Heart Failure in Patients with Diabetes and Chronic Kidney Disease: Challenges and Opportunities

Kris Vijay^a Brendon L. Neuen^b Edgar V. Lerma^{c, d}

^aAbrazo Arizona Heart Institute and Hospital, Phoenix, AZ, USA; ^bThe George Institute for Global Health, Newtown, NSW, Australia; ^cUniversity of Illinois at Chicago College of Medicine, Chicago, IL, USA; ^dAdvocate Christ Medical Center, Oak Lawn, IL, USA

Keywords

Heart failure · Comorbidity · Diabetes mellitus · Chronic kidney disease

Abstract

Background: Heart failure (HF), diabetes mellitus (DM), and chronic kidney disease (CKD) are commonly occurring and interlinked conditions. Approximately 25%–40% of patients with HF have DM, and approximately 40%–50% of patients with HF have CKD. Both DM and CKD are associated with increased risk of incident HF. Furthermore, 40% of people with DM develop CKD, making DM the leading cause of kidney failure globally. Importantly, 16% of patients with HF have both comorbid DM and CKD, and the combination of these 3 comorbidities is associated with substantially increased risk for hospitalization and mortality. Mechanisms that underlie the relationships between HF, DM, and CKD are complex but likely relate to shared cardiovascular and metabolic risk factors, as well as downstream effects on inflammation, oxidative stress, and neurohormonal pathways. **Summary:** This review outlines the epidemiology and links between HF, DM, and CKD, as well as current clinical evidence for the treatment of individuals with a combination of these comor-

bidities. A case study of a patient with concomitant HF, DM, and CKD is discussed to explore potential treatment approaches for patients in whom all 3 comorbidities exist. **Key Messages:** Treatment plans for patients with a combination of these 3 comorbidities should consider the available clinical evidence.

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Introduction

Heart failure (HF) is a major global health issue that commonly occurs in the presence of diabetes mellitus (DM) and chronic kidney disease (CKD) (Fig. 1). Considering the prevalence of each individual condition, the Global Burden of Disease Study 2017 reported that approximately 64 million people had HF, 476 million had DM, and 698 million had CKD [1]. DM occurs in 40% of patients with acute HF and 25% of patients with chronic HF [2], while CKD occurs in 53% of patients with acute HF, 42% of patients with chronic HF [3], and 40% of patients with DM (Fig. 1) [4]. Importantly, 16% of patients with HF have comorbid DM and CKD, with the resulting

Fig. 1. Complex interplay among HF, DM, and CKD and common factors associated with their development [1–6].

disease triad associated with worse clinical outcomes [5]. As the number of Americans living with HF is expected to increase by 46% between 2012 and 2030 [6], efforts are urgently needed to improve the treatment of patients with multimorbidities and HF. Issues and evidence relevant to the comanagement of HF, CKD, and DM are described herein.

The Complex Interaction between HF, DM, and CKD

Interactions between HF and DM

DM is associated with an increased risk of cardiovascular disease (CVD), cardiovascular (CV) mortality, and a more severe disease course. The likelihood of developing CVD is 1.5-fold higher in patients with DM than in patients without DM, and the likelihood of experiencing CV-related events (e.g., myocardial infarction or stroke) is higher in patients with severe or uncontrolled DM [6]. Furthermore, DM increases the risk of developing HF, with greater risk observed in women with DM than in men with DM [2]. The high prevalence of HF (Fig. 1) and increased risk of new-onset HF in individuals with DM compared to individuals in general or matched populations [2] support a shared pathogenesis between the 2 conditions.

DM can contribute to the development of both CVD and HF via cellular, molecular, and systemic mecha-

nisms, which have been described extensively elsewhere [7]. In brief, DM is characterized by hyperglycemia and insulin resistance, which trigger a cascade of deleterious effects. In particular, these features can drive inflammation, dyslipidemia, endothelial dysfunction (leading to coronary artery disease, fibrosis, left ventricular [LV] hypertrophy, and cardiomyocyte dysfunction), and autonomic dysfunction (leading to systolic and diastolic dysfunction) [7]. Conversely, HF may be an independent risk factor for DM through mechanisms related to neurohormonal activation and chronic inflammation [8]. Metabolic risks may be further heightened by the use of glucose-lowering medication that can increase the risk of mortality and hospitalization in patients with or without HF [2].

