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REVIEW

What to do with foundation therapies for heart failure for patients with end-stage kidney disease on haemodialysis

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Abstract

There is a significant burden of cardiovascular disease morbidity and mortality in the end-stage kidney disease population, driven by traditional and non-traditional risk factors. Despite its prevalence, heart failure is difficult to diagnose in the dialysis population due to overlapping clinical presentations, limitations of investigations, and the impact on the cardiorenal axis. 'Foundation therapies' are the key medications which improve patient outcomes in heart failure with reduced ejection fraction and include beta-blockers, renin-angiotensin-aldosterone system inhibitors and sodium-glucose cotransporter-2 inhibitors. They are underutilised in the dialysis population due to the exclusion of chronic kidney disease patients from major trials and legitimate clinical concerns e.g. hyperkalaemia, intradialytic hypotension and residual kidney function preservation. A coordinated cardiorenal multidisciplinary approach can guide appropriate diagnostic considerations (biomarkers interpretation, imaging, addressing unique complications of kidney disease), optimise dialysis management (prescription length, frequency and ultrafiltration targets) and when at euvolaemia facilitate the stepwise introduction of appropriate foundation therapies.

Key words: Dialysis; End-stage kidney disease; Foundation therapies; Heart failure; Management

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Introduction

Cardiovascular disease (CVD) remains the leading cause of death for patients with end-stage kidney disease (ESKD) (United States Renal Data System, 2023). In this population CVD is driven by the clustering of traditional and non-traditional risk factors, leading to changes in cardiovascular structure and function that are associated with poor patient outcomes (Aoki et al, 2005; Chiu et al, 2014a). These structural changes, including left ventricular (LV) hypertrophy, LV cavity dilatation, increased aortic stiffness and the development of interstitial myocardial fibrosis, associate with the commonest modes of death for patients with ESKD; arrhythmia, sudden cardiac death and heart failure.

Heart failure (HF) is a major challenge for patients with chronic kidney disease (CKD). To be diagnosed with HF, patients need to have relevant clinical signs and symptoms. The most recent European Society of Cardiology guidelines divide patients with HF into 3 groups, based on the severity of LV impairment: Heart failure reduced ejection fraction (HFrEF), LV ejection fraction of <41%; heart failure moderately reduced ejection fraction (HFmrEF), LV ejection fraction of 41-49%; and heart failure preserved ejection fraction (HFpEF), LV ejection fraction ≥50% with objective evidence of cardiac structural or functional abnormalities consistent with diastolic dysfunction or raised filling pressures (including raised natriuretic peptides) (McDonagh et al, 2021). Over 50% of patients with CKD have some form of HF and over one quarter of patients with ESKD on haemodialysis have HFrEF (United States Renal Data System, Löfman et al, 2017). The relationship between the processes of haemodialysis itself and the pathogenesis of HF for patients on haemodialysis are complex and bi-directional, so while there are clear guidelines on diagnosis and management of patients with HFrEF/HFmrEF generally (Cuthbert, 2021), there are unique challenges for patients on haemodialysis in both the diagnosis and treatment.

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This article will review and discuss the challenges in diagnosis and management of HFrEF/HFmrEF (hereafter referred to as HFrEF), in patients on haemodialysis. We discuss the factors to consider when prescribing HF medications and describe a framework to support clinicians in optimising HF pharmacotherapy for this vulnerable group.

Diagnosis of heart failure

Heart failure is a *clinical syndrome* consisting of key symptoms and signs (Bozkurt et al, 2021). The syndrome of HF is the consequence of structural or functional abnormalities in the heart that result in elevated intracardiac pressures with or without impaired cardiac output at exercise or rest (McDonagh et al, 2021). Diagnosis requires two components: 1. confirmation that the clinical syndrome is of cardiac origin; 2. the aetiology for the cardiac structural or functional abnormality.

Diagnosis of HF usually requires coordination from a HF multidisciplinary team. Clinical history and examination identify the cardinal symptoms and signs, patient risk factors (lifestyle, family history, comorbidities), precipitating events (myocardial infarction, valvular pathology) and consider differentials. Investigations such as electrocardiogram, urinalysis, chest x-ray, and blood tests provide supporting evidence for the diagnosis, identify aggravating factors and explore differentials (e.g. liver or renal impairment) (National Institute for Health and Care Excellence (Great Britain) 2018; McDonagh et al, 2021). Imaging is essential to identify structural and/or functional cardiac abnormalities; transthoracic echocardiogram in the first instance and potentially followed by transoesophageal echocardiogram or cardiac magnetic resonance imaging (National Institute for Health and Care Excellence (Great Britain) 2018).

