of recent advances and future prospects for the management of heart failure. Following a brief presentation, we drew on our clinical and research experience to discuss the current and potential future management paradigm. Case studies, featuring distinct presentations of heart failure in two patients, were provided to aid the discussion. We further discussed approaches to educate the public and improve clinical practice, reviewing evidence for new drugs, identifying unmet needs, and identifying research priorities for the future.

Discussion

The absolute benefit in EMPEROR-Preserved was small, patients did not feel better or live longer, and ejection fraction at baseline was more akin to mildly reduced ejection fraction. The evidence for SGLT2 inhibitors also largely derived from the outpatient setting, and caution is warranted when using these drugs for in-patients with acute heart failure, as it is currently uncertain whether decreases in estimated glomerular filtration rate (eGFR) result from these drugs or are a harmful side effect of diuretics, and this can cause a degree of clinical confusion

and ambiguity that may inadvertently increase length of stay. Since the discussion, the EMPagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalised for acUte Heart faiLure (de novo or decompensated chronic HF) Who Have Been StabilisEd (EMPULSE) trial has provided encouraging data on the safety and efficacy of initiating empagliflozin in acute heart failure, allaying some of these concerns (20) . In addition, results of the DELIVER trial have also been published since the discussion and are encouraging for patients with LVEF >40% (2). A post-hoc analysis of the DAPA-HF trial has also demonstrated a favourable association between a decline in eGFR after initiation of dapagliflozin and improved heart failure and renal outcomes (21).

Neither the oral soluble guanylate cyclase stimulator vericiguat nor the cardiac myosin activator omecamtiv mecarbil are yet available in the UK, but these drugs may provide further treatment options for patients with HFrEF. In the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) study, vericiguat reduced the incidence of death from cardiovascular causes and hospitalisation for heart failure compared with placebo (22). In the Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) trial, omecamtiv mecarbil had a lower incidence of a composite of a heart failure event or death from cardiovascular causes than those who received placebo, although the number needed to treat was very large when applied to patients with LVEF <40% (23). These drugs are likely to be restricted to niche populations in whom they are identified to work best: potentially those with most advanced disease, those who cannot tolerate sacubitril–valsartan due to low blood pressure and those with a sarcomeric cause for their heart failure.

Evolutions in care

It is important to ensure that patients have received optimised and contemporary medical therapy before they are referred for cardiac resynchronisation therapy or an implantable cardioverter-defibrillator.

A personalised plan should be in place for every patient to outline stages throughout the pathway where medication use can be reviewed. This should cover not only de-escalation but also defined escalation of therapy that can be managed by primary care or through 'rescue packs' of drugs such as diuretics that patients keep at home. This strategy is used for patients with other long-term conditions such as chronic obstructive pulmonary disease, which can reduce the need for clinic visits and provide patients with some reassurance should their symptoms worsen. Telemonitoring programmes can support this type of approach, with patients directed to alter their diuretic dose based on deviations from their ideal weight.

The continued need for implantable devices also needs to be considered, particularly for patients with non-ischaemic pathology in whom heart function may recover. Current guidelines recommend that use of implantable devices is considered after 3 months of optimal medical therapy (14). However, some patients continue to experience reverse remodelling after this time point and such patients have a markedly lower risk of major arrhythmia in the long-term. Factors that indicate prognosis and the chance of recovery can be useful to support the decision to maintain or remove the implant—for example, patients without evidence of fibrosis and with low NT-proBNP levels are more likely to have a favourable prognosis, while those with fibrosis and an unfavourable genetic profile are less likely to recover and may benefit from devices at an earlier stage (24).

However, de-escalation must be approached with great caution in patients without a triggering factor such as pregnancy, as it is not possible to unequivocally identify which therapy or combination of therapies has been effective in improving ejection fraction, particularly in the modern era of parallel initiation of medications. Research is needed to predict outcomes and biochemical consequences when therapies are tapered down based on disease characteristics in order to personalise therapy, as well as to predict the small number of patients with dilated cardiomyopathy who relapse suddenly after doing well on treatment for some years (25) . Careful consideration will need to be given to which clinicians take the lead on medicines optimisation and de-escalation. Hospital or primary care pharmacists could have a key role, as they will be able to take a more holistic view of the patient's overall medication list. However, close collaboration led by experienced disease specialists is needed to determine which drugs could be de-escalated and to identify patients at risk of relapse, which includes patients who developed heart failure following infection with COVID-19.

