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Challenges in Management of Heart Failure and Chronic Kidney Disease in Primary Care Settings

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Abstract:

The management of heart failure (HF) and chronic kidney disease (CKD) in primary care settings presents unique challenges that can complicate patient outcomes. One of the significant hurdles is the complexity of coexisting conditions often seen in these patients, as heart failure and chronic kidney disease frequently co-manifest. This dual burden can lead to a vicious cycle, where the progression of one condition exacerbates the other. Primary care providers must navigate medication adjustments carefully, as many renally excreted drugs used in the management of heart failure may require dosage modifications in patients with CKD to avoid toxicity. Additionally, the overlapping symptoms of both conditions—such as fatigue, fluid overload, and dyspnea—can lead to misdiagnosis or under-treatment, further complicating the management strategies employed. Furthermore, the limited resources and time constraints typical of primary care settings pose significant barriers to effective management. Given the need for comprehensive assessments and interdisciplinary approaches in managing patients with heart failure and CKD, primary care providers may struggle to provide the level of individualized care that these complex patients require. Access to specialists, renal dietitians, and social workers can also be limited, making it difficult to implement multidisciplinary care plans that could enhance patient outcomes. Additionally, disparities in health literacy and socioeconomic factors can impede patient adherence to treatment regimens, follow-up appointments, and lifestyle modifications critical for managing both heart failure and CKD. These multifaceted challenges underscore the necessity for enhanced training, resources, and support systems within primary care to optimize the management of these prevalent and interacting conditions.

Keywords: Chronic kidney disease, heart failure, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, sodium-glucose cotransporter inhibitors. Management.

Introduction:

Chronic heart failure (HF) is one of the greatest medical challenges of the 21st century. It is estimated that HF currently affects 1–2% of the adult population in developed countries. Moreover, the prevalence of HF rises significantly among people over 70, reaching 10%. According to data from the European Society of Cardiology (ESC) Long-Term Registry, most outpatients with HF (60%) have a reduced left ventricle ejection fraction (LVEF), about one quarter (24%) have mildly reduced LVEF, and the remainder (16%) have preserved LVEF [1].

Chronic kidney disease (CKD) is also a very serious public health problem. The prevalence of CKD in the general population is estimated at about 9–16%, and it has increased by almost 30% over the last three decades [2].

Approximately half of patients with HF have CKD, according to a meta-analysis by Damman et al. HF

and CKD often coexist. Similar findings were reported by McAlister et al., who discovered kidney injury characteristics in 53% of patients with acute HF and 43% of individuals with chronic HF [3].

However, as few studies provide precise figures, it would be challenging to estimate the number of CKD patients who also have HF. According to the CKD portion of the recommendations for the diagnosis and treatment of HF, the majority of research to date has excluded individuals with HF based on an estimated glomerulus filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 [1].

As a result, for many of us in routine clinical practice, advanced chronic kidney disease is a sort of "no man's land." The risk of death is doubled when HF and CKD coexist, according to research. When the eGFR number falls below 60 mL/min/1.73 m^2, there is a significant increase in mortality; patients with heart failure and end-stage kidney disease have the highest death rates, which occur when the eGFR is less than 15 mL/min/1.73 m^2 [3].

Dialysis patients are also included in the latter category. Consequently, there is little question that these demographic needs extra care. A patient with substantial renal impairment, however, has two challenges in practice: first, when making treatment decisions, and second, when detecting heart failure. The three main symptoms and indicators of heart failure (HF) are peripheral edema, pulmonary congestion, and dyspnea. In order to diagnose heart failure, echocardiography and natriuretic peptide plasma concentration are essential [1].

In contrast, overhydration during severe renal failure results in comparable symptoms and indicators, affects the structure and function of the heart, and complicates the interpretation of natriuretic peptide concentration [4].

This study covers the epidemiology, pathogenesis, and current medical treatment of heart failure in people with chronic kidney disease.

Prevalence of HF in CKD:

According to the US Renal Data System, the prevalence of heart failure (HF) in people 65 and older with chronic kidney disease (CKD) was nearly 26% in 2016, while the prevalence among patients without CKD was 6%. 8. The prevalence of all forms of HF was higher in patients with CKD than in patients without CKD, and it rose with increasing CKD stage severity when patients were categorized according to whether they had reduced or preserved left ventricular ejection fraction (HFrEF and HFpEF, respectively). Approximately 44% of patients with end-stage renal disease (ESRD) develop heart failure (HF), with 10% having HFpEF, 13% having HFrEF, and 21% having an unidentified [5].