The biomarker, N-terminal pro-B type natriuretic peptide (NT-proBNP), is released in response to increased intracardiac pressures and has an important role in the diagnosis and prognosis of HF (Kragelund et al, 2005). NT-proBNP levels <400 ng/litre in the absence of treatment, reduce the probability of HF whereas higher levels are associated with increases in cardiovascular death and hospitalisation (Zile et al, 2016; National Institute for Health and Care Excellence (Great Britain) 2018). The National Institute for Health and Care recommends individuals with an NT-proBNP >2000 ng/litre be seen by a HF specialist within 2 weeks, and those with an NT-proBNP ≥400 to ≤2000 ng/litre should be seen within 6 weeks (National Institute for Health and Care Excellence (Great Britain), 2018).

Challenges in end-stage kidney disease

The diagnosis and clinical evaluation of HF in patients with ESKD are challenging due to the overlapping clinical presentations, the limitations of investigations and the intricate balance between heart and kidney health culminating in cardiorenal syndrome (Thind et al, 2018).

Overlapping clinical presentations

Volume status creates a unique challenge in the assessment of HF in ESKD. Individuals receiving maintenance haemodialysis, have significant day-to-day fluctuations in volume status due to weekly dialysis schedules, interdialytic gaps with fluid gains, session length, and patient factors, e.g. urine output, treatment tolerance (ultrafiltration and intradialytic hypotension), and dietary adherence (sodium and fluid intake) (Joseph et al, 2020). Consequently, the cardinal symptoms and signs of kidney failure may be incorrectly (although not unreasonably) attributed to HF and vice-versa (Chawla et al, 2014).

Limitations of investigations

Fluctuations in volume status impact the findings from conventional echocardiography in ESKD. Individuals will have increased plasma volume pre-dialysis, often resulting in fluid overload. Conventional echocardiography is based on geometric assumptions of normal LV loading. In states of volume overload, LV mass is overestimated and LV ejection fraction is underestimated compared to imaging at euvolaemia (Chiu et al, 2014b; Wang et al, 2021). Ideally, echocardiograms should be performed at euvolaemia during non-dialysis days, but this can be challenging in clinical practice.

Elevated NT-proBNP is associated with increased mortality in the haemodialysis population (Locatelli et al, 2013). However, NT-proBNP is renally excreted, with levels

increasing as kidney function declines. There is variable elimination through dialysis leading to inconsistent yet significant decreases in NT-proBNP pre and post haemodialysis (Locatelli et al, 2013). This reduces the positive predictive value of NT-proBNP for HF if the diagnostic values for the general population are applied to patients on haemodialysis. Higher NT-proBNP cut-offs may be used in CKD and ESKD when evaluating for HF (Krupicka et al, 2013).

Cardiorenal syndrome

The evolving area of cardiorenal medicine reflects the acknowledgement that cardiac and renal disease rarely occurs in isolation. The interactions via the cardiorenal axis result in multidirectional cycles of deterioration. An established example of this relationship is the neurohormonal responses in HF activating the renin-angiotensin aldosterone system (Ronco et al, 2018); increasing preload and afterload, exacerbating renal ischaemia leading to deterioration in both kidney and cardiac function (Ma et al, 2022). Impairments in cardiac and renal function should no longer be considered separately inpatient care.

Heart failure assessment and diagnosis in end-stage kidney disease

Assessment and management of individuals with suspected or confirmed HF in ESKD should be guided by a cardiorenal multidisciplinary team (Sankaranarayanan et al, 2020). Establishing volume status and understanding fluctuations that occur around the dialysis schedule is essential to guiding diagnosis and management. Imaging, particularly echocardiography, should occur on a non-dialysis day, with the patient as close to euvolaemia as possible via ultrafiltration during dialysis. Cardiac biomarker levels, such as NT-proBNP, should be measured at consistent time points, e.g. pre-dialysis and avoiding the long interdialytic gap, to facilitate interpretations in trends over time and avoid large fluctuations due to dialysis therapy. Higher cut-off values for NT-proBNP may be appropriate, but this should not undermine the clinical significance and association with poorer outcomes. Furthermore, it is essential kidney failure specific aggravating factors for HF, such as anaemia, are given special consideration, as their chronicity, clinical impact and response to treatment will be different to the non-kidney failure population.