Interactions between HF and CKD

CKD may be a disease multiplier [9, 10], wherein as disease severity worsens (Fig. 2), the risks of CV events, hospitalization, and mortality increase [11]. For example, patients with stage 3 or 4 CKD or microalbuminuria are at higher risk of CV-related mortality than those with normal kidney function or normal albuminuria [11]. In addition, in the Atherosclerosis Risk in Communities study of nearly 15,000 individuals without HF, the presence of stage ≥ 3 CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²) was independently associated with a 1.9-fold increased risk of incident HF

Fig. 2. Prognosis of CKD by GFR and albuminuria category: Kidney Disease: Improving Global Outcomes (KDIGO) 2012 [11]. The colors represent low risk (green; i.e., if no other markers of kidney disease, no CKD), moderately increased risk (yellow), high risk (orange), and very high risk (red). Reproduced with permission from the KDIGO Work Group [11].

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (mL/min/1.73 m ²) Description and range	G1	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60–89	Green	Yellow	Orange
	G3a	Mildly to moderately decreased	45–59	Yellow	Orange	Red
	G3b	Moderately to severely decreased	30–44	Orange	Red	Red
	G4	Severely decreased	15–29	Red	Red	Red
	G5	Kidney failure	<15	Red	Red	Red

compared with the reference group, who all had an eGFR of ≥90 mL/min/1.73 m² [9].

Complex, bidirectional mechanisms underpin the interaction between CKD and HF. Patients can experience impaired kidney function secondary to heart disease, heart disease secondary to impaired kidney function, or concurrent dysfunction of both organs, termed cardiorenal syndrome. In cardiorenal syndrome, acute or chronic failure of either organ can induce impairment of the other organ [9, 10]. Systemic complications (e.g., DM) also contribute to renal and cardiac injury. Injuries to both organs can then drive inflammation, oxidative stress, hemodynamic changes, and neurohormonal activation (i.e., of the renin-angiotensin-aldosterone system [RAAS] and systemic nervous system). Independently, renal injury can also cause anemia, metabolic abnormalities, and volume overload leading to cardiac injury, while cardiac injury can cause hemodynamic changes leading to renal injury [9, 10].

In patients with cardiorenal syndrome, differentiating primary and secondary disease can be challenging because of these diseases' common risk factors and pathophysiology [9]. A multidisciplinary treatment approach is therefore needed to optimize care for patients with HF and CKD [9]. In particular, since anemia is common in CKD and can independently increase the risk of hospitalization and mortality in individuals with HF, clinical

practice guidelines recommend the evaluation and treatment of iron deficiency anemia in this patient population [12].

Interactions between DM and CKD

The link between DM and CKD, independent of HF, is beyond the scope of the current review. However, it is important to acknowledge that DM is the leading cause of CKD [4]. Moreover, patients with DM and CKD are at high risk for CVD, including HF [4]. In patients with DM, risk factors for CKD include older age, male sex, smoking, obesity, and hypertension [6]. Among these risk factors, obesity and hypertension can stimulate inflammatory, fibrotic, and hemodynamic changes (e.g., activation of the RAAS), resulting in high intraglomerular pressure as well as glomerular hyperfiltration with eventual progression to CKD [13].

Outcomes of HF, DM, and CKD

There is now increased research focus on the impact of comorbidities across the spectrum of HF [14, 15]. In particular, DM and CKD are common comorbidities associated with both HF with reduced ejection fraction (HFrEF) (LV ejection fraction [LVEF] ≤40%) and HF with preserved ejection fraction (HFpEF) (LVEF >50%) [14, 15]. These comorbidities are thought to drive HFpEF development via systemic inflammation and its effects on cardiac

function. By contrast, cardiac insult is thought to precede HFrEF, with later development of DM and CKD [14, 15]. However, more research is needed to clarify the mechanisms that underlie the progression of DM and CKD to HFpEF versus those linking HFrEF to DM and CKD.

