CKJ REVIEW

Left ventricular dysfunction with preserved ejection fraction: the most common left ventricular disorder in chronic kidney disease patients

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ABSTRACT

Chronic kidney disease (CKD) is a risk factor for premature cardiovascular disease. As kidney function declines, the presence of left ventricular abnormalities increases such that by the time kidney replacement therapy is required with dialysis or kidney transplantation, more than two-thirds of patients have left ventricular hypertrophy. Historically, much research in nephrology has focussed on the structural and functional aspects of cardiac disease in CKD, particularly using echocardiography to describe these abnormalities. There is a need to translate knowledge around these imaging findings to clinical outcomes such as unplanned hospital admission with heart failure and premature cardiovascular death. Left ventricular hypertrophy and cardiac fibrosis, which are common in CKD, predispose to the clinical syndrome of heart failure with preserved left ventricular ejection fraction (HFpEF). There is a bidirectional relationship between CKD and HFpEF, whereby CKD is a risk factor for HFpEF and CKD impacts outcomes for patients with HFpEF. There have been major improvements in outcomes for patients with heart failure and reduced left ventricular ejection fraction as a result of several large randomized controlled trials. Finding therapy for HFpEF has been more elusive, although recent data suggest that sodium-glucose cotransporter 2 inhibition offers a novel evidence-based class of therapy that improves outcomes in HFpEF. These observations have emerged as this class of drugs has also become the standard of care for many patients with proteinuric CKD, suggesting that there is now hope for addressing the combination of HFpEF and CKD in parallel. In this review we summarize the epidemiology, pathophysiology, diagnostic strategies and treatment of HFpEF with a focus on patients with CKD.

Keywords: cardiovascular, chronic kidney disease, heart failure, mineralocorticoid receptor antagonism, sodium-glucose cotransporter 2

BACKGROUND

It is well recognized that chronic kidney disease (CKD) is a risk factor for premature cardiovascular disease (CVD), and that CVD is the leading cause of death in patients with all stages of CKD [1, 2]. Although CKD increases the risk of all subtypes of CVD, as the estimated glomerular filtration rate (eGFR) declines, the risk of heart failure (HF) and cardiac death increases compared with that of myocardial infarction (MI) and stroke [3]. This aligns with the increasing prevalence of left ventricular hypertrophy (LVH) as eGFR declines such that more than two-thirds of patients with eGFR <30 mL/min/1.73 m^2 have been reported to have LVH [4]. While left ventricular systolic dysfunction certainly is common, affecting 16% of patients at the commencement of dialysis, with LVH as the dominant ventricular lesion, it stands to reason that the driver of HF events in patients with CKD, including those on dialysis, is the syndrome of heart failure with preserved ejection fraction (HFpEF) [5, 6]. Effective HF treatments have not been assessed reliably in advanced CKD and dialysis. Patients with advanced CKD are often excluded from trials in HF [7–9]. There have been significant developments in our understanding of risk factors for and outcomes of HFpEF in patients with and without CKD. In this review, we describe the epidemiology, pathophysiology, diagnostic strategies and new evidence for therapies in managing HFpEF, with a particular focus on patients with CKD.

HFpEF in the general population

The European Society of Cardiology (ESC) clinical practice guidelines recommend categorizing HF into distinct phenotypes based on the left ventricular ejection fraction (LVEF) [10]. Historically, the basis for this is the original landmark treatment trials that showed improved outcomes in patients with HF and LVEF <40% and this group is described as heart failure with reduced ejection fraction (HFrEF). Patients with heart failure and mildly reduced ejection fraction (HFmrEF; LVEF 41–49%) resemble patients with HFrEF in terms of outcomes and response to therapies [11, 12]. Patients with HFpEF (LVEF ≥50%) have essentially a 'normal' ejection fraction. Table 1 highlights the differences between HFrEF and HFpEF.

The diagnosis of HF requires the presence of typical signs (e.g. pulmonary crackles, raised jugular venous pressure) and symptoms (e.g. fatigue, breathlessness) in the context of cardiac structural or functional abnormality and further corroborated by elevated concentrations of circulating natriuretic peptides or evidence of cardiogenic pulmonary or systemic congestion [13]. Myocardial dysfunction is the most common cause of HF and can be divided into systolic, diastolic or both [10].

The diagnosis of HFpEF can be challenging, especially in the context of coexisting non-cardiac causes of dyspnoea, including obesity and chronic lung disease. There is also substantial phenotypic heterogeneity. Approximately three-quarters of unrecognized cases of HF are in patients with HFpEF [14], hence the true prevalence of HFpEF may be underestimated.

Epidemiology of HFpEF and HFrEF and associated outcomes

HFpEF accounts for ~50–60% of HF cases in the community [15–17] and similar proportions are reported in hospitalized patients [18–20]. Compared with patients with HFrEF or HFmrEF, those with HFpEF are more often female and tend to be older [20, 21]. Table 1 highlights some clinical and epidemiological differences between HFrEF and HFpEF. Relative to HFrEF,

Table 1. Summary of demographic, pathophysiological, diagnostic and therapeutic differences between HFrEF and HFpEF

Characteristics		HFpEF	HFrEF
Demographics		Older age, female predominance	Younger age, male predominance
Risk factors		Ageing, hypertension, obesity, physical inactivity	Ischaemic heart disease, smoking
Pathophysiology		Coronary microvascular inflammation	Direct cardiomyocyte injury and loss
Natriuretic peptides		Lower levels	Higher levels
LV morphology and other properties	LVEF	≥50%	<50%
	LV remodelling	Concentric remodelling	Eccentric remodelling
	LV volumes	Normal	Increased
	Systolic dysfunction (other than EF)	+	++
	Diastolic dysfunction	++	+
	Aortic stiffness	++	+
	Disturbance of LV relaxation or compliance	++	+
Response to HF therapy	ACEi[a]	−	++
	ARB[a]	−	++
	SGLT2 inhibitors[b]	++	++
	ARNI	−	++
	Bteablockers	−	++
	MRA	+	++
Cause of death		Predominantly non-CV death	Predominantly CV death

[a]Trials have not demonstrated clinically meaningful benefit in HFrEF but ARBs/ACEis have proven long-term benefits in the progression of CKD.
[b]Lower risk of HF hospitalization in HFpEF.

the incidence and prevalence of HFpEF have been growing by 10% every 10 years [21, 22] and this widening gap is thought to reflect the ageing population and the growing prevalence of obesity, diabetes, hypertension and other conditions linked to the development of HFpEF [21]. The prevalence of atrial fibrillation, CKD and other non-cardiovascular comorbidities is higher in patients with HFpEF than in HFrEF. There is growing evidence for the central role of inflammation [19, 23] as well as coronary microvascular and macrovascular disease [24] in the pathogenesis of HFpEF.

Although some studies report that mortality rates for patients with HFpEF and HFrEF are similar [25–27], others report lower mortality in HFpEF [15, 17, 19, 28]. Consistent with the observation that the prevalence of non-cardiovascular comorbidities is higher in patients with HFpEF than it is in HFrEF, patients with HFpEF tend to have higher non-cardiovascular mortality than patients with HFrEF. Conversely, cardiovascular mortality is higher in patients with HFrEF. These findings are observed both in clinical trial populations [29] and in epidemiological studies [30]. Rates of hospitalization and the duration of hospitalizations [31] are similar for HFpEF and HFrEF and the decrease in quality of life in the two groups appears similar and substantial [32].

Diagnosis of HFpEF

Diagnostic algorithms based on clinical assessment, electrocardiogram (ECG) and echocardiography have been produced by the Heart Failure Association (HFA) to diagnose HF in the presence of preserved ejection fraction and to document whether diastolic dysfunction is present. Fig. 1 highlights diagnostic algorithms for HFpEF, which have been tailored to the assessment of suspected HF in CKD.