Foundation therapies for heart failure

In HFrEF, key medications have been demonstrated to reduce mortality. These ‘foundation therapies’ are beta-blockers, drugs which target the renin-angiotensin-aldosterone system (RAAS), and most recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors. Drugs which target the RAAS fall into four classes: angiotensin converting enzyme inhibitors (ACEi); angiotensin II receptor blockers (ARB); mineralocorticoid receptor antagonists (MRA); and angiotensin receptor-neprilysin inhibitors (ARNI).

Landmark trials in heart failure with reduced ejection fraction populations

Beta-blockers

Beta-blockade has been shown to improve symptom burden, morbidity and survival at all stages of HFrEF in the general HF population. The CIBIS-II trial looked at patients with mild-moderate HF and LV systolic dysfunction. The addition of bisoprolol to diuretics and ACEi led to a 34% reduction in mortality and 20% reduction in hospital admissions and the trial was stopped early due to benefit (CIBIS-II Investigators, 1999). These improvements were also apparent when carvedilol was tested in patients with severe HF (NYHA IV and LVEF < 25%) (Packer et al, 2001).

Renin-angiotensin-aldosterone system blockade

There is overwhelming evidence that RAAS blockade improves symptoms and mortality in HFrEF. The addition of enalapril to conventional therapy in the SOLVD trial reduced mortality (SOLVD Investigators, 1991). The largest reduction in deaths was those attributed to progressive HF, with fewer hospitalisations for HF in the treatment group. ARBs are

recommended if ACEi are not tolerated, although some meta-analyses have not found ARBs to be significantly associated with all-cause mortality reduction in HF populations (Tai et al, 2017). The addition of spironolactone to ACEi and diuretic therapy in patients with NYHA IV HF offered a 30% relative risk reduction in all-cause mortality and in hospitalisation for cardiac causes (Pitt et al, 1999). The reduction in mortality was largely attributed to fewer deaths from HF and sudden cardiac death. The spironolactone group also experienced better symptom improvement than placebo in terms of NYHA status. Sacubitril-Valsartan is an ARNI which is recommended to replace ACEi/ARB therapy for patients with HFrEF who are still symptomatic despite beta-blockade, ACEi/ARB and MRA therapies. The PARADIGM-HF trial found those who were switched from ACEi/ARB therapy to sacubitril-valsartan had a 20% relative risk reduction in the composite outcome of cardiovascular death or hospitalisation (McMurray et al, 2014).

Sodium-glucose cotransporter-2 inhibitors

The addition of SGLT2 inhibitors (regardless of diabetic status) has been shown to reduce cardiovascular death or worsening HF, with a relative risk reduction of 26% and 25% when dapagliflozin and empagliflozin were trialled respectively in patients with established HF (McMurray et al, 2019; Packer et al, 2020).

The inclusion of patients with kidney disease in landmark trials

The presence of advanced CKD or ESKD was an exclusion criterion in all the trials above. This may partly explain the lower prescription of these drugs in patients with reduced renal function (Patel et al, 2021), however, there is evidence from these trials that patients with kidney disease may benefit. The CIBIS-II trial of bisoprolol vs placebo excluded patients with serum creatinine > 300 micromol/L but post-hoc analyses showed that the benefit of bisoprolol was sustained across estimated glomerular filtration rate (eGFR) subgroups compared to placebo (Castagno et al, 2010). The SOLVD trial of enalapril included 41% of patients with eGFR < 60 mL/min/1.73m^2, with a mean eGFR of 49 mL/min/1.73m^2 and again, the reduction in all-cause mortality was demonstrated in this sub-cohort (Bowling et al, 2013). Similar findings have been demonstrated in the key trials testing MRAs, ARNIs and SGLT2 inhibitors (Packer et al, 2018; Ferreira et al, 2019; The EMPA-KIDNEY Collaborative Group, 2023).

Prescription of foundation therapies across chronic kidney disease stages

Despite the high risk of CVD for patients who have CKD and HF, foundation therapies are poorly used, especially in advanced stages of CKD. Data from a 2014-19 American heart failure registry showed that the prescription of evidence-based therapies at hospital discharge declined with the stage of CKD and was especially low in patients on dialysis (Patel et al, 2021). Data from the same registry demonstrated that while the prescription of therapies has improved, it remains low in patients on dialysis compared to those with normal renal function and those with non-dialysis CKD (Pandey et al, 2016).