Regardless of the type of HF, the combined effect of HF, DM, and CKD leads to an increased risk of hospitalization and mortality in the patients who are impacted [5]. Real-world data from almost 90,000 individuals in the United Kingdom reported hospitalization and mortality rates during the first year after HF diagnosis in patients with HF ($n = 21,815$), HF + CKD ($n = 26,881$), HF + DM ($n = 7,893$), and HF + DM + CKD ($n = 10,638$). CV-related hospitalization rates were highest in patients with all 3 conditions (89.1%) compared to patients with HF only (35.1%), HF + CKD (46.4%), and HF + DM (49.2%). Non-CV-related hospitalization rates were also highest among patients with all 3 conditions (223.2 events per 100 person-years [ppy]) compared to patients with other morbidities (HF only, 62.2 ppy; HF + CKD, 71.7 ppy; HF + DM, 85.1 ppy). Last, mortality rates were 78.6% in patients with HF + CKD + DM, 20.5% in patients with HF only, 24.9% in patients with HF + CKD, and 25.1% in patients with HF + DM [5].

Case Study of Concomitant HF, DM, and CKD

A 64-year-old woman, nonsmoker, with a 15-year history of DM, retinopathy that improved approximately 70% following laser surgery, home-recorded blood pressure approximately 140/90 mm Hg, and a stent implanted in her superficial femoral artery 5 months earlier, developed edema and dyspnea on exertion that appeared to respond to treatment with furosemide. An electrocardiogram showed sinus rhythm with nonspecific ST changes (heart rate, 78 beats per minute; QRS duration, 100 ms). Left heart catheterization demonstrated nonocclusive 3-vessel disease; LVEF was 36% by echocardiography. The patient's eGFR was 48 mL/min/1.73 m², and spot urinary albumin:creatinine ratio was 350 mg/g. Other laboratory blood results showed glycated hemoglobin 7.6%, eGFR 47 mL/min/1.73 m², triglycerides 324 mg/dL, low-density lipoprotein cholesterol 82 mg/dL, hemoglobin 10.6 g/dL, brain natriuretic peptide 456 pg/mL, and uric acid 16 mg/dL. Potassium and sodium levels were normal. Medications concurrent with furosemide included atenolol, aspirin, clopidogrel, irbesartan, and metformin; lovastatin was stopped many years earlier because of joint pain that was attributed to taking the drug.

Challenges in the Management of This Case

This patient had multiple clinical features indicating high risk of CV events and progression of CKD. These clinical features included evidence of LV systolic dysfunction in conjunction with established peripheral artery disease, diabetic retinopathy, and CKD with severely increased albuminuria.

Because this patient had signs and symptoms of HFrEF, optimizing comprehensive disease-modifying medical therapy should be a priority. Management options are presented in the following sections and focus on newer-generation treatments for patients with HF; other treatment options for patients with DM or CKD alone are beyond the scope of this review article.

Evidence in Management from Clinical Trials

Angiotensin receptor-neprilysin inhibitor (ARNI), β -blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors are currently recommended as first-line medications in all patients with HFrEF [16]. ARNI is the preferred RAAS inhibitor compared to angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) [16], based on evidence that sacubitril/valsartan reduces the risk of hospitalization for HF and CV-related mortality versus enalapril in patients with HFrEF [17]. In patients with newly diagnosed symptomatic HFrEF, an evidence-based β -blocker, with or without a diuretic, may be started at the same time as an ARNI. MRAs should also be added to the regimen; however, close monitoring of electrolytes and renal function is warranted [16]. Finally, SGLT2 inhibitors, in addition to foundational guideline-directed medical therapy, have been shown to reduce the risk of hospitalization and mortality in patients with HFrEF, regardless of the presence of DM [16]. To reduce the risk for atherosclerotic CVD, a statin can also be considered, alongside comprehensive lifestyle modifications. Taken together, our patient case study may benefit from replacing irbesartan with ARNI and metformin with an SGLT2 inhibitor.

