Nephrol Dial Transplant (2023) 38: 1798–1806
https://doi.org/10.1093/ndt/gfad011
Advance Access publication date 23 January 2023

REVIEW

Management of heart failure in patients with kidney disease—updates from the 2021 ESC guidelines

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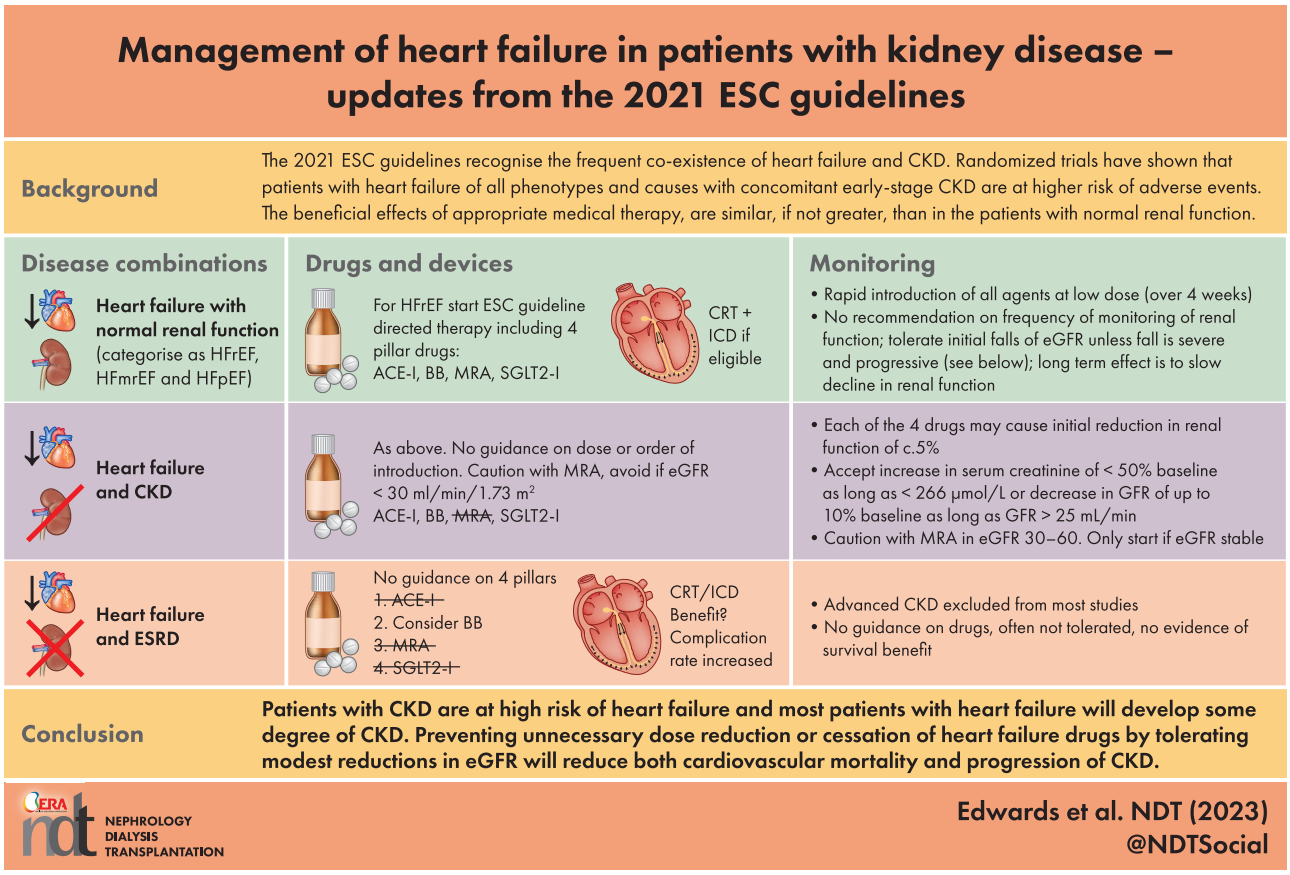
GRAPHICAL ABSTRACT



ABSTRACT

The wide overlap between the syndromes of chronic kidney disease (CKD) and chronic heart failure (HF) means that familiarity with the 2021 European Society of Cardiology guidelines is of importance to nephrologists. The common risk factors for the two syndromes together with the adverse cardiac structural remodelling associated with CKD means that many kidney disease patients experience breathlessness and fall within the HF phenotypes categorized in the guidelines. The management of HF is evolving rapidly leading to significant changes in the latest guideline iteration. The 2021 guidelines have changed from the 2016 version firstly by an increased focus on identifying the three phenotypes of HF to guide appropriate evidence-based management. Secondly, a new

and simplified treatment algorithm for HF with reduced ejection fraction involving the rapid sequential initiation and up-titration of four 'pillars' of drug treatment—angiotensin-converting enzyme inhibitors or angiotensin-neprilysin inhibitors, beta blockers, mineralocorticoid receptor antagonists and now, thanks to convincing trial data, sodium-glucose co-transporter 2 inhibitors. Thirdly, guidelines for device therapy have been changed with down-graded advice on indications for primary prevention implantable cardioverter defibrillator therapy for patients with non-ischaemic HF and for cardiac resynchronization therapy with left bundle branch block (LBBB) and a QRS duration <150 ms. There are updated treatment plans for HF associated with non-cardiovascular comorbidities including CKD.

