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Heart failure with reduced ejection fraction and the intersection of cardio-renal-metabolic medicine #CaReMe

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Diabetes and chronic kidney disease (CKD) are important comorbidities in patients with heart failure (HF) that can complicate the clinical management and have major implications for morbidity and mortality. In addition, the presence of these comorbidities, particularly advanced CKD, is a limitation for the implementation of guideline-directed therapies in patients with HF with reduced ejection fraction (HFrEF). Though clinical trials in patients with HFrEF trials included varying percentages of patients with diabetes and/or CKD, patients with advanced CKD have been excluded in most HF studies. Thus, management recommendations for these patients often have to be extrapolated from subgroup analyses. This article summarizes pathophysiological aspects of the interaction of HFrEF, CKD, and diabetes and addresses clinical aspects for the screening of these comorbidities. Moreover, current treatment options for patients with HFrEF and CKD and/or diabetes are discussed and novel strategies such as the use of the selective mineralocorticoid receptor antagonist Finerenone are addressed.

Diabetes and chronic kidney disease (CKD) are important comorbidities in patients with heart failure (HF).[1,2] When HF and one or both comorbidities coexist, cardiovascular morbidity and mortality are greatly increased[3,4] and for optimal clinical care it is of utmost importance to screen patients with HF for the presence of diabetes and CKD and vice versa. Moreover, with respect to therapeutic options to reduce CV risk in HF with advanced CKD, patients are often ineligible or intolerant to therapies proven efficacious in patients with more preserved kidney function. This review summarizes the current understanding of the importance of diabetes and CKD for the management of patients with HF with reduced ejection fraction (HFrEF), including novel treatment options.

Pathophysiology of cardio-renal-metabolic disease

Clinical and experimental data over the last decades revealed increasing evidence for the close interrelation of the metabolic system, the heart, and the kidney. It is now recognized that chronic dysfunction of the heart, the kidneys or the metabolic system such as diabetes may induce

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dysfunction in the other organs and that organ cross-talk plays a crucial role in perpetuating disease progression (reviewed in Jankowski *et al.*[5]). As such, diabetes with hyperglycaemia, insulin resistance, and increased levels of adipokines have been shown to affect kidney function, secondarily contributing to fluid retention, albuminuria, and a decline of glomerular filtration rate (GFR)[6] while leading to vascular dysfunction, atherosclerosis, and HF.[7,8] Cardiac dysfunction with neurohumoral activation, volume overload, and change in substrate utilization promotes insulin resistance and increases levels of free fatty acids with metabolic consequences in various organs. In the kidney, these cardiac abnormalities promote hypertension, albuminuria, and also a decline in kidney function.[9]

Finally, the presence of CKD leads to an activation of the renin–angiotensin–aldosterone system, as well as the sympathetic nervous system. These maladaptive pathways may exert a spectrum of deleterious effects, ranging from fluid and sodium retention to hypertension and oxidative stress which then affect the metabolic system, e.g. by increasing insulin resistance. In the heart, CKD promotes ventricular hypertrophy and fibrosis and subsequently the development of HF, while, in the vascular system, CKD contributes to calcification with vascular dysfunction (reviewed in Jankowski *et al.*[5]) (*Figure 1*).

This, as of yet, incompletely understood interaction can, in part, explain the worse prognosis of patients with these comorbidities.