Key points

- Treatment options for heart failure differ depending on left ventricular ejection fraction. More targeted approaches stratified by disease mechanism largely remain an ambition.
- Established drug combinations have been available for heart failure with reduced ejection fraction (HFrEF) for 40 years, with effective therapies for heart failure with preserved ejection fraction (HFpEF) only discovered more recently.
- Emerging potential therapies for HFpEF includes sodium-glucose co-transporter 2 (SGLT2) inhibitors, spironolactone, and therapies to target underlying amyloidosis and fibrosis.
- Sacubitril–valsartan and SGLT2 inhibitors form cornerstones of therapy for patients with symptomatic HFrEF and elevated natriuretic peptides. Other agents such as vericiguat and omecamtiv mecarbil are likely to have a more limited role, perhaps for specific subgroups of patients.
- For patients with improved cardiac function, individualised approaches to therapy that are stratified by disease mechanism and aim to minimise the risk of relapse while maximising quality of life should be the ambition.

References

1. Butler J, Packer M, Filippatos G, Ferreira JP, Zeller C, Schnee J, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. Eur Heart J. 2022 Feb 3;43(5):416–26.

2. Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. Nat Med. 2022 Sep;28(9):1956–64.

3. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014 Apr 10;370(15):1383–92.

4. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation. 2015 Jan 6;131(1):34–42.

5. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. Circ Res. 2019 May 24;124(11):1598–617.

6. Cleland JGF, Ferreira JP, Mariottoni B, Pellicori P, Cuthbert J, Verdonschot JAJ, et al. The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: the heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. Eur Heart J. 2021 Feb 7;42(6):684–96.

7. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. N Engl J Med. 2018 Feb 1;378(5):417–27.

8. Branch KR, Probstfield JL, Eikelboom JW, Bosch J, Maggioni AP, Cheng RK, et al. Rivaroxaban With or Without Aspirin in Patients With Heart Failure and Chronic Coronary or Peripheral Artery Disease. Circulation. 2019 Aug 13;140(7):529–37.

9. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. 2018 Jan 1;39(1):26–35.

10. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, et al. Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction: Detailed Phenotypes, Prognosis, and Response to Spironolactone. JACC Heart Fail. 2020 Mar;8(3):172–84.

11. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007–16.

12. Halliday BP, Prasad SK. The Interstitium in the Hypertrophied Heart. JACC Cardiovasc Imaging. 2019 Nov;12(11 Pt 2):2357–68.

13. Lewis GA, Dodd S, Clayton D, Bedson E, Eccleson H, Schelbert EB, et al. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. Nat Med. 2021 Aug;27(8):1477–82.

14. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599–726.

15. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet Lond Engl. 2020 Jul 11;396(10244):121–8.

16. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. The Lancet. 2019 Jan 5;393(10166):61–73.

17. Halliday BP, Owen R, Gregson J, S Vassiliou V, Chen X, Wage R, et al. Myocardial remodelling after withdrawing therapy for heart failure in patients with recovered dilated cardiomyopathy: insights from TRED-HF. Eur J Heart Fail. 2021 Feb;23(2):293–301.

18. Beezer J, Al Hatrushi M, Husband A, Kurdi A, Forsyth P. Polypharmacy definition and prevalence in heart failure: a systematic review. Heart Fail Rev. 2022 Mar;27(2):465–92.

19. Unlu O, Levitan EB, Reshetnyak E, Kneifati-Hayek J, Diaz I, Archambault A, et al. Polypharmacy in Older Adults Hospitalized for Heart Failure. Circ Heart Fail. 2020 Nov;13(11):e006977.

20. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022 Mar;28(3):568–74.

21. Adamson C, Docherty KF, Heerspink HJL, de Boer RA, Damman K, Inzucchi SE, et al. Initial Decline (Dip) in Estimated Glomerular Filtration Rate After Initiation of Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction: Insights From DAPA-HF. Circulation. 2022 Aug 9;146(6):438–49.

22. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020 May 14;382(20):1883–93.

23. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. N Engl J Med. 2021 Jan 14;384(2):105–16.

24. Halliday BP, Cleland JGF, Goldberger JJ, Prasad SK. Personalizing Risk Stratification for Sudden Death in Dilated Cardiomyopathy: The Past, Present, and Future. Circulation. 2017 Jul 11;136(2):215–31.

25. Ragavan A, Hogan J, Halliday BP. The spectrum of heart failure with improved ejection fraction: persistent congestion, to heart failure remission and perhaps recovery? Eur J Heart Fail. 2022;24(7):1180–2.

Funding

This initiative is sponsored by Boehringer-Ingelheim through the provision of an unrestricted educational grant. Boehringer-Ingelheim has had no influence over the content.

Acknowledgement

Editorial support provided by CESAS Medical.

Competing interests

FZA has previously received a research grant funded by Medtronic, and received consultancy fees from AstraZeneca, Medtronic, Pfizer, Pharmacosmos, Servier and Vifor; JB has received honoraria or consultation fees from Vifor, Novartis, Pharmacosmos, AstraZeneca, Boehringer Ingelheim and Eli Lilly; JGFC reports research grants and honoraria from Abbott, Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Medtronic, NI Medical, Pharmacosmos, Servier, and Vifor Pharma; AF has received honoraria or consultation fees from Astra-Zeneca, Boehringer-Ingelheim, Eli Lilly, Medtroinc, Edwards Scientific; BH declares no conflicts; AJL has received honoraria or consultation fees from AstraZeneca; PP has received consultancy honoraria and/or sponsorship support from Boehringer Ingelheim, Pharmacosmos, Novartis, Vifor, AstraZeneca and Caption Health and research support from Bristol Myers Squibb in the past 5 years, not connected with this manuscript; HOS has received grants/research support from Abbott and honoraria or consultation fees from AstraZeneca and Novartis; CJT has received honoraria or consultation fees from Roche.