Keywords: cardiorenal syndrome, cardiovascular, CKD, echocardiography, guidelines, heart failure

INTRODUCTION

Heart failure (HF) affects 1%–2% of the population in developed countries and at least 10% of those over 65 years of age [1]. There is extensive overlap between the syndromes of chronic HF and chronic kidney disease (CKD) not just because they share common risk factors such as diabetes and hypertension, but also because of the high prevalence of coronary disease and the even higher prevalence of non-ischaemic abnormalities of left ventricular structure and function in CKD. Historically, these changes have been termed uraemic cardiomyopathy, although the term CKD-associated cardiomyopathy might be more appropriate given the high prevalence of changes evident in mild–moderate CKD [2]. The complex bidirectional relationship between cardiac and kidney function is well recognized but not fully understood [3,4]. Standard HF therapies are chronically under-utilized in CKD, which reflects historical concerns about efficacy and observed reductions in estimated glomerular filtration rate (eGFR) with initiation of treatments [5, 6].

Clinical trials have shown that most of the guideline-directed HF medications are effective in improving prognosis in patients with mild or moderately reduced kidney function but these trials have usually excluded patients with advanced CKD (eGFR <25–30 mL/min/1.73 m^2), leading to a lack of evidence on which to base treatment in this group [6]. Perhaps the major contribution of the new 2021 European Society of Cardiology (ESC) Heart Failure guidelines to the field of cardio-renal medicine is to stress the long-term benefits of medical therapy both on prognosis and on kidney function in HF. The updated 2021 ESC guidelines reflected the increasing complexity of HF management in its scope and size; they now extend to 128 pages [7, 8]. The major changes from the previous 2016 version with respect to HF with reduced ejection fraction are summarized in Fig. 1.

In this review we aim to familiarize the nephrology community with the major updates that have emerged from the latest guidelines and where possible highlight applicability to the CKD-HF patient. Through sub-topics we outline (i) the proposed diagnostic pathway including natriuretic peptides and imaging, predominantly echocardiography; (ii) the changing terminology in HF classification, specifically the three phenotypes based on left ventricular (LV) ejection fraction (LVEF) and applicability of evidence-based treatment for patients with concomitant CKD; and (iii) the role of device therapies in HF with EF <35% and the reasons for judicious use in CKD. Finally, we outline newer therapies that have been prospectively evaluated in CKD cohorts but which were published after the 2021 guidelines.

HEART FAILURE DIAGNOSIS

As in previous guidelines, the diagnosis of HF requires the presence of typical symptoms, usually breathlessness on exertion, fatigue and ankle swelling, with signs such as elevated venous pressure and peripheral oedema. These features are non-specific, common in CKD and cannot be used alone to make a diagnosis. The recommended diagnostic tests are an electrocardiogram (ECG) (a normal ECG makes a diagnosis of HF unlikely), plasma natriuretic peptide (NP) concentration, usually N-terminal pro-brain natriuretic peptide (BNP), echocardiography and chest radiography. Echocardiography allows the measurement of LVEF and the classification of patients into HF with reduced EF (HFrEF <40%), HF with mildly reduced EF (HFmrEF 41%–49%) and HF with preserved EF (HFpEF >50%). For the diagnosis of HFpEF other abnormalities of cardiac structure and function such as left atrial enlargement and evidence of diastolic dysfunction are required together with elevated NPs. Guidance is given on further investigation with cardiac magnetic resonance imaging, coronary angiography, cardio-pulmonary exercise testing and right heart catheterization for the diagnosis of specific causes of HF and for optimizing management including evaluation for heart transplantation or mechanical circulatory support [7].

The use of NPs is strongly recommended, and it is usefully stated that a plasma NT-proBNP of <125 pg/mL makes a diagnosis of chronic HF highly unlikely (negative predictive value 94%–98%). The magnitude of any elevation in NP is of prognostic value. A list of other causes of an elevated NP is given which includes those of cardiac origin, such as atrial fibrillation and left ventricular hypertrophy, and non-cardiac causes, including 'renal dysfunction'. No specific guidance is given on the use of NPs for the diagnosis of HF in patients with CKD although there are data suggesting that renal excretion varies minimally with an eGFR ≥30 mL/min/1.73 m^2. This supports the diagnostic accuracy of standard cut-off for NPs in HF until the onset of CKD stage 4 [9]. In the diagnosis of acute HF where specific cut-offs are higher, a similar accuracy for patients with stage 3 CKD was identified and using age-specific cut-offs (450 pg/L for those under 50 years, 900 pg/L for those 50–75 years and 1800 pg/L for those over 75 years) proposed to negate the need to consider specific cut-offs based on renal function [10]. For patients requiring dialysis, elevated NPs are strongly associated with cardiovascular and total mortality but provide no diagnostic value for HF or left ventricular systolic dysfunction [11].