More advanced imaging techniques (stress testing, invasive haemodynamic measurements, cross-sectional imaging) may assist in the workup [33]. The first step is pretest assessment ('P') involving clinical assessment, ECG, basic echocardiography and functional/anatomical ischaemia testing (if indicated). This step excludes patients with significant coronary artery disease, valvular heart disease, chronic lung disease or anaemia. This is followed by a diagnostic workup ('E') centring on echocardiography and natriuretic peptide quantification. If 'E' is inconclusive, then F1 should be considered invasive or non-invasive stress testing for diastolic dysfunction. An aetiological search should be carried out (F2) [33, 34].

Echocardiography is advised to assess the breathless patient with a clinical suspicion of HF [35, 36]. Table 2 summarizes echocardiographic parameters and their relevance to diagnosing HFpEF, while Fig. 2 demonstrates imaging indicators of HFpEF graphically.

The LVEF should be quantified using three-dimensional [5] or Simpson's biplane and a cut-off of ≥50% (HFA) used to identify preserved LVEF [1, 6, 33, 37] and measurements made to ensure the left ventricle (LV) is not dilated (LV end-diastolic volume, LV end-diastolic dimension). The so-called HFpEF phenotype is a non-dilated LV, with preserved LVEF, LVH and a dilated left atrium (LA). These findings support but do not exclude HFpEF [38].

The additional echocardiographic measurements recommended to support a diagnosis of HFpEF [33] are identical to the recommendations for the identification of LV diastolic dysfunction [39, 40]—mitral flow velocities, mitral annular e′ velocity, E:e′ ratio, peak velocity of tricuspid regurgitation (TR) jet and left atrial maximum volume index (LAVI). Through a combination of measurements, one can identify if LV filling pressure is

normal or abnormal and using cut-offs specified by the HFA can diagnose HFpEF if ≥5 points are present. Besides LVEF, global longitudinal strain (GLS) measurement is a more subtle measure of LV dysfunction [41] in HFpEF [42] and is a marker of adverse outcomes [43]. Diastolic metrics include the early diastolic velocity of mitral annular motion (e′) and in HFpEF the values are decreased. Mitral flow velocities (E/A) represent the pressure gradient between the left atrium (LA) and LV and are affected by changes in LV relaxation, LA pressure (E wave) and LV compliance and LA contractile function (A wave) [44]. The E:e′ ratio is an indirect estimate of mean pulmonary capillary wedge pressure [39] and associates with LV fibrosis [45]. Correlation between E:e′ and invasive filling pressure in HFpEF vary widely in correlation strength ($r = 0.02–0.87$) but has prognostic utility [46].

A peak tricuspid regurgitation jet >2.8 m/s is an indirect marker of LV diastolic dysfunction and indicates increased pulmonary artery systolic pressure (PASP) [39].

LAVI or the LA maximal volume indexed to body surface area is associated with LV filling pressures [39] and increases with worsening measures of diastolic dysfunction [47].

Diastolic stress testing

Patients with diastolic dysfunction may not be able to increase LV relaxation with exercise compared with healthy controls and hence have increased LV filling pressures to achieve the required cardiac output, i.e. exercise unmasks diastolic dysfunction. Guidelines are available for further investigation of suspected HFpEF [39, 48, 49] utilizing stress echocardiography.

Invasive measurements

Catheter measurements provide direct measurements of LV diastolic pressures and can be done at rest or with exercise [10, 50]. Utilizing left heart catheterization, demonstration of impaired LV relaxation at rest, tau (the time constant of LV relaxation $\tau > 48$ ms) or elevated LV filling pressures at rest (LV end diastolic pressure ≥16 mmHg) confirms definite evidence of HFpEF [33]. With right heart catheterization, demonstration of elevated mean pulmonary capillary wedge pressure confirms HFpEF [10].

Cardiac magnetic resonance imaging (CMRI)

CMRI is a non-invasive diagnostic test for cardiac anatomy, function and pathology [33, 51, 52]. CMRI is more accurate at measuring LVEF, LV mass and LAVI [53] and has utility in the context of patients with suboptimal acoustic windows. CMRI can identify the presence of coronary syndromes by identifying subendocardial scarring and perfusion defects due to epicardial or microvascular disease [24]. Several pathologies can present with HFpEF. CMRI has utility in differentiating between these pathologies, including hypertrophic, infiltrative, restrictive cardiomyopathies [54, 55], myocarditis [51] and other aetiologies [10, 33].

HFpEF in patients with CKD

HF is highly prevalent in patients with CKD, with HFpEF accounting for half of these cases [56]. CKD and HF occur in a bidirectional fashion, with 55% of patients with HFrEF and HFpEF having CKD stage G3a or higher in a large meta-analysis [57]. The prevalence of HF increases with the severity of CKD and it is present in up to 44% of patients on haemodialysis (HD; 10% with HFpEF, 13% with HFrEF and 21% with unspecified) [58]. In patients with a kidney transplant,
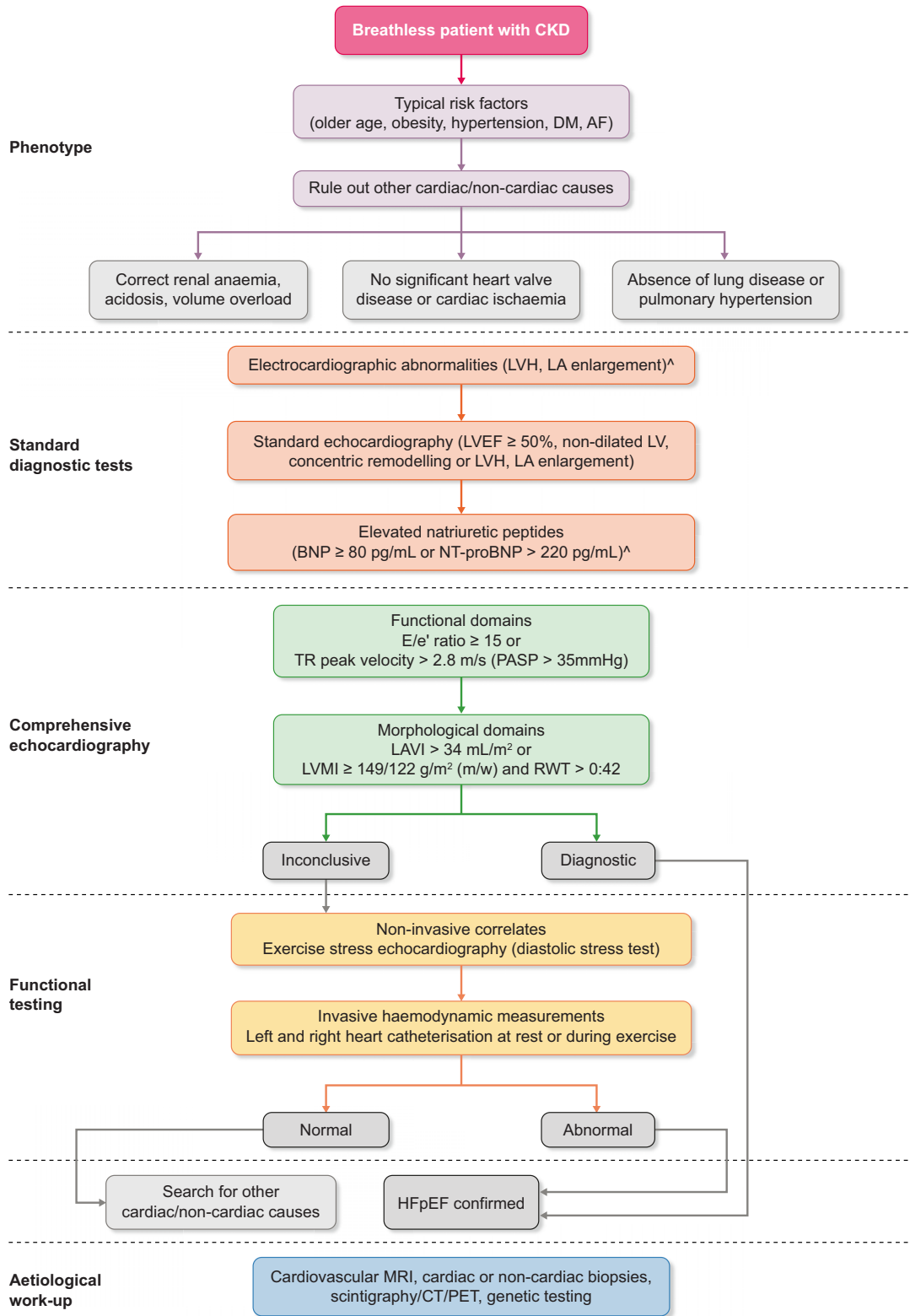
Breathless patient with CKD