Epidemiology of CKD in Heart Failure:

Coexisting CKD is common in patients with heart failure. According to a comprehensive meta-analysis, CKD affects around half (49%) of heart failure patients (not including registry studies). In a major U.S. population-based investigation, the incidence of heart failure among CKD patients was 18/1000 person-years. About 44% of dialysis patients have heart failure, and half of them have a lower ejection fraction [6].

Heart failure is more common in individuals with declining renal function. Patients with heart failure and chronic kidney disease (CKD) have a poor prognosis that gets worse as kidney function declines and their death rate rises (odds ratio, 2.34; 95% CI, 2.20 to 2.50; $P<0.001$).[7].

Diabetes, hypertension, or ischemic renal disease are the most common causes of concomitant CKD. Examine a 54-year-old guy who exhibits fluid overload and is close to ESKD. He has diabetes, hypertension, and heart failure as a result of significant coronary artery disease. Such patients have a bad prognosis and are challenging to manage. Although the majority of studies found that patients with CKD were older, possibly due to age-related declines in GFR, the presence of CKD was linked to greater mortality when age was taken into account [8].

Furthermore, a considerable proportion of heart failure patients also experience AKI as a result of several diseases, including medication toxicity, sepsis, and kidney hypoperfusion, with serious consequences [9].

On the other hand, sustained AKI due to sepsis or hypovolemia has longer-term effects than eGFR deterioration brought on by the start of renin-angiotensin-aldosterone system inhibitors (RAASis) [10].

Pathophysiology and the Interdependence of Heart and Kidney Function:

The similarities in the etiology of HF and CKD, such as diabetes and hypertension, as well as the overlapping physiological processes, can be used to explain their overlap. By decreasing renal blood flow, impairing renal hemodynamics, and causing ischemic injury, HF causes and maintains chronic kidney disease. Anemia, uremia, excessive renin-angiotensin-aldosterone, sympathetic activation, fluid overload, and other variables cause CKD to contribute to progressive left ventricular (LV) remodeling, fibrosis, and cardiac failure. The synergistic effects of HF and CKD, where the presence of one accelerates the progress of the other, are therefore not surprising [11].

CV homeostasis depends on the heart and kidney. The natriuretic peptide system, the renin–angiotensin aldosterone system (RAAS), and the sympathetic nervous system (SNS) are among the neurohormonal systems that regulate the reciprocal relationship between renal hemodynamics and cardiac hemodynamics in healthy individuals. In order to create a vicious cycle, renal disease or malfunction can lead to heart disease or dysfunction and vice versa. Furthermore, the reciprocal kidney-heart relationship frequently goes hand in hand with conditions that affect both organs simultaneously, typically diabetes and hypertension, which are substantial risk factors for atherosclerosis [12].

A systemic low-grade inflammation brought on by CKD causes vascular and myocardial remodeling, which in turn causes valvular calcification, myocardial fibrosis, hypertension, atherosclerosis, vascular calcification, and vascular senescence. This is how HF develops in CKD [13].

Hemodynamic, neurohormonal, and CVD-related mechanisms accelerate the development of CKD after HF. Renal failure is accelerated by hemodynamic processes (decreased cardiac output and increased systemic venous pressure), which also enhance salt and fluid retention, enhancing renal interstitial compression and systemic and renal congestion [14].

While neurohormonal causes include RAAS and SNS hyperactivity, CVD-related processes include a variety of pathways that cause CKD to advance, such as the exacerbation of local and systemic inflammatory processes and alterations in immunological responses [15].

A common etiology of heart and kidney failure is fibrosis. An organ injury starts a complicated series of cellular and molecular events that lead to tissue fibrosis. This fibrogenic reaction may be adaptive at first, but if it persists, it can lead to parenchymal scarring, cellular malfunction, and organ failure. Fibrosis is the common denominator of neurohormonal overactivity, inflammation, and endothelial dysfunction brought on by oxidative stress in both the kidney and the heart ultimately resulting in CKD, CVD, and HF [16].

Finally, both CKD and HF are frequently accompanied by anemia, which is due to a constellation of diverse factors, including relative erythropoietin deficiency, uremia-induced inhibitors of erythropoiesis, short erythrocyte survival, and disturbed iron homeostasis. The decrease in endogenous erythropoietin together with the anemia-related reduced oxygen transport aggravates tissue hypoxia and neurohormonal overactivity, facilitating the further deterioration of renal and cardiac function [17].