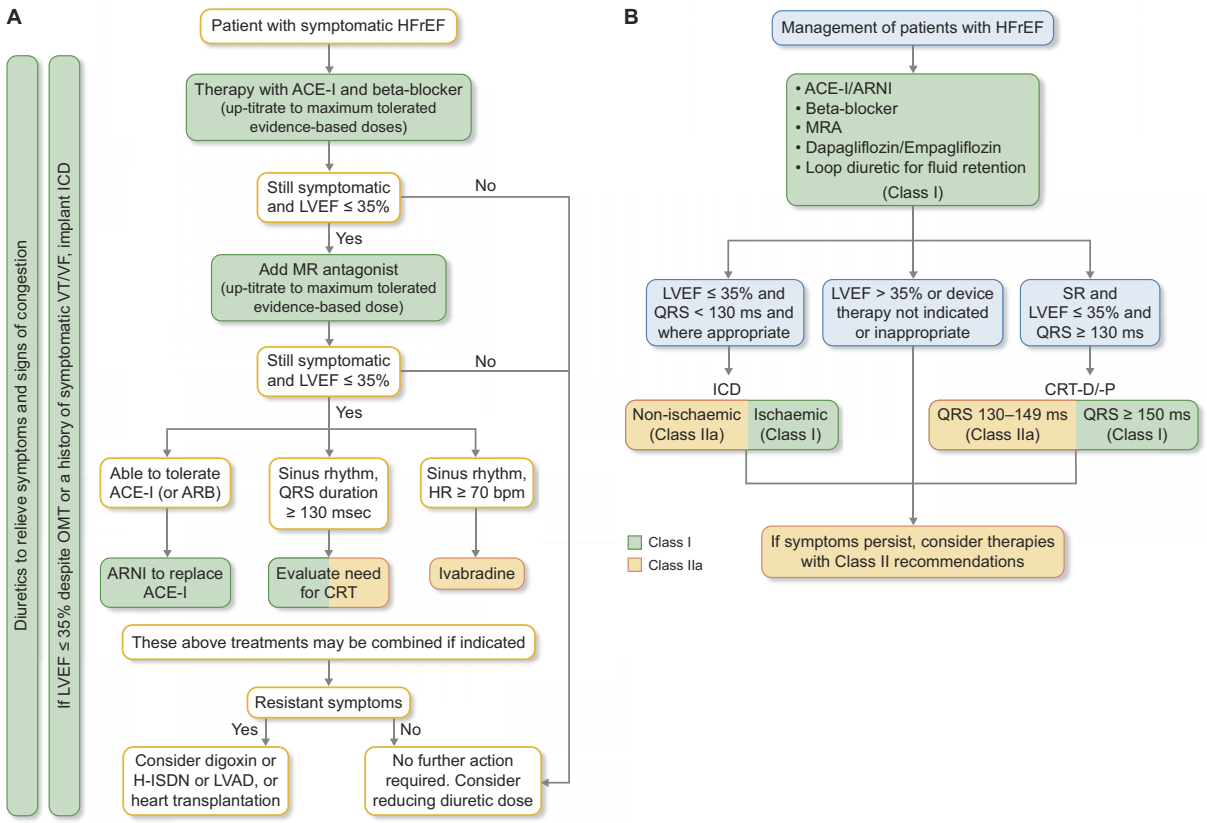


Figure 1: The evolution of the 2016 and 2021 Heart Failure Guidelines for Heart Failure with reduced Ejection Fraction. (**A**) HFrEF management in the 2016 guidelines. (**B**) HFrEF management in the 2021 guidelines. The major updates are: (i) addition of SGLT2 I, (ii) classification of the four foundational pillars including ACE-I/ARNI, BB, MRA and SGLT2-I, (ii) rapid initiation of the four 'pillar' treatments at low doses ideally within 4 weeks with sequential up-titration and (iv) reclassification of the recommendation for primary prevention ICD in non-ischemic cardiomyopathy and cardiac resynchronization therapy with pacemaker/defibrillator in with QRS duration <150 ms.

HEART FAILURE PHENOTYPE CLASSIFICATION; WHY THE CHANGE TO HFmrEF?

The 2021 guidelines changed the terminology for patients with evidence of HF and an LVEF of 40%–49% from HF with 'mid-range' EF to 'mildly reduced' HF, cleverly keeping the abbreviation of HFmrEF. This was a pragmatic alteration introduced in part because of the inherent inaccuracy of EF measurement on echo (±5%) which might lead some patients with borderline results to be misclassified and deprived of prognostically important medications. Although there are no dedicated randomized controlled trials (RCTs) examining this phenotype of patients exclusively, retrospective analyses of HFrEF trials including patients with LVEF 40%–50% indicate prognostic benefit from the same drugs, albeit with reduced effect sizes [12]. This has significance for patients with CKD given that milder reductions in LVEF >40% are more common in early-stage CKD and LVEF <40% is seen as a late feature of CKD-associated cardiomyopathy [2].

HEART FAILURE TREATMENT RECOMMENDATIONS

While clinical trials over almost 40 years have enabled the guidelines to recommend multiple drugs with clear evidence of prognostic benefit in HFrEF, data for HFmrEF and HFpEF phenotypes have been less consistent, a difficulty widely thought to reflect heterogeneity and comorbidities across the patient cohorts as well as differential treatment effects. There are major changes in recommended treatment in the 2021 guidelines which are detailed below. The most important by far is the introduction of sodium-glucose co-transporter 2 inhibitors (SGLT2-I) for patients with HFrEF independent of diabetic status.