Phenotype

Typical risk factors
(older age, obesity, hypertension, DM, AF)

Rule out other cardiac/non-cardiac causes

Correct renal anaemia, acidosis, volume overload

No significant heart valve disease or cardiac ischaemia

Absence of lung disease or pulmonary hypertension

Standard diagnostic tests

Electrocardiographic abnormalities (LVH, LA enlargement)^

Standard echocardiography (LVEF ≥ 50%, non-dilated LV, concentric remodelling or LVH, LA enlargement)

Elevated natriuretic peptides
(BNP ≥ 80 pg/mL or NT-proBNP > 220 pg/mL)^

Comprehensive echocardiography

Functional domains
E/e' ratio ≥ 15 or
TR peak velocity > 2.8 m/s (PASP > 35mmHg)

Morphological domains
LAVI > 34 mL/m^2 or
LVMI ≥ 149/122 g/m^2 (m/w) and RWT > 0:42

Inconclusive

Diagnostic

Functional testing

Non-invasive correlates
Exercise stress echocardiography (diastolic stress test)

Invasive haemodynamic measurements
Left and right heart catheterisation at rest or during exercise

Normal

Abnormal

Search for other cardiac/non-cardiac causes

HFpEF confirmed

Aetiological work-up

Cardiovascular MRI, cardiac or non-cardiac biopsies, scintigraphy/CT/PET, genetic testing

FIGURE 1: Diagnostic algorithm for approaching a patient with CKD and suspected HFpEF. DM, diabetes mellitus; AF, atrial fibrillation; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; RWT, relative wall thickness.

Table 2. Summary of echocardiographic indices and their role in diagnosis of HFpEF and HFrEF

Evaluation systolic function		Interpretation
LVEF	Contour endocardial borders in end-diastole and systole on apical 4 and 2 chamber	Systolic function—preserved in HFpEF [1, 6, 33, 37]
Left ventricular end diastolic volume (LVEDV)	Contour LV endocardium in end diastole	Chamber size—normal or decreased in HFpEF
Global longitudinal strain	Contour endocardial borders in end diastole and systole on apical 4, 3 and 2 chamber	Systolic function—may be decreased in HFpEF [41, 42, 43].
Diastolic function		
E′ septum and E′ lateral wall	Tissue Doppler sample volume at septal and lateral basal LV regions	Early diastolic velocity of mitral annular motion—decreased in HFpEF
Mitral flow velocities (E/A)	PW Doppler sample volume at the tips of the mitral valve leaflets to gain peak velocity in early diastole (E wave), peak velocity in late diastole (A wave)	Progressive diastolic dysfunction: delayed relaxation (E/A <0.8), pseudonormalization (E/A 0.8–1.5) and restrictive pattern (E/A ≥2) [39, 40, 44]
E:e′ ratio	Ratio of peak mitral valve inflow velocity during early diastole (E wave) to the average septal/lateral mitral annular early diastolic velocity (e′)	Increased in HFpEF and when >15, diagnostic of increased LV filling pressures [39, 45, 46]
Peak TR jet velocity	Peak velocity through tricuspid valve during systole, measured by using continuous wave (CW) Doppler aligned over colour flow to obtain the highest velocity	TR velocity >2.8 m/s is an indirect marker of LV diastolic dysfunction and indicates increased pulmonary artery systolic pressure (PASP) [39]
LAVI, or the LA maximal volume indexed to body surface area	Measured using two orthogonal long-axis views	Increased in HFpEF [39, 47]
LVH [LVMI, regional wall thickness (RWT)]	LVMI uses 2-dimensional measurements in one view while RWT allows classification into concentric (>0.42) or eccentric hypertrophy (≤0.42).	May be increased in HFpEF

HF risk decreases compared with dialysis but the exact prevalence of HFpEF is unknown, as HF is most commonly reported using administrative data rather than diagnostic testing.

The diagnosis of HFpEF in patients with CKD is challenging. Typical HF manifestations overlap with symptoms of fluid overload due to sodium and water retention as a result of CKD itself. Serum brain natriuretic peptide (BNP) levels require different threshold levels in CKD and typical echocardiographic findings (such as concentric remodelling or LVH and left atrial enlargement) are common but might not represent an incident HF event [59].

CKD and HFpEF share common risk factors, such as older age, diabetes, hypertension and cardiovascular disease. Although they may evolve independently of one another, the presence of one condition appears to accelerate the presentation and progression of an other. Experimental studies suggest a common pathway of endothelial dysfunction and inflammation leading to both cardiac and renal fibrosis [60, 61]. More interestingly, several observations suggest CKD in the pathogenic processes leading to HFpEF [62]. In the Prevention of Renal and Vascular End-stage Disease (PREVEND) trial [63], baseline elevations in urinary albumin excretion and cystatin C (in addition to atrial fibrillation and female sex) increased the risk of new-onset HFpEF but not HFrEF. In another study from the Swedish Heart Failure Registry, CKD was more common in HFpEF than in HFrEF but less strongly associated with mortality, suggesting that it represents one of many comorbidities and may have more of a bystander role than it does in HFrEF [64]. Decreased eGFR is independently associated with an increased risk of all-cause mortality, cardio-vascular mortality and hospitalization in patients with HFpEF [64–66].

Imaging the heart in CKD

Early studies with echocardiography showed that at the time of commencing renal replacement therapy, the majority of CKD patients had normal LVEF and cardiac dimensions, but 32% had LV dilation with preserved systolic function and 74% had concentric LVH [67, 68]. The association of CKD with abnormalities in cardiac structure is now well established [4]. Cardiac structural abnormalities common to CKD include LVH, ventricular dilation and myocardial fibrosis [6]. The development of these features, in association with decreased cardiac function, often without coronary artery disease, is consistent with cardiomyopathy specifically related to CKD—sometimes termed 'uraemic cardiomyopathy' [69]. Decreased LVEF is a late finding of uraemic cardiomyopathy [70], however, earlier abnormalities in myocardial function can be demonstrated by echocardiographic assessment of GLS. In CKD, echocardiographic assessment of GLS has been shown to associate with histologically confirmed myocardial fibrosis [71] and to be predictive of clinical outcomes [71, 72]. So echocardiography is of great utility in CKD. Echocardiography has limitations, requiring suitable windows for ultrasound and, in advanced CKD, dialysis associated fluid shifts may lead to overestimation of ventricular indices [73]. CMRI is an invaluable tool in the assessment of cardiac structural and functional changes in CKD.
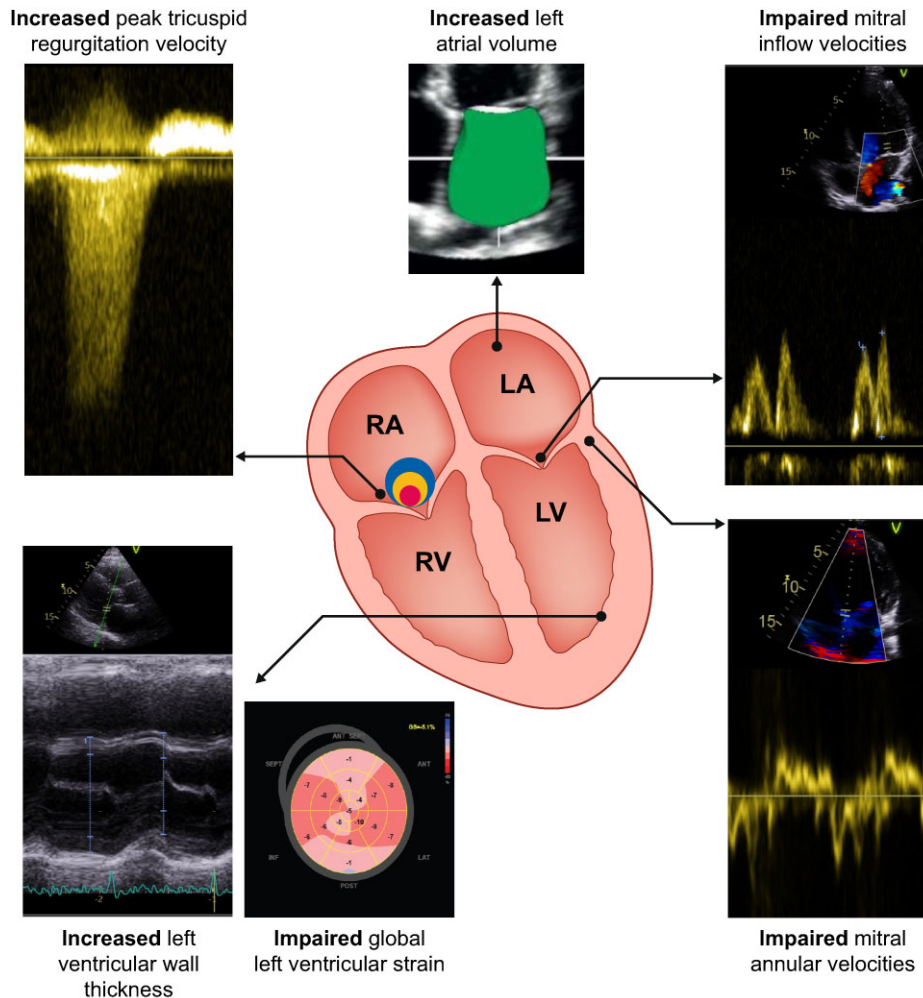
Increased peak tricuspid regurgitation velocity