Figures

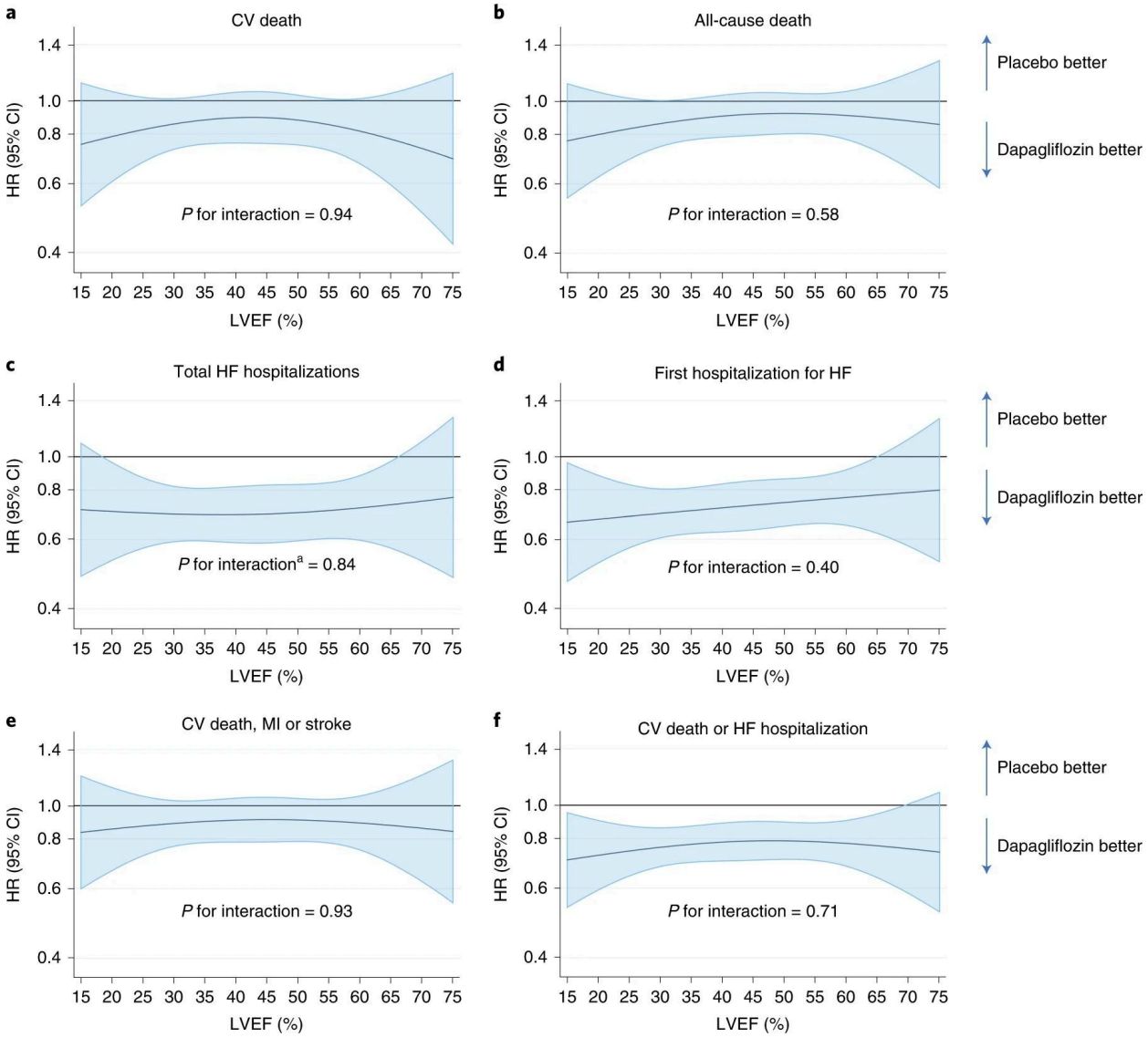

Figure 1. Outcomes with dapagliflozin in patients with heart failure. (Reproduced under CC license. Original figure from Jhund PS et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. Nat Med 28, 1956–1964 (2022). (2)