Heart failure with reduced ejection fraction

The major strategy change in the 2021 guidelines has been termed the 'Foundational 4 Pillars' (Fig. 2). These consist of the three traditional drug classes: (i) angiotensin-converting

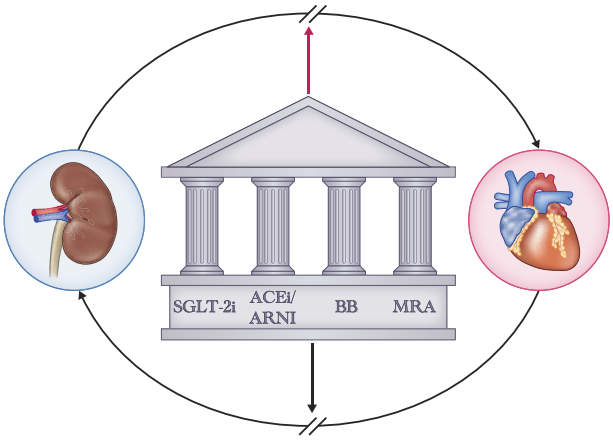


Figure 2: The 'Foundational 4 Pillars'. The 2021 ESC guidelines advocates the rapid introduction of all four pharmacological agents at low doses to reduce cardiovascular mortality and morbidity. These agents have also been demonstrated to be effective in CKD and renal outcomes. As HF and CKD often co-exist and exacerbate each other, using these drugs for both conditions should halt progressive decline of both organs in these patients.

enzyme inhibitors (ACE-I) or angiotensin receptor neprilysin inhibitors (ARNI), which are recommended to replace ACE-I in ambulatory persistently symptomatic patients or in stable hospitalized patients who are ACE-I naïve patients, or angiotensin receptor antagonists (ARB) if these are not tolerated; (ii) beta blockers (BB); and (iii) mineralocorticoid receptor antagonists (MRA). The fourth pillar is SGLT2-I (currently dapagliflozin or empagliflozin), which receive a new Class I recommendation irrespective of diabetic status. These drugs were introduced to treat hyperglycaemia in type 2 diabetes by causing glycosuria but have been incorporated into HF guidelines because of findings of impressive reductions in cardiovascular mortality (and in the case of dapagliflozin, total mortality) and in hospitalization for HF (HHF) in large placebo controlled RCTs in patients with HFrEF irrespective of diabetic status and in CKD with eGFR >30 mL/min/1.73 m^2 [13–15]. The new algorithm has moved away from slow sequential introduction and up-titration of drugs and instead focusses on rapid, low-dose introduction of the four 'pillar' treatments over 4 weeks. The order in which these therapies are introduced remains debated and in CKD is perhaps more complex because of their effects on renal haemodynamics and on the risk of hyperkalaemia. A proposed strategy for initiation and monitoring according to eGFR has recently been proposed involving careful monitoring and the use of MRA in moderate CKD (eGFR 30–60 mL/min/1.73 m^2) only if eGFR remains stable on ACE-I, BB and SGLT2-I [16].

The rationale for the change from ESC 2016 'traditional recipe' reflects the prolonged duration (>6 months) of sequential introduction and up-titration if clinicians continue to strive to achieve target doses of each individual drug. This outdated approach has been superseded firstly because consistent data show that a low dose of each of four agents yields significantly greater benefit than that observed with individual dose titration. Secondly, sub-analyses of recent large-scale trials have shown the magnitude of treatment benefit of each pillar drug to be independent of other agents reflecting different mechanisms of action [17]. Thirdly, trial data show that the Kaplan–Meier for curves for the effects of the four pillar drugs on mortality and morbidity begin to separate early, within 30 days [18]. Finally, this approach appears to improve safety and tolerability as evidenced by lower rates of renal dysfunction and lower rates of hyperkalaemia. The 2021 guidelines provide no recommendation on monitoring of kidney function or dose titration if eGFR falls slightly (3–4 mL/min/1.73 m^2), as is commonly observed within 2–3 weeks of initiation [19]. In a later section on concomitant HF and CKD, the authors do note that although all the four pillar drugs including SGLT2-I cause an initial reduction in eGFR of around 5%, a moderate early decrease in renal function should not prompt their interruption. They state that an increase in serum creatinine of <50% above baseline, as long as it is <266 μmol/L (3 mg/dL), or a decrease in eGFR of <10% from baseline, as long as eGFR is >25 mL/min/1.73 m^2, can be considered as 'acceptable'. In the longer term, SGLT2-I and the other pillar drugs slow the progressive decline in eGFR, reduce proteinuria and ultimately preserve kidney function compared with placebo and should not be discontinued without strong reason [15, 20].

It is interesting to consider whether a similar approach to the four 'pillar' drugs could be applied to the management of CKD patients, especially those with diabetic nephropathy. The established approach of ACE-I/ARB could be combined with rapid prescription of SGLT2-I and MRA. Indeed, trials with both SGLT2-I and the new non-steroidal MRA finerenone mandated treatment with maximally tolerated doses of ACE-I/ARB. There is also strong theoretical and emerging evidence that the combination of SGLT2-I and MRA may have synergistic beneficial effects.