As described above, there are multiple evidence-based treatment options for HFrEF. Recently, data have also emerged showing benefit of ARNI and SGLT2 inhibitors in some patients with HFpEF [18–20]. The PARADIGM-HF trial demonstrated the superiority of sacubitril/valsartan ($n = 4,187$) versus enalapril ($n = 4,212$) in reducing CV death and first hospitalization for HF in patients with HFrEF ($p < 0.001$) [17]. The PIONEER-HF trial con-

Fig. 3. Percentage of patients regardless of the treatment group who had CKD (**a**) and DM (**b**) in HF trials by the year of trial publication [17, 19, 20, 23, 24, 35–51].

firmed the safety of in-hospital initiation of sacubitril/valsartan following hemodynamic stabilization in patients with HFrEF [21]. In the PARAGON-HF trial ($n = 4,822$), fewer primary composite outcome events (CV death and hospitalizations for HF) were observed with sacubitril/valsartan versus valsartan in patients with HFpEF; however, the difference was not statistically significant ($p = 0.06$) [19]. Subgroup analyses of PARAGON-HF showed potentially greater benefit of sacubitril/valsartan in female than in male patients, as well as in patients with LVEF $\leq 57\%$ [19]. In February 2021, sacubitril/valsartan received approval for an expanded indication from the US Food and Drug Administration. The prescribing information now indicates that sacubitril/valsartan is approved to treat adults with chronic HF; benefits are most clearly evident in patients with below-normal LVEF,

based on data from PARADIGM-HF and PARAGON-HF [22]. The DAPA-HF ($n = 4,744$) and EMPEROR-Reduced ($n = 3,730$) trials demonstrated the superiority of dapagliflozin and empagliflozin versus placebo, respectively, in reducing events for the primary composite outcomes in patients with HFrEF (DAPA-HF: CV death and worsening HF; EMPEROR-Reduced: CV death and hospitalization for worsening HF; $p < 0.001$ for both trials) [23, 24]. In the EMPEROR-Preserved trial ($n = 3,730$), empagliflozin was superior to placebo in reducing the primary composite outcome of CV death and hospitalization for HF in patients with HFpEF, defined as LVEF $> 40\%$ ($p < 0.001$) [20].

Renal benefits of ARNI have been shown in patients with HFrEF and HFpEF. Compared to an ACEi or ARB, ARNI is associated with smaller declines in eGFR in pa-

Table 1. Recommended HF therapies and their use in CKD or DM

Recommended HF therapy [16, 18]	Prevention of mortality in CKD	Prevention of mortality in DM	Other considerations
RAAS inhibitors			
ARNI	Benefit [25]	Benefit [35]	Risk of hypotension and angioedema [17]
ACEi	Benefit [36]	Benefit [52]	Risk of hypotension, angioedema, hyperkalemia, or elevated serum creatinine, including in CKD [17, 36]
ARB	Possible benefit* [37]	Benefit* [38]	Risk of hypotension, hyperkalemia, or elevated serum creatinine, including in CKD [37, 38]
Evidence-based β -blockers, MRAs, and SGLT2 inhibitors			
β -Blocker	Benefit [53]	Benefit [52]	Risk of headache, orthostatic hypotension, hyperkalemia, and hyperglycemia [53]
MRA	Benefit* [54]	Benefit* [54]	Risk of hyperkalemia [54]
SGLT2 inhibitor	Benefit [34, 55]	Benefit* [23, 28–31]	Risk of diabetic ketoacidosis (rare in type 2 DM), genitourinary infections, and volume depletion (multiple) [23, 28–30, 56]

* On a combined end point that included mortality and other morbid events.

tients with HFrEF and HFpEF and with reduced risk of renal events in patients with HFpEF [25, 26]. Furthermore, based on a secondary analysis of PARADIGM-HF, ARNI also attenuates the rate of decline in eGFR among patients with comorbid HFrEF and DM [27]. Importantly, in individuals taking an RAAS inhibitor (e.g., ARNI, ACEi, ARB, or MRA), hyperkalemia is a concern, especially among those with impaired kidney function [16]. Although potassium-binding agents, such as patiomer, have been approved by the US Food and Drug Administration, more data are needed to support their use in patients with HF [16].

The newer generation of glucose-lowering drugs has also been shown to exert protective effects of varying magnitude on both the heart and the kidneys. In particular, the CV benefits of SGLT2 inhibitors [28–31] and glucagon-like peptide 1 receptor agonists [32, 33] have been shown in patients with DM, and the renal benefits of SGLT2 inhibitors have been shown in patients with CKD [34].

HF trials have largely excluded patients with advanced CKD; therefore, most evidence is based on the experience of patients with moderate CKD (i.e., stage 3), who are reasonably well represented in randomized controlled trials. Figure 3a shows the percentage of patients in HF studies who also had CKD. Given that DM is a common comorbidity in these patients, Figure 3b shows the percentage of patients in HF studies who also had DM.