HF with reduced ejection fraction (HFrEF), which is defined as an ejection fraction less than 40%, is the subject of this review. Nonetheless, there is increasing recognition of the substantial mortality and morbidity associated with HF with preserved ejection fraction (HFpEF). When an ejection fraction (EF) is ≥50% and HF symptoms are present, the condition is known as HFpEF. It is associated with increased LV stiffness and decreased LV relaxation. Although the exact etiology of HFpEF is still unknown, a number of variables, such as endothelial dysfunction, LV hypertrophy, and systemic inflammation, have been linked to the development of poor LV filling [18].

It is presently thought that HFpEF is more common than HFrEF in CKD patients and that HFpEF is probably caused by impaired renal function [11].

Even though HF is the most common subtype, there aren't many proven therapies that improve prognosis. Regardless of diabetes status, individuals with HFpEF treated with empagliflozin had a lower combined risk of cardiovascular death or hospitalization, according to the recently released EMPEROR-Preserved research [17].

Major Limitation of Cardiovascular Trials: The Exclusion of Patients with Renal Disease:

CKD patients are disparagingly excluded from most CV trials on the basis of various criteria (e.g., serum creatinine 1.5 mg/dL or more, 2.3 mg/dL or more, 3 mg/dL or more, or eGFR less than 30 mL/min/1.73 m^2) [18].

Because of concerns that possible medication buildup could lead to problems, HF trials have excluded individuals with CKD in stages 4 and 5. Trials assessing β-blockers, RAAS inhibitors (RAASi), and angiotensin receptor/neprilysin inhibitors (ARNI) frequently exclude CKD patients, which reduces the evidence supporting or refuting the use of these medications in CKD patients with heart failure. To achieve evidence-based care and prevent consequences, clinical research in patients with concomitant cardiac and renal disorders must be encouraged [19].

Heart Failure Management in Patients with Chronic Kidney Disease:

The management of CKD is still challenging, despite the fact that it contributes to an increasing burden of morbidity and mortality in HF patients. Since individuals with CKD with HF may be more vulnerable to the metabolic and renal side effects of different HF medications, there is typically less usage of HF medication [20].

Patients with alterations in renal function linked to renin-angiotensin-aldosterone inhibitors (RAASis) are commonly referred back and forth between nephrologists and cardiologists, making the management of combined HF and CKD more expensive and fragmented. This leads to repeated hospital stays and frequently the cessation of medical treatment that follows guidelines [21].

Multidisciplinary cardiology and renal clinics have been suggested as an evidence-based strategy to considerably lower all-cause mortality in order to address this issue. These clinics have also demonstrated trends in a decrease in both cardiovascular and all-cause hospitalizations among patients with chronic kidney disease. Lastly, the use of HF medicines in patients with advanced-stage CKD (stages 4-5) is not well supported by evidence [22].

Diagnostic Challenges

The primary care setting frequently encounters issues with timely and accurate diagnosis of both conditions. Patients often present with nonspecific symptoms such as fatigue, edema, and dyspnea, which may lead to diagnostic ambiguities. Moreover, testing and biomarkers that indicate one condition may be influenced by the other; for instance, elevated levels of B-type natriuretic peptide (BNP) are commonly associated with heart failure but can also be elevated in patients with kidney disease [12].

Another diagnostic hurdle lies in the potential underestimation of kidney function, particularly in older adults, due to reliance on serum creatinine levels alone. Estimated glomerular filtration rate (eGFR) may fail to reflect true renal function variations, especially in patients with fluctuating fluid status common in heart failure. Thus, primary care providers often face the challenge of discerning when to initiate further evaluation, such as referral to nephrology or cardiology, without explicit diagnostic clarity [23].

Therapeutic Dilemmas

Once diagnosed, the treatment of patients with both heart failure and chronic kidney disease becomes increasingly complex. Many standard therapies for heart failure, particularly those aiming to enhance cardiac output—such as diuretics, ACE inhibitors, or angiotensin receptor blockers—can have deleterious effects on kidney function. Diuretics are often employed to manage fluid overload in heart failure; however, their use carries the risk of renal impairment, electrolyte imbalances, and further exacerbation of CKD. This dichotomy presents a challenge as physicians must balance symptom management with the potential for worsening renal function [8].

In addition, the interplay between medications used to manage heart failure and those aimed at controlling CKD complicates decision-making. For example, non-steroidal anti-inflammatory drugs (NSAIDs) can further strain renal function, and careful consideration is required when prescribing these alongside other medications that may impact kidney health. Moreover, the graduated use of

angiotensin-converting enzyme (ACE) inhibitors is often intended for better heart failure management despite their potential adversities in patients with reduced kidney function [23].