Increased left atrial volume

Impaired mitral inflow velocities

Increased left ventricular wall thickness

Impaired global left ventricular strain

Impaired mitral annular velocities

FIGURE 2: Imaging findings non echocardiography to consider in assessment of HFpEF.

CMRI can detect altered GLS in patients with CKD, which has been associated with outcomes [74]. In a study of HD patients, CMRI-GLS was associated with left ventricular mass index (LVMI) and negatively correlated with LVEF [75]. Improvements in cardiac strain have been demonstrated following kidney transplantation [76]. In contrast, acute deteriorations in cardiac strain, myocardial perfusion and segmental LV dysfunction were demonstrated during dialysis in an impressive study that scanned people during an HD session [77]. Gadolinium contrast-enhanced CMRI previously demonstrated gadolinium enhancement consistent with diffuse myocardial fibrosis that is associated with LVH in patients with kidney failure [78, 79]. Gadolinium contrast agents are no longer routinely used in advanced CKD because of their association with nephrogenic systemic fibrosis [80]. However, non-contrast CMRI techniques have rapidly developed. T1 mapping is a promising non-invasive surrogate marker of myocardial fibrosis. T1 times have been demonstrated to be abnormally long in HD populations when compared with controls [75, 81]. Although T1 times correlate with histological findings of myocardial fibrosis in other conditions, such as aortic stenosis [82], recent studies have increased uncertainty about the influence of myocardial oedema and fluid shifts on their reproducibility in people requiring dialysis [83].

The use of N-terminal pro-brain natriuretic peptide (NT-proBNP) for assessing cardiac function in CKD

The diagnosis of HFrEF has been made considerably easier by the use of serum levels of natriuretic peptides, in particular, NT-proBNP to indicate patients who are likely to have LV systolic dysfunction [84]. Current ESC guidelines suggest measurement of NT-proBNP in patients with symptoms of HF and proceeding to echocardiography if NT-proBNP is >125 pmol/L. Below this value, HF is unlikely [10]. Furthermore, NT-proBNP has prognostic value, with patients with the highest NT-proBNP at greatest risk of mortality, irrespective of the presence of HFrEF or HFpEF [85].

In patients with CKD not on dialysis, NT-proBNP (or BNP) can be used in the diagnosis of LV systolic dysfunction with similar accuracy to non-CKD controls, although higher diagnostic threshold values are required [86, 87]. It is less clear how well NT-proBNP performs as a diagnostic tool for HFpEF in the setting of CKD. There is clear evidence that NT-proBNP correlates with LV mass in people with CKD, so it is likely to highlight patients at risk of developing clinical HF [88], irrespective of whether there is a specific diagnostic cut point for NT-proBNP as a diagnostic tool in the breathless patient [89]. NT-proBNP has been shown to correlate with CKD-specific changes on CMRI [86]. In people on

dialysis, BNP and NT-proBNP have prognostic value but a limited role in the diagnosis of HF [90, 91].

Fluid status assessment to improve HF outcomes in CKD

Bioimpedance body composition monitoring uses electrodes to pass electrical currents through the body to derive the proportions of fluid, lean tissue mass and fat. Two randomized controlled trials (RCTs) failed to show meaningful clinical benefit from using bioimpedance to guide fluid management in patients on peritoneal dialysis [92] and HD, respectively [93]. The BioImpedance Spectroscopy To maintain Renal Output (BISTRO) trial [94] will assess the impact of bioimpedance-guided fluid management on residual renal function in >500 dialysis patients and will also report on cardiovascular events as secondary outcomes.

Point-of-care lung ultrasound is a promising tool in the assessment of fluid status in CKD but does not yet have hard clinical outcome data supporting its use [95–97]. Lung ultrasound has been shown to more frequently detect interstitial fluid than traditional clinical assessment in dialysis cohorts [98], and these findings (presence of 'B-lines') are associated with increased mortality in this population [99]. In a trial of 71 dialysis patients, ultrasound-guided lung dry weight assessment led to improved blood pressure [100] and improved LV dimensions (but not function) [101]. In a separate trial in dialysis patients at high cardiovascular risk, lung ultrasound successfully relieved lung congestion compared with standard care, but without an improvement in the primary outcome (composite of all-cause death, non-fatal myocardial infarction and decompensated HF) [102].

RCTs addressing HFpEF not targeting CKD populations

There has been dramatic progress in improving outcomes in patients with HFrEF with renin–angiotensin system inhibitors (RASis), beta-blockers, mineralocorticoid receptor antagonists (MRAs) and most recently sodium-glucose cotransporter 2 inhibitors (SGLT2is), all based on large RCTs [103]. The same has not been the case for HFpEF. Table 3 summarizes the major clinical trials in HFpEF and clinical trials relevant to CKD. One of the first large RCTs to address HFpEF showed no benefit in outcomes with irbesartan compared with placebo [104], and similarly, no overall benefit was seen with spironolactone compared with placebo in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) [105]. There were major regional differences observed in TOPCAT, with a definite significant benefit with MRAs in many countries [106]. The angiotensin receptor–neprilysin inhibitor sacubitril–valsartan showed no statistically significant benefit compared with valsartan alone in a large RCT in HFpEF despite the benefit with this agent in HFrEF [107, 108].

The advent of SGLT2is offers a new therapeutic paradigm in HFpEF. Early insights into the potential benefit of SGLT2is in HFpEF came from the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST) RCT where, compared with placebo, sotagliflozin was associated with a significantly lower incidence of the primary outcome of cardiovascular mortality or hospitalization for HF patients with baseline LVEF >50% but not those with LVEF <50% [109]. In the landmark Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial, empagliflozin was associ-

ated with a lower incidence of combined cardiovascular death or hospitalization for HF [110]. These results have prompted the licencing of empagliflozin as a treatment for HF in the USA regardless of LVEF and demonstrate that SGLT2is represent the first therapy to demonstrate efficacy in HFpEF. Finally, the EMPULSE trial demonstrated that in patients with acute HF, the addition of empagliflozin 10 mg daily was associated with a combined improvement in HF outcomes and/or quality of life compared with placebo, with no differences between subgroups with HFpEF or HFrEF [111].