Clinical concerns about foundation therapies in end-stage kidney disease

There are legitimate challenges and concerns with starting certain foundation therapies for HF in patients on haemodialysis. These concerns stem, in part from limited clinical trial data, but also concerns about causing intra-dialytic hypotension, hyperkalaemia and maintaining residual renal function.

Intra-dialytic hypotension (IDH) is a challenge for patients on dialysis and is more common in patients with HF (Sars et al, 2020). Intra-dialytic hypotension occurs during dialysis when fluid removal from mechanical ultrafiltration outpaces refilling of the vascular space leading to circulatory collapse from a reduction in LV end-diastolic filling. It confers a poor prognosis and is distressing for patients and staff (Flythe et al, 2015). Episodes of IDH are more common when large volumes of fluid are ultrafiltrated rapidly during dialysis or with pre-existing cardiovascular compromise (Hamrahian et al, 2023).

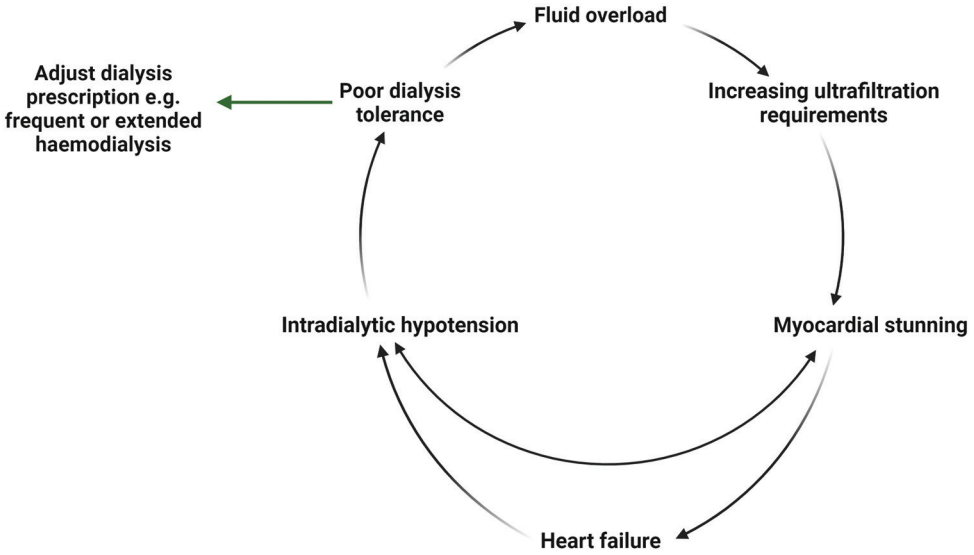

Figure 1. The pathophysiological mechanisms behind the cardiorenal axis in patients on haemodialysis. Created with BioRender.com.

While it is true that patients on haemodialysis with HF are more likely to be affected by IDH, the relationship is bi-directional as the processes of dialysis themselves, particularly rapid ultrafiltration of fluid during dialysis, causes myocardial stunning events that drive the development of HF and predisposes to IDH (Burton et al, 2009a; 2009b) (Figure 1). A common scenario that causes clinicians difficulty is treating patients with HFrEF who are chronically volume overloaded and struggling with frequent IDH that stops them from achieving euvolaemia. For this group, the initiation of foundation therapies for HFrEF that lower blood pressure is a potential disaster and foundation therapies may precipitate more frequent (and worse) episodes of IDH, which limit the ability to achieve euvolaemia. It is for these reasons that both the European Society of Cardiology and Kidney Disease Outcome Quality Initiative recommend that for patients with HFrEF, foundation therapies should be considered only when patients have achieved euvolaemia on haemodialysis. If patients cannot achieve euvolaemia on a standard dialysis prescription, then more frequent or extended hours haemodialysis should be considered to abrogate the effects of rapid ultrafiltration on myocardial stunning. It is a poor prognostic sign if these patients cannot achieve euvolaemia and in this scenario foundation therapies for HF are not the solution.