β-blockade

The benefits of β-blockers for HFrEF patients' symptoms and prognosis are well-established. Along with sodium-glucose co-transporter 2 inhibitors (SGLT2is), mineralocorticoid receptor antagonists (MRAs), and angiotensin receptor-neprilysin inhibitors (ARNIs), they constitute one of the four pillars of HF therapy [23].

By reducing the negative effects of sympathetic activity on cardiac muscle, β-blockade helps patients with heart failure. [1] Beta-blockade has been demonstrated in RCTs and subsequent meta-analyses to improve HF symptoms and LV function while lowering hospitalizations and mortality in individuals with HFrEF. [25].

Patients with both HFrEF and CKD 1–3 benefit from using β-blockers, according to subgroup and post-hoc analysis of big RCTs like MERIT-HF and CIBIS-II. According to a recent meta-analysis of ten double-blind, placebo-controlled RCTs, individuals with moderate CKD (estimated glomerular filtration rate [eGFR]: 30–60 ml/min/1.73 m²) and HFrEF benefited from β-blockers. Nevertheless, there weren't enough individuals with advanced CKD to make any inferences [26].

In individuals with advanced chronic kidney disease, there is evidence to support the use of carvedilol in relation to particular β-blockers. Carvedilol was linked to a lower risk of sudden death and an improved mortality rate in a group of HFrEF patients receiving hemodialysis. Although there is a solid body of evidence supporting HFrEF, there is conflicting evidence about the effectiveness of β-blockade in HFpEF patients, and there is a dearth of information on individuals with severe chronic kidney disease [11].

Renin–Angiotensin–Aldosterone Inhibition:

The advantages of RAASis in patients with HFrEF with CKD stages 1–3 have been demonstrated by large, multicenter, placebo-controlled RCTs, such as SAVE, CONSENSUS, and SOLVD (for angiotensin-converting enzyme inhibitor [ACEi]) and CHARM and VALHEFT (for angiotensin II receptor blocker [ARB]). The majority of these trials have routinely excluded patients with advanced chronic kidney disease [27].

The use of ACEIs in patients with HF and CKD may be hampered by their adverse effects, which include hyperkalemia and elevated creatinine. According to recent observational data, the prescription of RAASis gradually decreases as the stage of CKD worsens. On-target, efferent arteriolar vasodilation and the ensuing drop in filtration pressure at each nephron are the causes of the alterations in renal function linked to RAASis. Serum creatinine increases of up to 30% are typically seen to be benign, with no long-term adverse effects, and can be seen as a direct hemodynamic consequence of RAASis [20].

Regarding treatment, neither ACEIs nor ARBs significantly affected cardiac or all-cause mortality in patients with CKD and HFpEF. According to meta-analyses of many trials, patients with HFpEF may not have the same level of benignity from decreasing renal function linked to ACEi/ARB usage as those with HFrEF [11].

Mineralocorticoid Receptor Antagonists:

Mineralocorticoid receptor antagonists (MRAs) have been shown to reduce hospitalizations and mortality in people with HFrEF and stage 1–3 CKD [28].

About half of the 1,658 patients in the RALES study had an eGFR <60 ml/min/1.73 m², and the risk reduction for hospitalizations and mortality was comparable for participants with and without renal function [29].

Patients with compromised renal function were more likely to experience hyperkalemia. Additionally, eplerenone has been proven to improve outcomes such as hospitalization for a cardiovascular event or mortality from cardiovascular events in individuals with post-MI HF (EF <40%). Although patients with advanced chronic kidney disease were not included in this investigation, the eplerenone group had a higher incidence of hyperkalemia but no corresponding increase in mortality [30].

There is insufficient data to support the use of any MRA in individuals with HF and stage 4–5

CKD.Studies like the Top Cat and I-PRESERVE trials of MRA in general populations with HFpEF did not demonstrate an improvement in the primary outcomes of patients with HFpEF, such as hospitalization or death from a cardiovascular cause. Patients with advanced chronic kidney disease (defined in I-PRESERVE as serum creatinine >221 μmol/l and in the TOPCAT trial as eGFR <30 ml/min/1.73 m²) were not included in these trials. In the I-PRESERVE experiment, decreasing renal function with MRAs was linked to a worse outcome, just like ACEi/ARBs in HFpEF [31].

Sodium–Glucose Co-transporter 2 Inhibitors:

Regardless of diabetes status, SGLT2i treatment has been demonstrated to lower mortality and hospitalizations in individuals with HFrEF. It is currently one of the four pillars of medical therapy for HF patients that is guided by guidelines [23].