Interventions to alleviate HFpEF in CKD

There are few trials that have directly investigated interventions for HFpEF specific to CKD. Most RCTs have employed changes in LV parameters, namely LVMI and LVEF, as an outcome that is a reasonable surrogate for the risk of developing HFpEF. A number of pharmacological interventions often used in HFrEF have been investigated in CKD. In dialysis patients with dilated cardiomyopathy, the beta-blocker carvedilol shows significant improvement in LV function and dilatation with an associated improvement in survival after 2 years [112]. A meta-analysis of five RCTs exploring the effect of RASis with angiotensin-converting enzyme inhibition or angiotensin receptor blockers on LVMI in HD patients demonstrated a significant reduction in LVMI {mean difference 15.4 g/m^2 [95% confidence interval (CI) 7.4–23.3]; P < .001} but no statistical improvement in cardiovascular morbidity or mortality [113]. Spironolactone has also been shown to decrease LV mass in early CKD (stages 1 and 2) [114], but had no significant effect on LVMI in HD patients in one RCT or diastolic dysfunction in another similarly sized RCT [115, 116].

Other strategies that have theoretical benefits on cardiac outcomes have been tested. A number of studies have investigated the effect of anaemia correction in CKD. A meta-analysis of 15 studies including CKD patients demonstrated significant reductions in LVMI [−33.7 g/m^2 (95% CI −49.4 to −16.1), P < .05] in patients with anaemia (haemoglobin <100 g/L at baseline) given erythropoietin and aiming for a level ≤ 120 g/L. The effect was not altered by dialysis status and did not show significant regression of LVMI in patients with milder anaemia.

In one of the few outcome studies to demonstrate a benefit on HF outcomes in dialysis, the Proactive IV IrOn Therapy in HaemodiALysis Patients (PIVOTAL) study demonstrated high-dose intravenous iron to be safe and efficacious [117], with post hoc analyses demonstrating significant improvements in HF events [hazard ratio (HR) 0.66 (95% CI 0.46–0.94)] [118]. An RCT investigating the effect of intravenous iron in patients with chronic HF and CKD demonstrated significant improvement in LV systolic and diastolic diameters and LV function. LV wall thickness was decreased in the treatment arm but did not reach statistical significance [119].

Dysregulation of bone mineral metabolism with subsequent hyperparathyroidism and vascular calcification are associated with LVH [120]. However, interventions to decrease its effect on cardiac function have demonstrated variable effects. The Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity (PRIMO) study was an RCT investigating the effect of paricalcitol on cardiac structure and function in CKD patients and showed no effect on LVMI or other echocardiographic measures of diastolic function [121]. Post hoc analysis of the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial demonstrated use of the calcimimetic, cinacalcet for 64 months significantly decreased the risk of

Table 3. Summary of significant RCTs in addressing HFpEF and/or surrogates of HFpEF in patients with CKD and/or treated with dialysis

Trial [reference]	Population	N	Intervention	Duration	Primary outcome(s)	Comments
I-PRESERVE [104]	HF and LVEF ≥45% and creatinine <221 µmol/L	4128	Irbesartan 300 mg or placebo	Mean 49.5 months	Death and cardiovascular hospitalization	No improvement in primary outcome with irbesartan
TOPCAT [105]	HF and LVEF ≥45% and eGFR >30 mL/min/1.73 m^2	3445	Spironolactone 15–45 mg or placebo	Mean 3.3 years	Cardiovascular death and HF hospitalization	No difference in primary outcome between groups
PARAGON-HF [107]	HF and LVEF ≥ 45% and eGFR > 30 mL/min/1.73 m^2	4822	Sacubitril–valsartan or valsartan	Median 35 months	Cardiovascular death and HF hospitalization	No difference in primary outcome between groups
SOLOIST [109]	Patients with type 2 DM recently hospitalized with HF and eGFR >30 mL/min/1.73 m^2	1222	Sotagliflozin 200–400 mg or placebo	Median 9.0 months	Cardiovascular death and HF hospitalization	Significant benefit [HR 0.69 (95% CI 0.52–0.85)] with sotagliflozin. Benefit in subgroup LVEF ≥50% [HR 0.48 (95% CI 0.27–0.86)]
EMPEROR-Preserved [110]	Symptomatic HF and LVEF ≥40% and eGFR >20 mL/min/1.73 m^2	5988	Empagliflozin 10 mg or placebo	Median 26.2 months	Cardiovascular death and HF hospitalization	Significant benefit with empagliflozin [HR 0.79 (95% CI 0.69–0.90)]
EMPULSE [111]	HF regardless of LVEF and eGFR >20 mL/min/1.73 m^2	530	Empagliflozin 10 mg or placebo	90 days	Clinical benefit, composite of death, HF events and QoL	Empagliflozin clinical benefit compared with placebo-stratified win ratio [1.36 (95% CI 1.09–1.68)]
SPIRO-CKD [137]	Non-diabetic CKD eGFR 30–89 mL/min/1.73 m^2	154	Spironolactone 25 mg or chlorthalidone 25 mg	40 weeks	LVM on CMR	No difference in LVM between groups
CREDENCE [129]	Diabetes and eGFR 30–89 mL/min/1.73 m^2 and albuminuria	4401	Canagliflozin 100 mg or placebo	Median 2.62 years	ESKD, doubling creatinine, death from renal or CV causes	Reduction in primary outcome with canagliflozin [HR 0.70 (95% CI 0.59–0.82)] HF hospitalization [HR 0.61 (95% CI 0.47–0.80)]
DAPA-CKD [130]	CKD eGFR 25–75 mL/min/1.73 m^2 and albuminuria	4304	Dapagliflozin 10 mg or placebo	Median 2.4 years	ESKD, decline in eGFR ≥50%, death from renal or CV causes	Reduction in primary outcome with dapagliflozin [HR 0.61 (95% CI 0.51–0.72)], HF hospitalization [HR 0.51 (95% CI 0.34–0.76)]
SPIN-DIAL [115, 116]	Patients on HD	129	Spironolactone (12.5–50 mg) or placebo	36 weeks	Assess safety and tolerability of intervention	No difference in diastolic function on echocardiography between groups
Hammer et al. [115]	Patients on HD	97	Spironolactone 50 mg or placebo	40 weeks	LVMI on CMRI	No difference in LVMI between groups
PIVOTAL [118]	Patients on HD >3 months and treated with ESA	2141	Proactive or reactive intravenous iron	Median 2.1 years	Death, myocardial infarction, stroke, HF hospitalisation	Proactive iron fewer primary end point events that reactive iron. Significant reduction in HF events with proactive iron [HR 0.66 (95% CI 0.46–0.94)]
PRIMO [121]	CKD, mild-moderate LVH, LVEF ≥50%, eGFR 15–60 mL/min/1.73 m^2	227	Paricalcitol or no therapy	48 weeks	LVMI on CMRI	No difference in LVMI between groups

Table 3. Continued

Trial [reference]	Population	N	Intervention	Duration	Primary outcome(s)	Comments
EVOLVE [122]	Patients on HD with hyperparathyroidism	3883	Cinacalcet or placebo	Mean 21.2 months	Death or cardiovascular event	No difference in primary outcome between groups. Fewer non-atherosclerotic CV events (including HF, sudden death) with cinacalcet [HR 0.84 (95% CI 0.74–0.96)]
Dörr et al. [124]	Patients on HD with hyperparathyroidism and LVH	62	Intravenous etelcalcetide or alfacalcidol	12 months	LVMI on CMRI	Significantly less progression LVMI with etelcalcetide
Odudu et al. [132]	Patients on HD	73	Dialysate 37°C or 0.5°C below body temperature	12 months	LVEF at CMRI	No change in primary endpoint but decreased LVMI with cool dialysis
FHN [131]	Patients on HD	245	Six times HD/week versus three times HD/week	12 months	Composite of mortality, QoL and LV mass	Decreased LV mass with frequent HD

CV: cardiovascular; DM: diabetes mellitus; ESKD: end-stage kidney disease; QoL: quality of life.

sudden cardiac death and HF [122]. Additionally, cinacalcet was associated with improvement of LVH on CMRI in a small RCT of 36 months, in HD patients [123]. More recently, suppression of fibroblast growth factor-23 by the calcimimetic etelcalcetide was associated with a significant reduction in CMRI assessed LVMI [124].