Hyperkalaemia is often cited as the reason it is difficult to commence RAAS therapies. While these concerns are legitimate, the limited trial data that exist for patients on haemodialysis with HFrEF suggest that the increase in serum potassium levels for patients started on telmisartan (Cice et al, 2010) or spironolactone (Taheri et al, 2009) is not large and the need to discontinue of therapies is infrequent. Moreover, in an era where we have efficacious potassium binder therapies (Weir et al, 2015; Fishbane et al, 2019), if patients do develop hyperkalaemia after initiation of a treatment, arguably they should be commenced on binder therapy, rather than discontinuing the medication.

There are clinical concerns about the effect RAAS therapies may have on residual renal function in patients on haemodialysis. This is reasonable as preservation of residual renal function associates with improved outcomes (Dopierała et al, 2023). There are no studies looking at the effects of these drugs on residual renal function in this population, but data from the STOP-ACE trial in patients with advanced kidney disease (eGFR < 20) is instructive in that there were no significant differences in time to starting dialysis or hyperkalaemia in patients randomised to continuing ACE/ARB therapy, compared to those randomised to discontinue (Bhandari et al, 2022). There was also a (non-significant) signal for increased cardiovascular events in patients randomised to discontinuing ACE/ARB therapy, highlighting the importance of therapy optimisation.

There are established clinical concerns when considering foundation therapies for the treatment of HFrEF in patients on haemodialysis. Undoubtedly certain patients will fall foul

of these problems, but it is equally clear that concerns limit the use of these medications for many patients who stand to benefit (Patel et al, 2021).

Evidence for foundation therapies for patients on haemodialysis with heart failure with reduced ejection fraction

There are a handful of randomised controlled trials that have evaluated the effects of certain foundation therapies in patients on haemodialysis. These studies, together with observational data, data from the general population, the principles of optimising dialysis and volume status, and a considered multiprofessional approach are central to effective management in the absence of definitive trial data.

Carvedilol was shown to reduce 2-year mortality compared to placebo in a study of 114 patients with established HF on haemodialysis (Cice et al, 2003). Of the 132 patients recruited during the run-in phase, the major limiting adverse events were hypotension (*n*=3), bronchospasm (*n*=5), bradycardia (*n*=4) and worsening HF (*n*=4). The study showed not only improvements in survival, but in LV geometry and function. Similarly, in a randomised controlled trial of 351 patients on haemodialysis with HFrEF, telmisartan use was associated with reductions in all-cause mortality, cardiovascular death, hospitalisation and LV function and geometry compared to placebo (Cice et al, 2010). Hyperkalaemia leading to discontinuation only occurred in 3% of the patients taking telmisartan and with relatively few episodes of hypotension leading to dropout in those taking telmisartan (18 on telmisartan compared to 7 controls).

There are no major outcome trials assessing the effects of MRAs, ARNIs or SGLT2 inhibitors in patients with HF on haemodialysis. Observational studies have reported conflicting results, all of which are subject to confounding by indication and the biases of observational data. Ongoing trials testing these agents will inform practice. Two trials are currently assessing the effects of MRAs in patients with ESKD on dialysis, although neither of these trials are exclusively in patients with HF (ACHIEVE, NCT03020303 and ALCHEMIST, NCT01848639). Two further trials are assessing the effects of ARNI therapy in ESKD on cardiovascular outcomes, death, hospitalisations and cardiac function in patients with established HF (NCT05243199 and ESARHD-HF, NCT04458285). There are also two trials evaluating the use of SGLT2 inhibitors in patients with ESKD (SDHF, NCT05141552 and The Renal LIFECYCLE Trial NCT05374291), although these are not specifically in patients with HF. For oligo-anuric patients on haemodialysis, it is hard to see how SGLT2 inhibitors will have a major effect on HF outcomes, given their mechanism of action is through the SGLT2 receptor in the proximal tubule. However, until data are available, clinicians should use their judgement about the use of these drugs in patients who may derive benefit.

Data from these studies will give important information about the effects of these medications on cardiovascular health in patients with ESKD but also important safety information that will support clinicians to use these medications where there is potential benefit, particularly for patients with HFrEF.

An incomplete evidence base, fear of use, and in some cases, licencing, limits confidence in attempting to optimise these foundation therapies. In patients who are well dialysed and achieving euvolaemia, there is no reason why clinicians should not attempt to optimise foundation therapies for HF as they would in the general population with appropriate monitoring. However, we recommend this is always done with multiprofessional approach. Figure 2 summarises a clinical support tool to help medical optimisation of foundation therapies for these patients.