Heart failure with mildly reduced ejection fraction

The HFmrEF (EF 41%–49%) phenotype includes up to 25% of all HF patients and has mortality rates similar to HFrEF [12]. There remains debate as to whether this represents a distinct phenotype or whether it reflects a transition phase depending on response to treatment and variability in the echo assessment of LVEF. To date there are no dedicated trials examining drug treatments in HFmrEF. Current evidence, drawn from observational studies and *post hoc* analyses of subsets of patients in HFrEF trials, suggests that patients with HFmrEF benefit prognostically from the three older 'pillar' drugs leading to weak Class IIa (should be considered, level of evidence C) ESC recommendations. Although SGLT2-I were not recommended in the guidelines, the landmark EMPEROR-Preserved trial in which over 30% of the 5988 patient cohort had an LVEF of 40%–50% demonstrated a reduction in cardiovascular death or HHF, primarily driven by lower risk of HHF [21]. Given these impressive clinical outcome benefits and the overlap between HFrEF, HFpEF and HFmrEF, increasing SGLT2-I use is anticipated. In patients with CKD, the presence of HFmrEF should probably be seen as another indication for treatment with an SGLT2-I. This view is supported by the recently published EMPA-KIDNEY trial

which confirmed safety and efficacy of empagliflozin across a range of kidney disease severities (eGFR 20–90 mL/min/1.73 m^2), levels of proteinuria and presence or absence of diabetes (see 'Heart failure patients with concomitant CKD' below) [22].

Heart failure with preserved ejection fraction

HFpEF remains the most heterogenous and problematic HF phenotype in terms of definition, aetiology, comorbidities, diagnostic criteria and evidence-based treatment. It accounts for about 50% of HF cases in the community and in patients with CKD [23]. Its prevalence in CKD may be underestimated. Both exercise intolerance and the echocardiographic features of HFpEF including concentric LV remodelling, left atrial dilatation and diastolic dysfunction are common and increase with CKD stage [24]. Abnormalities of both arterial and LV elastance are evident in HFpEF and have been reported in unselected patients with stage 2 and 3 CKD [25]. The guidelines focus on identifying the underlying cause of HFpEF (though they notably fail to mention CKD in this context) to direct appropriate treatment as well as excluding 'mimics' such as obesity, physical deconditioning and obstructive sleep apnoea, many of which are common in CKD.

At the time the guidelines were published, no large RCT in HFpEF had achieved a significant reduction in their primary endpoint, although there were very promising signals in subgroup analyses of trials of spironolactone (particularly data from North America) and ARNI [26, 27] and this potentially explains the continued high use of ACE-I, ARNI, BB and MRA by HF physicians. As mentioned above, the EMPEROR-Preserved trial showed that empagliflozin caused a reduction in the primary endpoint of cardiovascular death and HHF of 21%, driven primarily by a reduction in HHF. The effect size was comparable to the benefit observed in HFrEF and was consistent across sub-groups of EF [21]. We anticipate that treatment with SGLT2-I will become widely adopted for HFpEF as it has for the other phenotypes. The impressive recent progress made on defining the place of SGLT2-I in HF has made the 2021 guidelines seem already in need of revision and provides support for reconvening guidelines committees to provide an agile and updated response for clinicians as new robust data emerge.

DEVICES FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

Implantable cardiac defibrillators

As in 2016, implantable cardioverter defibrillator (ICD) implantation has a Class I indication for secondary prevention in survivors of ventricular arrhythmia causing haemodynamic instability who are expected to survive for >1 year. Implantation of ICDs for the primary prevention of sudden cardiac also continues to have a Class I indication for patients with symptomatic HFrEF [New York Heart Association (NYHA) II–III] with an EF of <35% due to coronary artery disease (but not within 40 days of an acute myocardial infarction) independent of QRS duration [28, 29]. There has, however, been a major shift in the 2021 guidelines for the use of primary prevention ICDs for patients with HFrEF due to non-ischaemic causes. The use of ICDs for this group receives only a Class IIa (should be considered) indication. Although the early landmark RCTs demonstrated significant total mortality reductions in HFrEF compared with treatment with amiodarone or medical therapy, albeit before high use of MRA and availability of ARNI and SGLT2-I, subsequent trials failed to find convincing effects on mortality in non-ischaemic disease [30, 31]. The DANISH trial randomized patients with symptomatic non-ischaemic HF and left ventricular EF ≤35% to ICD implantation or medical treatment alone. Total mortality was not reduced by ICDs even when follow-up was extended to 9 years, though sudden cardiac death was reduced by half. This probably reflects the diversity of causes of death in these patients. In a prespecified subgroup analysis, a significant age interaction was observed with reduction in all-cause mortality in patients under 68 years of age [31]. To date, however, no RCT provides compelling evidence of the benefit of ICDs for patients with non-ischaemic HFrEF despite the fact that repeated pooled analyses from RCTs have shown rates of ventricular arrhythmias to be similar between ischaemic and non-ischaemic groups.

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) attempts to synchronize left ventricular contraction by pacing the lateral wall of the left ventricle via the coronary sinus. Prospective randomized studies have shown that this improves LVEF, functional class, and rates of HHF and mortality in patients with HFrEF and an interventricular conduction delay (prolonged QRS duration) [32–34]. The 2021 guidelines are consistent with the 2016 recommendation providing a Class I indication for patients with symptomatic HF, EF ≤35% (despite optimized medical treatment), LBBB and a QRS duration ≥150 ms. However, there has been a down-grading of patients with LBBB and a QRS width of 130–149 ms to a Class IIa (should be considered) indication. This change was based on results of two trials that have demonstrated unfavourable effects in patients with a QRS <130 ms despite echocardiographic evidence of LV dys-synchrony [32, 35]. The choice of device, CRT-P (pacing only) or CRT-D (pacing and defibrillator), remains challenging due to the overlap of indications for ICD and CRT treatments, contradictory retrospective analyses and a lack of prospective randomized studies showing mortality benefit from CRT-D compared with CRT-P [36, 37]. The current guidelines are unchanged from 2016, with a Class I indication for CRT-D in patients with HFrEF in NYHA Class II–IV, sinus rhythm with LBBB and a QRS duration ≥150 ms, and a Class II (consideration) with QRS duration 130–149 ms.