Table 1 provides an overview of recommended therapies for HF and evidence for their effect in patients with CKD and/or DM. In general, treatment effects (e.g., on

hospitalization and mortality) have been consistent in patients with HF, regardless of comorbid CKD or DM (Table 1). A systematic review and meta-analysis of randomized controlled trials in patients with HF found that treatment with ARNI resulted in a lower risk of renal dysfunction than other RAAS inhibitors [57]. This effect of ARNI in slowing eGFR deterioration has been attributed to the additive effect of increased natriuretic peptides caused by neprilysin inhibition compared with ACEi [57].

In the past decade, almost 20 trials of different glucose-lowering agents have provided evidence on the CV and kidney effects of newer-generation drugs for DM. As a result, specific glucose-lowering agents are now recommended for the prevention of CV events and reduction of eGFR in individuals with DM. Table 2 details some of the more common glucose-lowering agents available. Broadly, dipeptidyl peptidase-4 inhibitors are neutral for atherosclerotic CVD [61–64] and HF [61, 64, 65] except for saxagliptin, which showed an increased risk of hospitalization for HF [63]. SGLT2 inhibitors [28–31] and glucagon-like peptide 1 receptor agonists [32, 33, 60, 66, 67] have also been shown to reduce the risk of CV and renal outcomes.

Conclusion

HF, DM, and CKD are complex, interlinked conditions. Treatment plans for patients with a combination of these comorbidities should consider the available clinical evidence while acknowledging that data are mainly limited to subgroup analyses of randomized controlled trials.

Table 2. Glucose-lowering therapies and their use in CKD and CVD [56]

Class of glucose-lowering therapy	Route of administration	Use in CKD	CV effects	Kidney effects	Other considerations
Metformin [56]	Oral	Contraindicated in patients with eGFR <30 mL/min/1.73 m ²	ASCVD: possible benefit HF: neutral	No direct evidence for kidney protection from randomized trials	GI side effects are common Potential for B12 deficiency
SGLT2 inhibitors [56]	Oral	Dose varies by product and country Can be continued until dialysis or transplantation in patients with eGFR <30 mL/min/1.73 m ² (canagliflozin and dapagliflozin) [34, 58]	ASCVD: benefit [31] HF: benefit	Prevents progression of CKD in patients with type 2 DM, CKD, and/or HF [31, 55, 59]	Risk of diabetic ketoacidosis, genitourinary infections, and volume depletion [23, 28–30, 56]
GLP-1 RAs [56]	Subcutaneous	No dose adjustment: dulaglutide, liraglutide, semaglutide Use of exenatide and lixisenatide restricted to patients with eGFR >30 mL/min/1.73 m ²	ASCVD: neutral (exenatide, lixisenatide); benefit (dulaglutide, liraglutide, semaglutide) HF: possible benefit [60]	Benefit on renal end points observed in CV outcome trials may be driven by albuminuria, with no clear effect on patient-level kidney outcomes (liraglutide, semaglutide, dulaglutide, exenatide)	FDA black box warning for risk of thyroid C-cell tumors in rodents (liraglutide, dulaglutide, exenatide semaglutide) GI side effects are common Possible risk of pancreatitis (rare) and injection site reactions
DPP-4 inhibitors [56]	Oral	All require dose adjustment in the setting of renal impairment, except linagliptin	ASCVD: neutral HF: potential risk of harm with saxagliptin	Neutral	Risk of joint pain and potential pancreatitis (rare)
Sulfonylureas [56]	Oral	Initiate conservatively; avoid glyburide	ASCVD: neutral HF: neutral	Neutral	FDA special warning on increased risk of CV mortality using older generations of agent
Thiazolidinediones [56]	Oral	No dose adjustment required	ASCVD: possible benefit (pioglitazone) HF: increased risk	Neutral	Generally not recommended in renal impairment owing to fluid retention/edema
Insulin [56]	Subcutaneous	Adjust dosing according to patient clinical response	ASCVD: neutral HF: neutral	Neutral	Increased risk of injection site reactions and hypoglycemia
ASCVD, atherosclerotic cardiovascular disease; DPP-4, dipeptidyl peptidase-4; FDA, US Food and Drug Administration; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide 1 receptor agonist.					

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Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest Statement

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