In 4,744 patients with New York Heart Association (NYHA) class IIIV HF with EF <40%, dapagliflozin was compared to conventional therapy or a placebo in the DAPA-HF study. 1,926 (40.6%) patients with stage 3 CKD were included in this investigation; however, patients with eGFR <30 ml/min/1.73 m² or rapidly worsening renal function were not. The primary composite outcome (cardiovascular death or worsening heart failure: HR 0.74; 95% CI [0.65–0.85]) was significantly lower. Both CKD and non-CKD patients experienced a decrease in the primary endpoint, with HRs of 0.72 (95% CI [0.59–0.86]) and 0.76 (95% CI [0.63–0.92]), respectively. The dapagliflozin group experienced fewer renal problems than the placebo/standard care group (the composite consisted of 50% sustained decline in eGFR, end-stage renal disease, or renal death), which further supported the drug's renal safety [32].

The use of empagliflozin in patients with heart failure was recently investigated in the EMPEROR-Reduced study, where the main outcome was either cardiovascular death or hospitalization due to worsening heart failure. Notably, 48% of patients in this trial had an eGFR <60 ml/min/1.73 m², and patients with an eGFR as low as 20 ml/min/1.73 m² were included. There was a 25% decrease in cardiovascular mortality and heart failure hospitalizations (HR 0.75; 95% CI [0.65–0.86]). Empagliflozin caused a slower reduction in eGFR than placebo (−0.55 versus −2.28 ml/min/1.73 m²/year), with a 95% CI [1.10–2.37] between-group difference of 1.7 ml/min/1.73 m²/year. Patients randomly assigned to take empagliflozin experienced a 50% (95% CI [32–77]) decrease in renal composite outcome (incidence of renal replacement therapy or sustained decline of eGFR). Additionally, empagliflozin was linked to fewer hospitalizations for heart failure, a slower drop in eGFR, and fewer adverse kidney events, which include a combination of chronic dialysis, kidney transplantation, or a prolonged decline in eGFR [33].

As with ACEi medication, there may be a brief, benign reduction in kidney function when SGLT2i is started. Nonetheless, individuals with and without HF experience a net decrease in the course of kidney disease [34].

Angiotensin Receptor and Neprilysin Inhibitors:

A naturally occurring endopeptidase called neprilysin is in charge of breaking down a variety of vasoactive peptides, including natriuretic peptides. The natriuretic peptide system, a crucial counter-regulatory mechanism against excessive RAAS activation, is enhanced by neprilysin inhibitors [35].

Neprilysin inhibitors are used in clinical settings in conjunction with angiotensin-receptor blockers, such as sacubitril/valsartan. According to the recently released 2021 ESC HF guidelines, either ACEIs or ARNIs, along with β-blockade and MRAs, constitute a core component of the triad of therapeutic agents in HF. Patients who are intolerant of either ACEIs or ARNIs are treated with ARB monotherapy. Current guidelines recommend replacing ACEi/ARB with an ARNI in patients who continue to experience symptoms after receiving optimal medical therapy and who have an eGFR >30 ml/min/1.73 m². ARNI therapy is now recognized as one of the four pillars of guideline-directed medical therapy for HF [23].

The PARADIGM-HF study demonstrated the superiority of ARNI over enalapril for patients with HFrEF, establishing the significance of ARNIs. Since ARNIs clearly outperformed ACEIs (HR 0.8; 95% CI [0.73–0.87]), the trial was terminated early. The study's primary outcome was a composite of cardiovascular death or hospitalization for heart failure. This study excluded patients with CKD whose eGFR was less than 30 ml/min/1.73 m². Sacubitril/valsartan demonstrated a lower likelihood

of causing nephrotoxicity compared to enalapril, as indicated by the fewer number of participants who discontinued its use due to renal impairment (0.7% compared to 1.4%). 4%; p=0.002). Compared to ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), ARNIs exhibited a slower rate of eGFR reduction. Additionally, side effects such as hyperkalemia occurred less frequently with ARNIs than with ACEIs or ARBs [36].

Conclusion:

There is a growing evidence base for novel therapies, including cardiac devices, in patients with HF and CKD. However, it is unclear what context and combination of therapies provide optimal management for HF and CKD. Incorporating specialist cardiology and renal health professionals into multidisciplinary care pathways would be the optimal approach to improve the quality of care provided to patients with HF and CKD.Novel therapies, including cardiac devices, are emerging for heart failure and kidney disease management. However, optimal management requires integrating cardiology and renal health professionals into multidisciplinary care

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