Future directions and conclusions

Patients with HFrEF on haemodialysis have among the poorest outcomes of any patient group and prescription of foundation therapies for HF is low. Although appropriately powered randomised trials are needed to establish the efficacy of treatments in this population, data are available that support their use in patients who are able to achieve euvolemia on

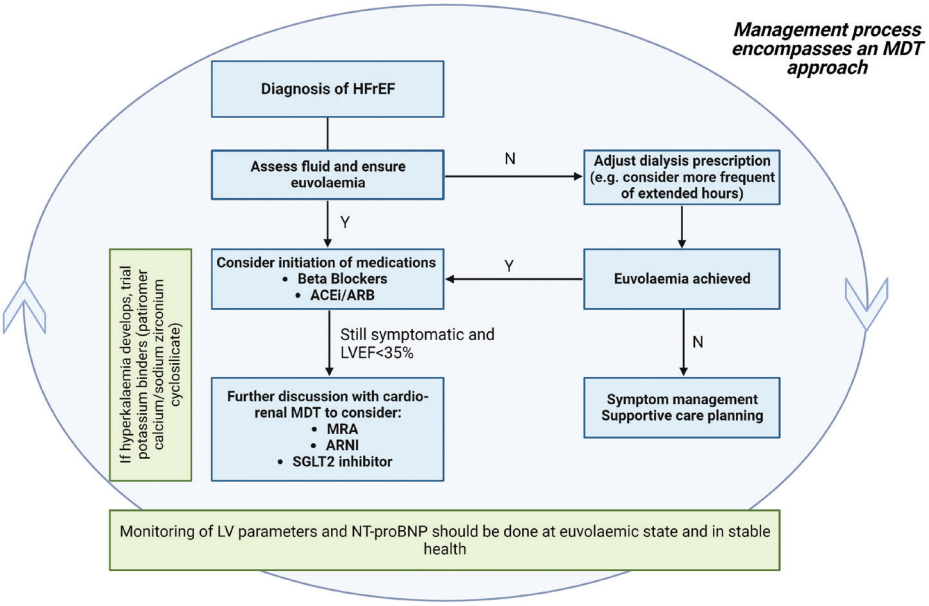

Figure 2. An approach to managing heart failure with reduced ejection fraction in patients on haemodialysis, describing the steps for medical optimisation to be undertaken with a multiprofessional approach. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HFrEF, Heart failure with reduced ejection fraction; LV, left ventricle; MDT, multidisciplinary team; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B type natriuretic peptide; SGLT2, sodium-glucose cotransporter-2. Created with BioRender.com.

haemodialysis. A multiprofessional approach is needed to optimise medical therapy for most patients, but work is also needed to gain consensus on what optimised medial therapy looks like in this patient group and to identify and overcome barriers to implementation that will limit the equitable access.

Key points

- Non-traditional cardiovascular risk factors (e.g., uraemia, chronic inflammation, myocardial stunning and renal bone disease) significantly contribute to pathological myocardial remodelling and fibrosis; heart failure is a frequent manifestation, and its prevalence is increasing in the dialysis population.
- Heart failure is a clinical syndrome with diagnosis requiring evidence that symptoms and signs are of cardiac origin and clear aetiology for the cardiac structural or functional abnormality. Heart failure with reduced ejection fraction (HFrEF) is common in the haemodiaysis population, however, there are unique challenges to diagnosis and an absence of a consensus on the approach to management.
- The foundation therapies (beta-blockers, renin-angiotensin-aldosterone system inhibitors and sodium-glucose cotransporter-2 inhibitors) improve mortality in patients with HFrEF; individuals with chronic kidney disease stages 4, 5 and those receiving maintenance haemodialysis have been excluded from key clinical trials.
- There are a small number of randomised clinical trials, alongside observational data and the principles of biological plausibility, that indicate the benefit of foundation therapies in the dialysis population; improvements in survival, cardiovascular mortality, hospitalisation, and cardiovascular disease surrogates.
- A considered stepwise approach, led by a cardiorenal multidisciplinary team, should be taken when managing individuals with both kidney failure on dialysis and HFrEF. Care should focus on achieving euvolaemia through dialysis (adopting alternative dialysis prescriptions as necessary) followed by initiation of the foundation therapies, with regular assessment for kidney disease specific aggravating factors such as renal anaemia.