Other agents with putative benefits on LVMI have been tried with variable results. An RCT investigating the effect of allopurinol in CKD patients demonstrated that 9 months of treatment was statistically associated with regression of CMRI-measured LVMI [125]. An association was not shown in a similar study in HD patients [126]. In a different study looking at the effect of treatment with levocarnitine in patients with biochemical evidence of deficiency, replacement therapy for 12 months was associated with regression of LVH compared with no supplementation [127].

Although baseline echocardiography was not performed in the large Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trials, which showed the benefit of SGLT2is on cardiorenal outcomes in CKD, there was a clear benefit on HF incidence with SGLTis in both RCTs [128, 129]. Further subgroups analysis of DAPA-CKD demonstrated no difference in benefits of dapagliflozin in patients with or without prior HF [130].

In patients on dialysis, there is a need to test non-pharmacological interventions to improve LV changes by modifying the doses and characteristics of dialysis. The Frequent Haemodialysis Network daily trial showed that dialysis six times a week was associated with improved LV volumes, measured by CMRI, compared with thrice-weekly treatments [131]. In an RCT of patients starting maintenance HD, reducing dialysate temperature by 1.2 ± 0.3°C was also associated with slowing progression of LVH and echocardiographic markers of diastolic dysfunction [132], but it did not have a statistically significant effect on LV function. Successful kidney transplantation is associated with improved fluid status and blood pressure and is considered the gold standard treatment for kidney failure given its benefits on morbidity and mortality. Regression of LVH has been demonstrated after successful transplantation using echocardiography [133], but this may have been confounded by improved fluid status and its effect on measuring LV mass. Studies using CMRI have not demonstrated a similar significant reduction in LV mass after transplantation but have shown a decrease in CMRI-measured markers of myocardial fibrosis [134, 135]. Nevertheless, HF remains a significant clinical concern post-transplant, occurring in 10–20% of patients in the first year [136].

CONCLUSIONS

Although it has long been recognized that CKD is a risk factor for HF and that LVH is more prevalent in patients with advanced CKD than impaired LV function, it is now clear that HFpEF is one of, if not the dominant subtype of cardiovascular disease in patients with advanced CKD. Recent evidence from positive clinical trials in HFpEF demonstrated that progress is finally being made in improving outcomes in this condition. Greater awareness of HFpEF combined with widespread implementation of evidence-based therapy with SGLT2is should be a priority. Emerging evidence for adjunctive strategies such as lung ultrasound and bioimpedance specifically to address cardiovascular outcomes give further hope that we are entering a new era for addressing HFpEF in patients with CKD, including those requiring dialysis.

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CONFLICT OF INTEREST STATEMENT

REFERENCES

1. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073–2081

2. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013; **382**: 339–352

3. Matsushita K, Coresh J, Sang Y et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. lancet. *Lancet Diabetes Endocrinol* 2015; **3**: 514–525

4. Paoletti E, De Nicola L, Gabbai FB et al. Associations of left ventricular hypertrophy and geometry with adverse outcomes in patients with CKD and hypertension. *Clin J Am Soc Nephrol* 2016; **11**: 271–279

5. House AA, Wanner C, Sarnak M et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019; **95**: 1304–1317

6. Parfrey PS, Foley RN, Harnett JD et al. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant* 1996; **11**: 1277–1285

7. Rossignol P, Agarwal R, Canaud B et al. Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints. *Eur Heart J* 2019; **40**: 880–886

8. Konstantinidis I, Nadkarni GN, Yacoub R et al. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med* 2016; **176**: 121–124

9. Damman K, Tang WH, Felker GM et al. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol* 2014; **63**: 853–871

10. McDonagh TA, Metra M, Adamo M et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42**: 3599–3726

11. Koh AS, Tay WT, Teng THK et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail* 2017; **19**: 1624–1634

12. Kapoor JR, Kapoor R, Ju C et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. *JACC: Heart Failure* 2016; **4**: 464–472

13. Bozkurt B, Coats AJ, 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. *J Card Fail* 2021; **23**: 352–380

14. van Riet EE, Hoes AW et al. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016; **18**: 242–252

15. Vasan RS, Larson MG, Benjamin EJ et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; **33**: 1948–1955

16. Kitzman DW, Gardin JM, Gottdiener JS et al. Importance of heart failure with preserved systolic function in patients ≥65 years of age. *Am J Cardiol* 2001; **87**: 413–419

17. Gottdiener JS, McClelland RL, Marshall R et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002; **137**: 631–639

18. Tribouilloy C, Rusinaru D, Mahjoub H et al. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. *Eur Heart J* 2008; **29**: 339–347

19. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res* 2019; **124**: 1598–1617

20. Lenzen MJ, Scholte op Reimer WJ, Boersma E et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the Euroheart Failure Survey. *Eur Heart J* 2004; **25**: 1214–1220

21. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2020; **17**: 559–573

22. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017; **14**: 591–602

23. Mooney L, Goodyear CS, Chandra T et al. Clonal haematopoiesis of indeterminate potential: intersections between inflammation, vascular disease and heart failure. *Clin Sci (Colch)* 2021; **135**: 991–1007

24. Rush CJ, Berry C, Oldroyd KG et al. Prevalence of coronary artery disease and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *JAMA Cardiol* 2021; **6**: 1130–1143

25. Bursi F, Weston SA, Redfield MM et al. Systolic and diastolic heart failure in the community. *JAMA* 2006; **296**: 2209–2216

26. Owan TE, Hodge DO, Herges RM et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355**: 251–259

27. Bhatia RS, Tu JV, Lee DS et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; **355**: 260–269

28. Kupari M, Lindroos M, Iivanainen AM et al. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. *J Intern Med* 1997; **241**: 387–394

29. Solomon SD, Anavekar N, Skali H *et al.* Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005; **112**: 3738–3744

30. Gerber Y, Weston SA, Redfield MM *et al.* A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern. Med.* 2015; **175**: 996–1004

31. Loop MS, Van Dyke MK, Chen L *et al.* Comparison of length of stay, 30-day mortality, and 30-day readmission rates in Medicare patients with heart failure and with reduced versus preserved ejection fraction. *Am J Cardiol* 2016; **118**: 79–85

32. Lewis EF, Lamas GA, O'Meara E *et al.* Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. *Eur J Heart Fail* 2007; **9**: 83–91

33. Pieske B, Tschöpe C, de Boer RA *et al.* How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019; **40**: 3297–3317

34. Smiseth OA, Morris DA, Cardim N *et al.* Multimodality imaging in patients with heart failure and preserved ejection fraction: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2022; **23**: e34–e61

35. Lang RM, Badano LP, Mor-Avi V *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 233–271

36. Lang RM, Badano LP, Tsang W *et al.* EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *J Am Soc Echocardiogr* 2012; **25**: 3–46

37. Galderisi M, Cosyns B, Edvardsen T *et al.* Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1301–1310

38. Reddy YNV, Carter RE, Obokata M *et al.* Evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018; **138**: 861–870

39. Nagueh SF, Smiseth OA, Appleton CP *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29**: 277–314

40. Smiseth OA. Evaluation of left ventricular diastolic function: state of the art after 35 years with Doppler assessment. *J Echocardiogr* 2018; **16**: 55–64

41. Voigt JU, Pedrizzetti G, Lysyansky P *et al.* Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 1–11

42. Kraigher-Krainer E, Shah AM, Gupta DK *et al.* Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2014; **63**: 447–456

43. Morris DA, Ma X-X, Belyavskiy E *et al.* Left ventricular longitudinal systolic function analysed by 2D speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis. *Open Heart* 2017; **4**: e000630

44. Schirmer H, Lunde P, Rasmussen K. Mitral flow derived Doppler indices of left ventricular diastolic function in a general population. The Tromsø Study. *Eur Heart J* 2000; **21**: 1376–1386