Device therapy in heart failure with concomitant CKD

Cardiovascular disease, predominantly HF and sudden cardiac death are estimated to cause approximately 50% of deaths in end-stage kidney disease [38, 39] and yet the prevalence of device therapy in this cohort (including pacemakers for

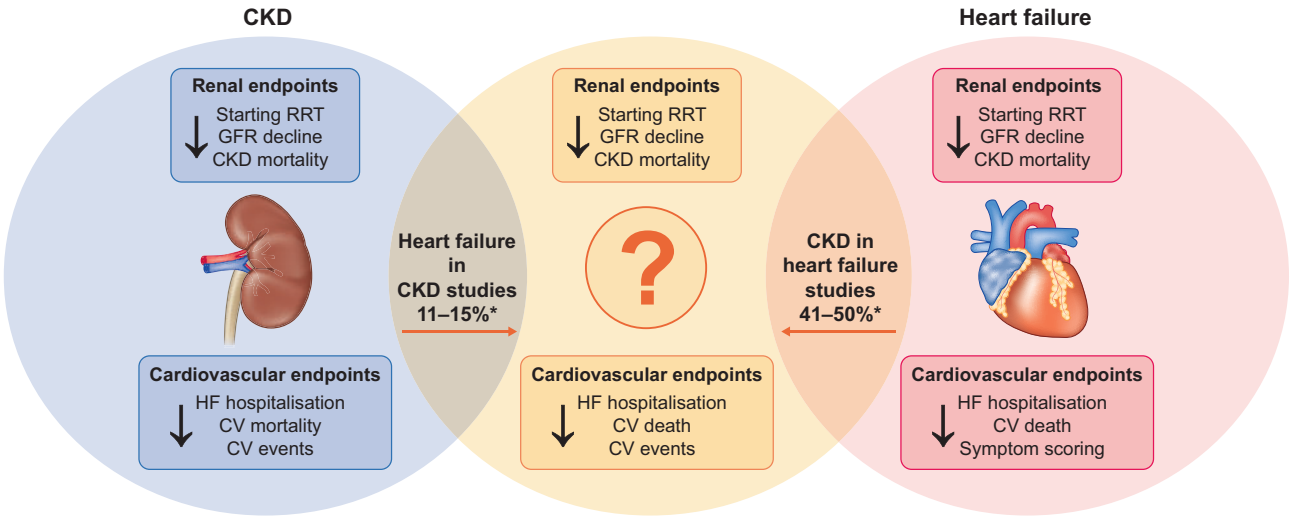


Figure 3: The overlap between SGLT2-I RCTs in those with CKD and HF. HF and CKD are closely associated and share common comorbidities and traditional risk factors. The renal and cardiovascular endpoints in this diagram are taken from four recent trials; two which recruited patients with CKD (CREDENCE and DAPA-CKD) and two which recruited patients with HF (DAPA-HF and EMPEROR-Preserved). Beneficial effects of treatment with SGLT2-I were seen on both renal and cardiovascular endpoints in both groups of trials. *The EMPEROR-Preserved trial excluded patients with a GFR <20 mL/min/1.73 m^2 and the DAPA-HF trial excluded participants with a GFR <30 mL/min/1.73 m^2. CV: cardiovascular; RRT: renal replacement therapy.

bradycardia) is estimated at only 5%–10%. In keeping with pharmacological trials, patients with advanced CKD (eGFR <30 mL/min/1.73 m^2) have been excluded from most device trials leading to a lack of evidence of efficacy. A meta-analysis of three ICD trials and further retrospective data found no survival benefits in patients with a guideline indication and eGFR <35 mL/min/1.73 m^2, a finding that likely reflects the competing risk of non-arrhythmic death [40]. In the only prospective trial investigating the value and safety of ICD implantation in dialysis patients with an LVEF ≥35% (patient with a Class I indication were excluded), ICD implantation was associated with no reduction in rates of sudden cardiac death or all-cause mortality after a median follow-up of 6.8 years and the trial was terminated due to futility and high rates of adverse events (27.5%) in the ICD group [41]. Furthermore, the high burden of non-cardiovascular comorbidities including vascular access issues, bacteraemia, bleeding and higher rates of lead-related complications are important factors to be considered given the absence of data showing improved survival. The 2021 guidelines acknowledge these data and highlights caution with ICD implantation in dialysis patients.