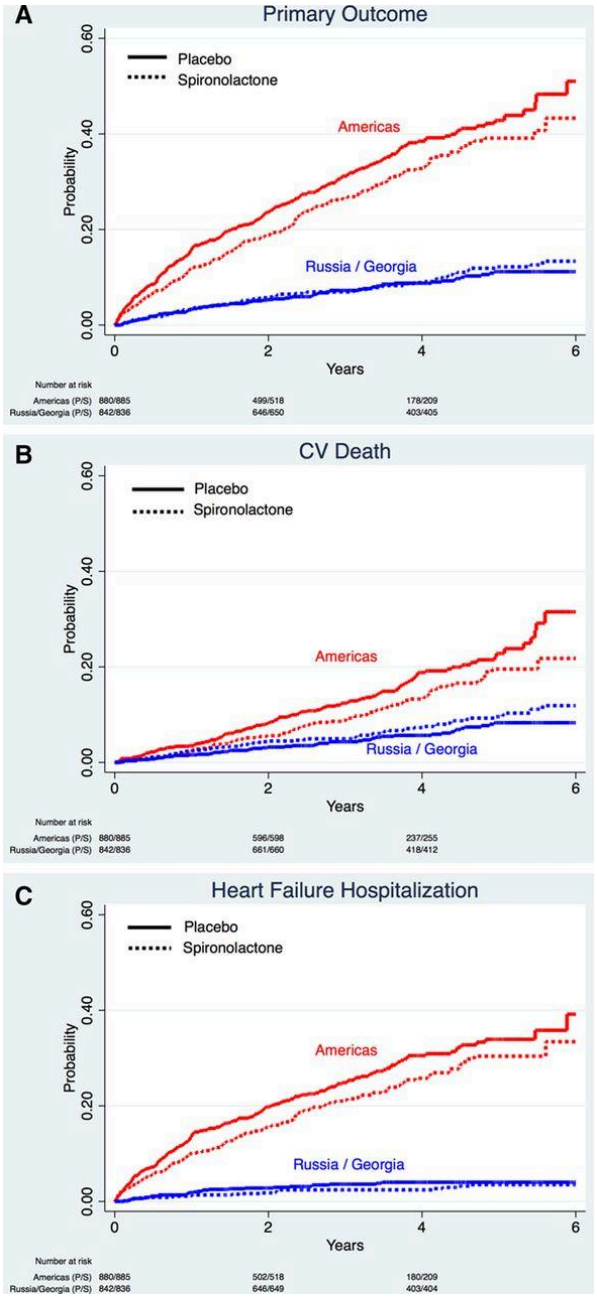

Figure 2. Outcomes with spironolactone in patients with heart failure in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) study by region—composite of death resulting from a cardiovascular cause, aborted cardiac arrest, or hospitalisation for the management of heart failure (a), cardiovascular death (b), and heart failure hospitalisation (c) (Original figure from Pfeffer et al Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial, Circulation 2015;131:34–42 (4).

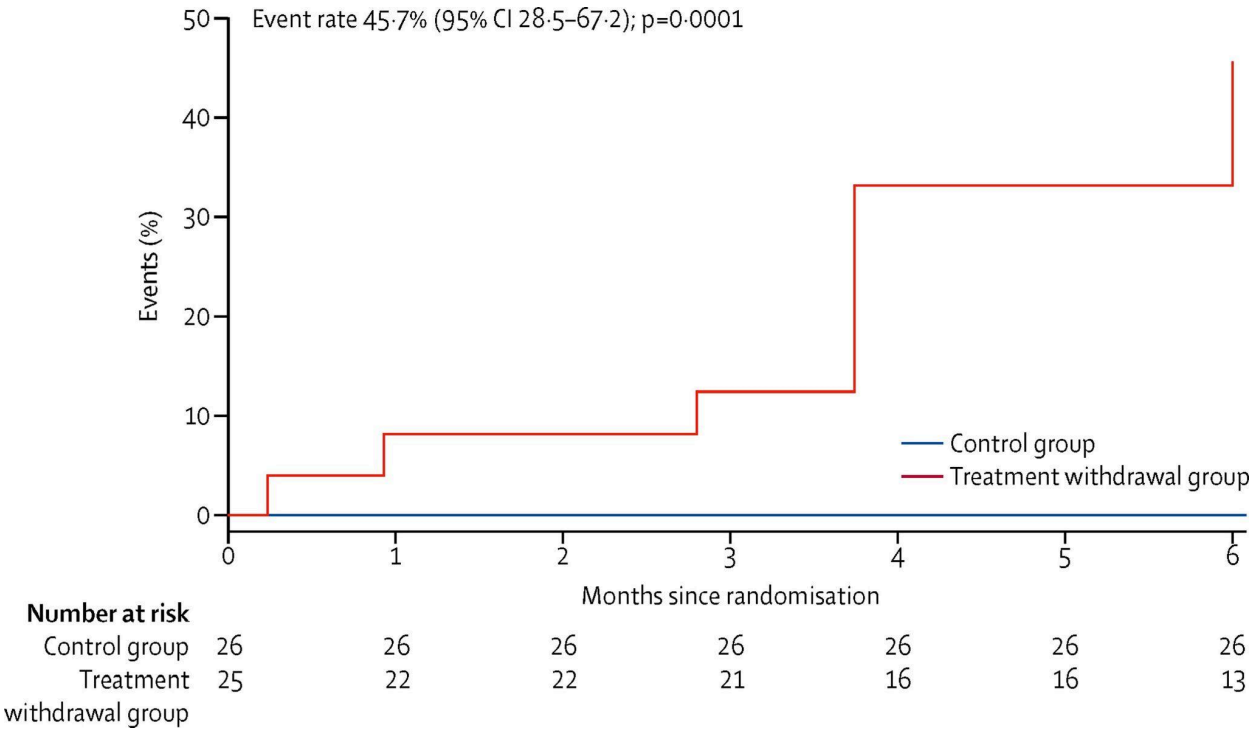

Figure 3. Time to relapse of cardiomyopathy* following cessation of treatment in the Therapy withdrawal in REcovered Dilated cardiomyopathy (TRED-HF) trial .

(Reproduced under CC license. Halliday et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2019;393:61-73) (16)