45. Kasner M, Westermann D, Lopez B *et al.* Diastolic tissue Doppler indexes correlate with the degree of collagen expression and cross-linking in heart failure and normal ejection fraction. *J Am Coll Cardiol* 2011; **57**: 977–985

46. Obokata M, Reddy YNV, Borlaug BA. The role of echocardiography in heart failure with preserved ejection fraction: what do we want from imaging? *Heart Fail Clin* 2019; **15**: 241–256

47. Pritchett AM, Mahoney DW, Jacobsen SJ *et al.* Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol* 2005; **45**: 87–92

48. Lancellotti P, Pellikka PA, Budts W *et al.* The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 1191–1229

49. Ha JW, Andersen OS, Smiseth OA. Diastolic stress test: invasive and noninvasive testing. *JACC Cardiovasc Imaging* 2020; **13**: 272–282

50. Obokata M, Kane GC, Reddy YN *et al.* Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation* 2017; **135**: 825–838

51. Ferreira VM, Schulz-Menger J, Holmvang G *et al.* Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 2018; **72**: 3158–3176

52. Cosyns B, Lochy S, Luchian ML *et al.* The role of cardiovascular imaging for myocardial injury in hospitalized COVID-19 patients. *Eur Heart J Cardiovasc Imaging* 2020; **21**: 709–714

53. Grothues F, Smith GC, Moon JC *et al.* Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002; **90**: 29–34

54. Seferović PM, Polovina M, Bauersachs J *et al.* Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; **21**: 553–576

55. Pereira NL, Grogan M, Dec GW. Spectrum of restrictive and infiltrative cardiomyopathies: part 2 of a 2 part series. *J Am Coll Cardiol* 2018; **71**: 1149–1166

56. Saran R, Robinson B, Abbott KC *et al.* US Renal Data System 2018 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2019; **73**: A7–A8

57. McAlister FA, Ezekowitz J, Tarantini L *et al.* Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. *Circ Heart Fail* 2012; **5**: 309–314

58. United States Renal Data System. *Annual Data Report 2016.* Chapter 9: Cardiovascular Disease in Patients with ESRD. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2016

59. Stewart GA, Gansevoort RT, Mark PB *et al.* Electrocardiographic abnormalities and uremic cardiomyopathy. *Kidney Int* 2005; **67**: 217–226

60. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013; **62**: 263–271

61. Ter Maaten JM, Damman K, Verhaar MC *et al*. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. *Eur J Heart Fail* 2016; **18**: 588–598

62. Fang JC. Heart failure with preserved ejection fraction: a kidney disorder? *Circulation* 2016; **134**: 435–437

63. Smink PA, Lambers Heerspink HJ, Gansevoort RT *et al*. Albuminuria, estimated GFR, traditional risk factors, and incident cardiovascular disease: the PREVEND (Prevention of Renal and Vascular End-Stage Disease) study. *Am J Kidney Dis* 2012; **60**: 804–811

64. Löfman I, Szummer K, Dahlström U *et al*. 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**: 1606–1614

65. Hillege HL, Nitsch D, Pfeffer MA *et al*. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006; **113**: 671–678

66. Smith DH, Thorp ML, Gurwitz JH *et al*. Chronic kidney disease and outcomes in heart failure with preserved versus reduced ejection fraction: the Cardiovascular Research Network PRESERVE Study. *Circ Cardiovasc Qual Outcomes* 2013; **6**: 333–342

67. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32(5 Suppl 3)**: S112–S119

68. Foley RN, Parfrey PS, Harnett JD *et al*. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; **47**: 186–192

69. Kunz K, Dimitrov Y, Muller S *et al*. Uraemic cardiomyopathy. *Nephrol Dial Transplant* 1998; **13**: 39–43

70. London GM, Pannier B, Guerin AP *et al*. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol* 2001; **12**: 2759–2767

71. Kramann R, Erpenbeck J, Schneider RK *et al*. Speckle tracking echocardiography detects uremic cardiomyopathy early and predicts cardiovascular mortality in ESRD. *J Am Soc Nephrol* 2014; **25**: 2351–2365

72. Liu YW, Su CT, Sung JM *et al*. Association of left ventricular longitudinal strain with mortality among stable hemodialysis patients with preserved left ventricular ejection fraction. *Clin J Am Soc Nephrol* 2013; **8**: 1564–1574

73. Stewart GA, Foster J, Cowan M *et al*. Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. *Kidney Int* 1999; **56**: 2248–2253

74. Rankin AJ, Zhu L, Mangion K *et al*. Global longitudinal strain by feature-tracking cardiovascular magnetic resonance imaging predicts mortality in patients with end-stage kidney disease. *Clin Kidney J* 2021; **14**: 2187–2196

75. Rutherford E, Talle MA, Mangion K *et al*. Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1 mapping. *Kidney Int* 2016; **90**: 845–852

76. Gong IY, Al-Amro B, Prasad GVR *et al*. Cardiovascular magnetic resonance left ventricular strain in end-stage renal disease patients after kidney transplantation. *J Cardiovasc Magn Reson* 2018; **20**: 83

77. Buchanan C, Mohammed A, Cox E *et al*. Intradialytic cardiac magnetic resonance imaging to assess cardiovascular responses in a short-term trial of hemodiafiltration and hemodialysis. *J Am Soc Nephrol* 2017; **28**: 1269–1277

78. Mark PB, Johnston N, Groenning BA *et al*. Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. *Kidney Int* 2006; **69**: 1839–1845

79. Schietinger BJ, Brammer GM, Wang H *et al*. Patterns of late gadolinium enhancement in chronic hemodialysis patients. *JACC Cardiovasc Imaging* 2008; **1**: 450–456

80. Collidge TA, Thomson PC, Mark PB *et al*. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort. *Radiology* 2007; **245**: 168–175

81. Graham-Brown MP, March DS, Churchward DR *et al*. Novel cardiac nuclear magnetic resonance method for noninvasive assessment of myocardial fibrosis in hemodialysis patients. *Kidney Int* 2016; **90**: 835–844

82. Bull S, White SK, Piechnik SK *et al*. Human non-contrast T1 values and correlation with histology in diffuse fibrosis. *Heart* 2013; **99**: 932–937

83. Rankin AJ, Mangion K, Lees JS *et al*. Myocardial changes on 3T cardiovascular magnetic resonance imaging in response to haemodialysis with fluid removal. *J Cardiovasc Magn Reson* 2021; **23**: 125

84. McDonagh TA, Holmer S, Raymond I *et al*. NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies. *Eur J Heart Fail* 2004; **6**: 269–273

85. Salah K, Stienen S, Pinto YM *et al*. Prognosis and NT-proBNP in heart failure patients with preserved versus reduced ejection fraction. *Heart* 2019; **105**: 1182–1189

86. Arcari L, Engel J, Freiwald T *et al*. Cardiac biomarkers in chronic kidney disease are independently associated with myocardial edema and diffuse fibrosis by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2021; **23**: 71

87. Mark PB, Stewart GA, Gansevoort RT *et al*. Diagnostic potential of circulating natriuretic peptides in chronic kidney disease. *Nephrol Dial Transplant* 2006; **21**: 402–410

88. Bansal N, Hyre Anderson A, Yang W *et al*. High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: the Chronic Renal Insufficiency Cohort (CRIC) Study. *J Am Soc Nephrol* 2015; **26**: 946–956

89. Vickery S, Price CP, John RI *et al*. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis* 2005; **46**: 610–620

90. Cheng YJ, Yao FJ, Liu LJ *et al*. B-type natriuretic peptide and prognosis of end-stage renal disease: a meta-analysis. *PLoS One* 2013; **8**: e79302

91. deFilippi CR, Herzog CA. Interpreting cardiac biomarkers in the setting of chronic kidney disease. *Clin Chem* 2017; **63**: 59–65

92. Tian N, Yang X, Guo Q *et al*. Bioimpedance guided fluid management in peritoneal dialysis: a randomized controlled trial. *Clin J Am Soc Nephrol* 2020; **15**: 685–694