IRON THERAPY FOR HEART FAILURE

Functional iron deficiency (ID), characterized by reduced iron availability and independent of anaemia, is estimated to be present in 55% of patients with chronic stable HF, a figure that is consistent across the HF phenotypes [42]. Iron is a key micronutrient for cellular metabolism of cardiomyocytes and in HF the presence of ID is postulated to impair cardiac energetics and myocardial performance. Data from a meta-analysis and single RCT using intravenous (IV) iron in the form of ferric carboxymaltose (FCM) demonstrated reduced rates of HHF, improved HF symptoms burden, exercise capacity and quality of life scores [43, 44]. The stage of HF (NYHA II–IV) is predictive of disordered iron status and the 2021 guidelines now give a Class I indication to periodically screen for ID defined as absolute ID with a ferritin <100 ng/mL or relative ID with the higher cut-off values for ferritin (100–299 ng/mL) if associated with reduced transferrin saturation (<20%). As in 2016, IV FCM is proposed for ID with symptomatic HF patients and LVEF <45% or recently hospitalized with LVEF <50%. Although not in the ESC guidelines due to the timing of the publications, both the IRONMAN and AFFIRM-AHF trials strengthen the case for the use of IV iron in patients with HF [45, 46]. In CKD, ID is common and given the common co-existing HFpEF/HFmrEF phenotypes treatment with FCM is supported [47]. The results of the PIVOTAL trial have done much to alleviate prior concerns regarding increased risks of thrombosis, vascular calcification, oxidative stress and infection in patients with CKD stage 4 [47, 48]. In haemodialysis, the use of high-dose IV iron sucrose in the PIVOTAL RCT, reduced HHF and death further supporting a direct effect of iron on cardiac tissue function [48]. Other formulations are not recommended in HF; oral iron replacement has no clinical benefit compared with placebo in intermediate endpoint trials and erythropoietin-stimulating agents, which increase haemoglobin but do not replete iron, failed to reduce all-cause death or HHF and increased the risk of thromboembolic events in the only large-scale randomized trial in patients with HFrEF [49].

HEART FAILURE PATIENTS WITH CONCOMITANT CKD

The 2021 guidelines address the co-existence of HF and CKD in a short section titled 'Non-cardiovascular co-morbidities'.

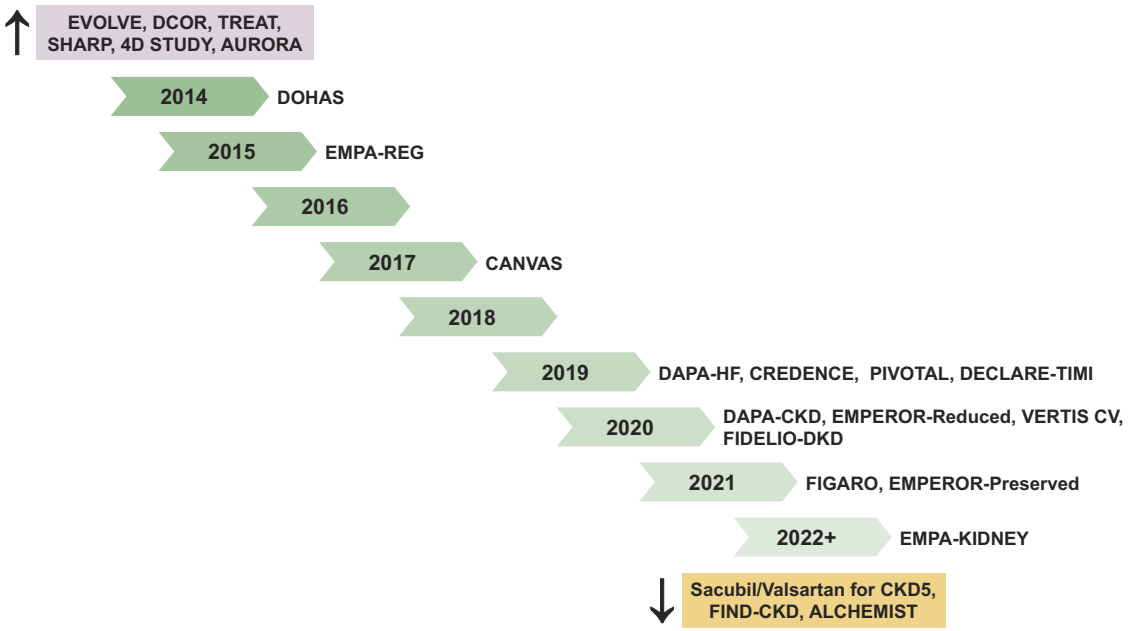


Figure 4: Timeline of randomized controlled drug trials in those with CKD with cardiovascular mortality or morbidity endpoints. This diagram details the progress made in our knowledge of reducing cardiovascular morbidity and mortality in patients with CKD. Studies in the purple box took place prior to 2014. Studies in the yellow box are currently registered as ongoing clinical trials with ClinicalTrials.gov and results are expected this year. ALCHEMIST: Aldosterone antagonist chronic haemodialysis interventional survival trial; AURORA: A study to evaluate the use of Rosuvastatin in subjects on regular haemodialysis: CANVAS: Canagliflozin and renal events in diabetes with established nephropathy clinical evaluation; CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy; DAPA-CKD: Dapagliflozin and prevention of adverse outcomes in chronic kidney disease; DAPA-HF: Dapagliflozin and prevention of adverse outcomes in HF; DECLARE-TIMI: Dapagliflozin effect on cardiovascular events-thombolysis in myocardial infarction; DOHAS: Dialysis outcomes HF Aldactone study: DCOR: The dialysis clinical outcomes revisited; EMPA KIDNEY: The study of heart and kidney protection with empagliflozin; EMPA-REG: Empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients; EMPEROR-Preserved: Empagliflozin outcome trial in patients with chronic HF with preserved ejection fraction; EMPEROR-Reduced: Empagliflozin outcome trial in patients with chronic HF with reduced ejection fraction; FIDELIO-DKD: The Finerenone in reducing kidney failure and disease progression in diabetic kidney disease; FIND CKD: A trial to learn how well finerenone works and how safe it is in adult participants with non-diabetic chronic kidney disease; FIGARO: Cardiovascular events with finerenone in kidney disease and type 2 diabetes; SHARP: Study of heart and renal protection; 4D STUDY: Die Deutshe diabetes dialyse studies; PIVITOL: Proactive Intravenous Iron Therapy in Haemodialysis Patients; TREAT: Trial to reduce cardiovascular events with Aranesp therapy; VERTIS CV: Evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial.