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Author Contributions
MGB, KLH and SFA were involved in the manuscript conception and final approval. MGB, KLH and SFA were involved in the manuscript draft, revision, figure preparation and final revision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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References

Aoki J, Ikari Y, Nakajima H et al. Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. Kidney Int. 2005;67(1):333–340. https://doi.org/10.1111/j.1523-1755.2005.00086.x

Bhandari S, Mehta S, Khwaja A et al. Renin–angiotensin system inhibition in advanced chronic kidney disease. N Engl J Med. 2022;387(22):2021–2032. https://doi.org/10.1056/NEJMoa2210639

Bowling CB, Sanders PW, Allman RM et al. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. Int J Cardiol. 2013;167(1):151–156. https://doi.org/10.1016/j.ijcard.2011.12.056

Bozkurt B, Coats A, Tsutsui H et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021;23(3):352–380. https://doi.org/10.1002/ejhf.2115

Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009a;4(5):914–920. https://doi.org/10.2215/CJN.03900808

Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009b;4(12):1925–1931. https://doi.org/10.2215/CJN.04470709

Castagno D, Jhund PS, McMurray JJ et al. Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial. Eur J Heart Fail. 2010;12(6):607–616. https://doi.org/10.1093/eurjhf/hfq038

Chawla LS, Herzog CA, Costanzo MR et al. Proposal for a functional classification system of heart failure in patients with end-stage renal disease: proceedings of the acute dialysis quality initiative (ADQI) XI workgroup. J Am Coll Cardiol. 2014;63(13):1246–1252. https://doi.org/10.1016/j.jacc.2014.01.020

Chiu DY, Sinha S, Kalra PA, Green D. Sudden cardiac death in haemodialysis patients: preventative options. Nephrology. 2014a;19(12):740–749. https://doi.org/10.1111/nep.12337

Chiu DY, Green D, Abidin N, Sinha S, Kalra PA. Echocardiography in hemodialysis patients: uses and challenges. Am J Kidney Dis. 2014b;64(5):804–816. https://doi.org/10.1053/j.ajkd.2014.01.450

CIBIS-II Investigators. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13

Cice G, Ferrara L, D'Andrea A et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol. 2003;41(9):1438–1444. https://doi.org/10.1016/S0735-1097(03)00241-9

Cice G, Di Benedetto A, D'Isa S et al. Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure: a double-blind, placebo-controlled trial. J Am Coll Cardiol. 2010;56(21):1701–1708. https://doi.org/10.1016/j.jacc.2010.03.105

Cuthbert JJ. European society of cardiology heart failure guidelines 2021: what should we be doing in current practice? 2021. https://www.britishcardiovascularsociety.org/resources/editorials/articles/european-society-cardiology-heart-failure-guidelines-2021-current-practice (accessed 8 March 2024)

Dopierała M, Schwermer K, Hoppe K, Kupczyk M, Pawlaczyk K. Benefits of preserving residual urine output in patients undergoing maintenance haemodialysis. Int J Nephrol Renovasc Dis. 2023;16:231–240. https://doi.org/10.2147/IJNRD.S421533

Ferreira JP, Abreu P, McMurray JJ et al. Renal function stratified dose comparisons of eplerenone versus placebo in the EMPHASIS-HF trial. Eur J Heart Fail. 2019;21(3):345–351. https://doi.org/10.1002/ejhf.1400

Fishbane S, Ford M, Fukagawa M et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. J Am Soc Nephrol. 2019;30(9):1723–1733. https://doi.org/10.1681/ASN.2019050450

Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol. 2015;26(3):724–734. https://doi.org/10.1681/ASN.2014020222

Hamrahian SM, Vilayet S, Herberth J, Fülöp T. Prevention of intradialytic hypotension in hemodialysis patients: current challenges and future prospects. Int J Nephrol Renovasc Dis. 2023;16:173–181. https://doi.org/10.2147/IJNRD.S245621

Joseph MS, Palardy M, Bhave NM. Management of heart failure in patients with end-stage kidney disease on maintenance dialysis: a practical guide. Rev Cardiovasc Med. 2020;21(1):31–39. https://doi.org/10.31083/j.rcm.2020.01.24

Kragelund C, Grønning B, Køber L, Hildebrandt P, Steffensen R. N-terminal pro–B-type natriuretic peptide and long-term mortality in stable coronary heart disease. N Engl J Med. 2005;352(7):666–675. https://doi.org/10.1056/NEJMoa042330