93. Sommerer C, Felten P, Toernig J *et al*. Bioimpedance analysis is not superior to clinical assessment in determining hydration status: a prospective randomized-controlled trial in a Western dialysis population. *Hemodial Int* 2021; **25**: 380–390

94. Davies SJ, Caskey FJ, Coyle D *et al*. Rationale and design of BISTRO: a randomized controlled trial to determine

whether bioimpedance spectroscopy-guided fluid management maintains residual kidney function in incident haemodialysis patients. *BMC Nephrol* 2017; **18**: 138

95. Koratala A, Ronco C, Kazory A. The promising role of lung ultrasound in assessment of volume status for patients receiving maintenance renal replacement therapy. *Blood Purif* 2020; **49**: 643–646

96. Zoccali C. Lung ultrasound in the management of fluid volume in dialysis patients: potential usefulness. *Semin Dial* 2017; **30**: 6–9

97. Covic A, Siriopol D, Voroneanu L. Use of lung ultrasound for the assessment of volume status in CKD. *Am J Kidney Dis* 2018; **71**: 412–422

98. Torino C, Gargani L, Sicari R *et al*. The agreement between auscultation and lung ultrasound in hemodialysis patients: the LUST Study. *Clin J Am Soc Nephrol* 2016; **11**: 2005–2011

99. Zoccali C, Torino C, Tripepi R *et al*. Pulmonary congestion predicts cardiac events and mortality in ESRD. *J Am Soc Nephrol* 2013; **24**: 639–646

100. Loutradis C, Sarafidis PA, Ekart R *et al*. The effect of dry-weight reduction guided by lung ultrasound on ambulatory blood pressure in hemodialysis patients: a randomized controlled trial. *Kidney Int* 2019; **95**: 1505–1513

101. Loutradis C, Papadopoulos CE, Sachpekidis V *et al*. Lung ultrasound-guided dry weight assessment and echocardiographic measures in hypertensive hemodialysis patients: a randomized controlled study. *Am J Kidney Dis* 2020; **75**: 11–20

102. Zoccali C, Torino C, Mallamaci F *et al*. A randomized multi-center trial on a lung ultrasound-guided treatment strategy in patients on chronic hemodialysis with high cardiovascular risk. *Kidney Int* 2021; **100**: 1325–1333

103. 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**: 3599–3726

104. Massie BM, Carson PE, McMurray JJ *et al*. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359**: 2456–2467

105. Pitt B, Pfeffer MA, Assmann SF *et al*. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**: 1383–1392

106. Pfeffer MA, Claggett B, Assmann SF *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

107. Solomon SD, McMurray JJV, Anand IS *et al*. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; **381**: 1609–1620

108. McMurray JJV, Packer M, Desai AS *et al*. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993–1004

109. Bhatt DL, Szarek M, Steg PG *et al*. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021; **384**: 117–128

110. Anker SD, Butler J, Filippatos G *et al*. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385**: 1451–1461

111. Voors AA, Angermann CE, Teerlink JR *et al*. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med* 2022; **28**: 568–574

112. 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**: 1438–1444

113. Tai DJ, Lim TW, James MT *et al*. Cardiovascular effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in hemodialysis: a meta-analysis. *Clin J Am Soc Nephrol* 2010; **5**: 623–630

114. Edwards NC, Steeds RP, Stewart PM *et al*. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. *J Am Coll Cardiol* 2009; **54**: 505–512

115. Hammer F, Malzahn U, Donhauser J *et al*. A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients. *Kidney Int* 2019; **95**: 983–991

116. Charytan DM, Himmelfarb J, Ikizler TA *et al*. Safety and cardiovascular efficacy of spironolactone in dialysis-dependent ESRD (SPin-D): a randomized, placebo-controlled, multiple dosage trial. *Kidney Int* 2019; **95**: 973–982

117. Macdougall IC, Bhandari S, White C *et al*. Intravenous iron dosing and infection risk in patients on hemodialysis: a prespecified secondary analysis of the PIVOTAL trial. *J Am Soc Nephrol* 2020; **31**: 1118–1127

118. Jhund PS, Petrie MC, Robertson M *et al*. Heart failure hospitalization in adults receiving hemodialysis and the effect of intravenous iron therapy. *JACC Heart Fail* 2021; **9**: 518–527

119. Toblli JE, Di Gennaro F, Rivas C. Changes in echocardiographic parameters in iron deficiency patients with heart failure and chronic kidney disease treated with intravenous iron. *Heart Lung Circ* 2015; **24**: 686–695

120. Patel RK, Oliver S, Mark PB *et al*. Determinants of left ventricular mass and hypertrophy in hemodialysis patients assessed by cardiac magnetic resonance imaging. *Clin J Am Soc Nephrol* 2009; **4**: 1477–1483

121. Thadhani R, Appelbaum E, Pritchett Y *et al*. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA* 2012; **307**: 674–684

122. Wheeler DC, London GM, Parfrey PS *et al*. Effects of cinacalcet on atherosclerotic and nonatherosclerotic cardiovascular events in patients receiving hemodialysis: the EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) trial. *J Am Heart Assoc* 2014; **3**: e001363

123. Eddington H, Chinnadurai R, Alderson H *et al*. A randomised controlled trial to examine the effects of cinacalcet on bone and cardiovascular parameters in haemodialysis patients with advanced secondary hyperparathyroidism. *BMC Nephrol* 2021; **22**: 106

124. Dörr K, Kammer M, Reindl-Schwaighofer R *et al*. Randomized trial of etelcalcetide for cardiac hypertrophy in hemodialysis. *Circ Res* 2021; **128**: 1616–1625

125. Kao MP, Ang DS, Gandy SJ *et al*. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**: 1382–1389

126. Rutherford E, Ireland S, Mangion K *et al*. A randomized, controlled trial of the effect of allopurinol on left ventricular mass index in hemodialysis patients. *Kidney Int Rep* 2021; **6**: 146–155

127. Higuchi T, Abe M, Yamazaki T *et al*. Levocarnitine improves cardiac function in hemodialysis patients with left ventricular hypertrophy: a randomized controlled trial. *Am J Kidney Dis* 2016; **67**: 260–270

128. Heerspink HJL, Stefansson BV, Correa-Rotter R *et al*. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; **383**: 1436–1446

129. Perkovic V, Jardine MJ, Neal B *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; **380**: 2295–2306

130. McMurray JJV, Wheeler DC, Stefánsson BV *et al*. Effects of dapagliflozin in patients with kidney disease, with and without heart failure. *JACC Heart Fail* 2021; **9**: 807–820

131. Chan CT, Greene T, Chertow GM *et al*. Effects of frequent hemodialysis on ventricular volumes and left ventricular remodeling. *Clin J Am Soc Nephrol* 2013; **8**: 2106–2116

132. Odudu A, Eldehni MT, McCann GP *et al*. Randomized controlled trial of individualized dialysate cooling for cardiac protection in hemodialysis patients. *Clin J Am Soc Nephrol* 2015; **10**: 1408–1417

133. Montanaro D, Gropuzzo M, Tulissi P *et al*. Effects of successful renal transplantation on left ventricular mass. *Transplant Proc* 2005; **37**: 2485–2487

134. Contti MM, Barbosa MF, del Carmen Villanueva Mauricio A *et al*. Kidney transplantation is associated with reduced myocardial fibrosis. A cardiovascular magnetic resonance study with native T1 mapping. *J Cardiovasc Magn Reson* 2019; **21**: 21

135. Patel RK, Mark PB, Johnston N *et al*. Renal transplantation is not associated with regression of left ventricular hypertrophy: a magnetic resonance study. *Clin J Am Soc Nephrol* 2008; **3**: 1807–1811

136. Lentine KL, Schnitzler MA, Abbott KC *et al*. De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications. *Am J Kidney Dis* 2005; **46**: 720–733

137. Edwards NC, Price AM, Mehta S *et al*. Effects of spironolactone and chlorthalidone on cardiovascular structure and function in chronic kidney disease: a randomized, open-label trial. *Clin J Am Soc Nephrol* 2021; **16**: 1491–1501