This section remains brief as in 2016 and exemplifies the difficulty in extrapolating prospective HF RCT data when advanced stage CKD (eGFR <20–30 mL/min/1.73 m^2) remains an exclusion criterion in most studies. The authors do emphasize that randomized trials have shown that patients with HF of all phenotypes and causes with concomitant early-stage CKD are at higher risk of events and that the beneficial effects of appropriate medical therapy, are similar, if not greater, than in the patients with normal renal function. They describe the significant benefits of using ACE-I/ARNI and BB in moderate CKD (eGFR >30 mL/min/1.73 m^2) based on data from landmark trials compared with subjects with normal renal function. Data from sub-group analyses have highlighted the absence of interaction between drug benefits and renal function. We would also highlight the consistent and accumulating evidence from SGLT2-I trial literature for the benefits of reducing the progression of renal disease irrespective of HF or existing atherosclerotic cardiovascular disease (Fig. 3). Indeed, the recently published EMPA-KIDNEY trial demonstrated that empagliflozin is both safe and efficacious in reducing the risk of kidney disease progression or death from a cardiovascular cause in a cohort with a wide range of renal function (eGFR 20–90 mL/min/1.73 m^2) and proteinuria [22]. Proportional benefits were observed across a range of renal diagnoses and with a less than a third of patients having known cardiovascular disease.

The guidelines do not provide specific guidance on the use of the four pillar therapies in patients with pre-existing CKD including order of introduction, dose adjustment or frequency of monitoring of kidney function, but independent groups have proposed strategies according to eGFR [16]. Given the clear evidence of benefit, the use of the four pillar drugs and their rapid introduction in HFrEF with non-dialysis CKD should be strongly supported by nephrologists allowing for usual cautions and close monitoring of serum potassium. Indeed, withholding this new treatment approach would seem only to perpetuate the often cited complaint of therapeutic nihilism in patients with CKD. More recent evidence on drugs such as finerenone (a non-steroidal MRA) and SGLT2-I provides reasons for optimism that the very high adverse cardiovascular event rate in CKD can be effectively reduced (Fig. 4). In DAPA-Kidney, the beneficial

effects of dapagliflozin on cardiovascular death and HHF in advanced CKD (eGFR 25–30 mL/min/1.73 m^2) were comparable to that seen in HFrEF with early-stage CKD [50]. Finerenone effectively reduced the same endpoints in patients with diabetic CKD [51]. Two reviews summarize these data well [52, 53].

Historically, renal medicine, unlike cardiology, has had a poor track record for producing good quality, large-scale RCTs [54]. Furthermore, patients with CKD stage 4 or higher are routinely excluded from cardiovascular trials [54]. Pressure should continue to be put on regulatory authorities demanding the inclusion of patients with CKD of all stages in trials by governments and learned societies such as the European Renal Association (ERA). Similar approaches together with incentivizing measures have already improved the recruitment of women, children, elderly people and ethnic minorities into RCTs.

The evidence-based renal landscape is changing rapidly. Even while writing this review, a number of pivotal and practice changing RCTs in both CKD and HF have been published utilizing SGLT2-I, non-steroidal MRA and iron, which do not feature in the published guidelines but would strongly support their use in CKD-HF phenotypes. The next challenge is to produce rapid communication channels which translate the results of these studies into more timely guidance for practising clinicians. Guidelines from expert societies take a long time to produce and can often end up disagreeing with each other, leading to confusion [55]. A collaborative approach from working groups of different societies such as the ESC and ERA would lead to guidance on 'crossover' clinical issues including HF and CKD that can be produced much more quickly and updated rapidly as evidence emerges.

SUMMARY

Nephrologists should take the chance to familiarize themselves with the 2021 ESC guidelines on HF as not only are patients with CKD at high risk of HF but also most patients with HF will develop some degree of CKD. Recent RCTs in both CKD and HF have contributed to our understanding of the overlapping nature of pharmacological treatments. Effective treatments are available to prolong life and reduce hospitalization with HF of all phenotypes. The guidelines correctly state that 'renal dysfunction and hyperkalaemia are the major causes of underuse of RAAS inhibitors, particularly MRA, in clinical practice'. Preventing unnecessary dose reduction or cessation of HF drugs by advising tolerance of small or moderate falls in eGFR will lead to cardiovascular mortality benefits and simultaneous long-term reductions in the rates of progression of CKD.

CONFLICT OF INTEREST STATEMENT

N.C.E. reports lecture fees from Novartis and Aspen. C.J.F. reports lectures fees from Bayer. A.M.P., R.P.S. and J.N.T. have no conflicts to declare.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

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Received: 29.10.2022; Editorial decision: 21.12.2022