Krupicka J, Janota T, Hradec J. Natriuretic peptides in heart failure. Cor Vasa. 2013;55(4):e370–e376. https://doi.org/10.1016/j.crvasa.2013.03.010

Locatelli F, Hannedouche T, Martin-Malo A et al. The relationship of NT-proBNP and dialysis parameters with outcome of incident haemodialysis patients: results from the membrane permeability outcome study. Blood Purif. 2013;35(1–3):216–223. https://doi.org/10.1159/000347076

Löfman I, Szummer K, Dahlström U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail. 2017;19(12):1606–1614. https://doi.org/10.1002/ejhf.821

Ma K, Gao W, Xu H, Liang W, Ma G. Role and mechanism of the renin-angiotensin-aldosterone system in the onset and development of cardiorenal syndrome. J Renin Angiotensin Aldosterone Syst. 2022;2022:3239057. https://doi.org/10.1155/2022/3239057

McDonagh TA, Metra M, Adamo M et al. 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. Eur Heart J. 2021;42(36):3599–3726. https://doi.org/10.1093/eurheartj/ehab368

McMurray JJ, Packer M, Desai AS et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004. https://doi.org/10.1056/NEJMoa1409077

McMurray JJ, Solomon SD, Inzucchi SE et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303

National Institute for Health and Care Excellence. Chronic heart failure in adults: diagnosis and management. 2018. https://www.nice.org.uk/guidance/ng106 (accessed 8 March 2024)

Packer M, Coats AJ, Fowler MB et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651–1658. https://doi.org/10.1056/NEJM200105313442201

Packer M, Claggett B, Lefkowitz MP et al. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. Lancet Diabetes Endocrinol. 2018;6(7):547–554. https://doi.org/10.1016/S2213-8587(18)30100-1

Packer M, Anker SD, Butler J et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–1424. https://doi.org/10.1056/NEJMoa2022190

Pandey A, Golwala H, DeVore AD et al. Trends in the use of guideline-directed therapies among dialysis patients hospitalized with systolic heart failure: findings from the American heart association get with the guidelines-heart failure program. JACC: Heart Fail. 2016;4(8):649–661. https://doi.org/10.1016/j.jchf.2016.03.002

Patel RB, Fonarow G, Greene S et al. Clinical profiles, medical therapies, and outcomes among patients hospitalized for HF across the spectrum of kidney function: the GWTG-HF registry. J Am Coll Cardiol. 2021;77(18):559–559. https://doi.org/10.1016/S0735-1097(21)01918-5

Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341(10):709–717. https://doi.org/10.1056/NEJM199909023411001

Ronco C, Bellasi A, Di Lullo L. Cardiorenal syndrome: an overview. Adv Chronic Kidney Dis. 2018;25(5):382–390. https://doi.org/10.1053/j.ackd.2018.08.004

Sankaranarayanan R, Douglas H, Wong C. Cardio-nephrology MDT meetings play an important role in the management of cardiorenal syndrome. Br J Cardiol. 2020;27(3):26. https://doi.org/10.5837/bjc.2020.026

Sars B, van der Sande FM, Kooman JP. Intradialytic hypotension: mechanisms and outcome. Blood Purif. 2020;49(1–2):158–167. https://doi.org/10.1159/000503776

Taheri S, Mortazavi M, Shahidi S et al. Spironolactone in chronic hemodialysis patients improves cardiac function. Saudi J Kidney Dis Transpl. 2009;20(3):392–397

Tai C, Gan T, Zou L et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2017;17(1):1–12. https://doi.org/10.1186/s12872-017-0686-z

The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388(2):117–127

The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293–302. https://doi.org/10.1056/NEJM199108013250501

Thind GS, Loehrke M, Wilt JL. Acute cardiorenal syndrome: mechanisms and clinical implications. Cleve Clin J Med. 2018;85(3):231–239. https://doi.org/10.3949/ccjm.85a.17019

United States Renal Data System. 2023 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2023

Wang X, Hong J, Zhang T, Xu D. Changes in left ventricular and atrial mechanics and function after dialysis in patients with end-stage renal disease. Quant Imaging Med Surg. 2021;11(5):1899–1908. https://doi.org/10.21037/qims-20-961

Weir MR, Bakris GL, Bushinsky DA et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211–221. https://doi.org/10.1056/NEJMoa1410853

Zile MR, Claggett BL, Prescott MF et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol. 2016;68(22):2425–2436. https://doi.org/10.1016/j.jacc.2016.09.931