Epidemiology and prognosis

HFrEF and diabetes

Patients with diabetes exhibit an elevated risk to develop HF with epidemiological studies showing a 2- to 4-fold increased risk of HF in patients with diabetes compared with those without diabetes.[1] Interestingly, patients with diabetes develop chronic HF at younger ages and frequently exhibit unrecognized HF. In people with Type 2 diabetes without known HF, a standardized diagnostic workup showed that previously unrecognized HF was present in 28% of subjects with about one quarter having HFrEF and three quarters having HFpEF.[10] Moreover, patients with HF show a high prevalence of either disturbed glucose metabolism or diabetes. Various epidemiological studies have shown that the prevalence of diabetes in subjects with HF varies between 25 and 40%. Data from the PARADIGM-HF study demonstrated that 13% of HFrEF patients had undiagnosed diabetes and 25% had pre-diabetes. Patients who have both comorbidities have worse prognoses. In the PARADIGM-HF study, those with HF and diabetes experienced more cardiovascular death (17%) compared with those without diabetes and a HbA1c < 6% (12%) over 27 months.[4] Recent data in patients with HFrEF from the placebo group of the EMPEROR-Reduced trial showed an event rate for the combined endpoint of CV-death of HF hospitalization of 24.6/100 patient-years in patients with T2DM while the event rate in those without diabetes was much lower at 17.6/100 patient-years. Interestingly, in this study, the event rate in HFrEF patients with pre-diabetes was comparable to those without glucose abnormalities.[11]

In addition, CKD and HF represent the two most common first presentations of cardiovascular or renal disease in those living with Type 2 diabetes.[12]

HFrEF and CKD

The incidence of HF starts to increase as eGFR drops below 90 mL/min/1.73 m^2, steadily rising as eGFR falls with an adjusted hazard ratio (HR) of 2.5 if eGFR is less than 30 mL/min/1.73 m^2.[2] In addition, the risk of HF increases as soon as urine albumin–creatinine ratio (UACR) exceeds 5 mg/g.[13] Patients with CKD initially often develop HFpEF due to left-ventricular hypertrophy and fibrosis, the two hallmarks of uraemic cardiomyopathy. However, many patients also develop coronary artery disease and at later stages HFrEF (reviewed in Jankowski *et al.*[5]). Epidemiological data suggest that patients with HFrEF who are at CKD Stages 4 and 5 have a 50% survival probability over 20 months, in contrast to patients with HFrEF without CKD in which about 75% are still alive after 20 months.[3]

Screening for cardio-renal-metabolic disease

Given the strong multi-directional relationship between HF, diabetes, and CKD for both incidence and prognosis, it is important to understand how to identify these partner comorbidities in a given patient.

Screening for HF among those with diabetes

The presence of diabetes puts one at-risk for HF (Stage A).[14] Many will also have other risk factors including hypertension, obesity, and/or cardiovascular disease. Therefore, arguably the most important tool in identifying HF in people with diabetes is a high index of suspicion. Comprehensive history and physical examination are the first steps in identifying those who may have HF.[15] This assessment should also include identifying associated risks for HF including hypertension, obesity, and albuminuria. In addition to the clinical assessment, other tests may include electrocardiography (ECG), natriuretic peptides such as *N*-terminal pro-B-type natriuretic peptide (NT-pro-BNP) or B-type natriuretic peptide (BNP), and echocardiography.[16]

- Electrocardiogram (ECG): In the context of HF assessment, a normal ECG makes the diagnosis of HF unlikely.[16] Routine screening with a resting ECG is recommended in those with diabetes and hypertension or suspected CVD by the 2019 ESC guidelines on diabetes.[17] The Diabetes Canada guidelines support the use of routine resting ECG in those aged >40 years, with long duration of diabetes, or in the presence of risk factors.[18] However, this is not a consistent recommendation among other diabetes guidelines.
- Natriuretic Peptide (NT-pro BNP or BNP): The utility of this biomarker in the diagnosis, exclusion, or prognostication of HF is well established in those who are symptomatic.[14,16] However, among asymptomatic people at risk of HF, there are some data to support their utility but there is no consensus on whether it should be implemented routinely in clinical practice. In the STOP-HF trial, 1374 asymptomatic people at risk of HF (hypertension, diabetes, or vascular disease) were randomized to screening with BNP testing or usual care.[19] Those with elevated BNP levels underwent echocardiography and collaborative team care involving a cardiovascular specialist. Nearly half (41.6%) of the intervention group had

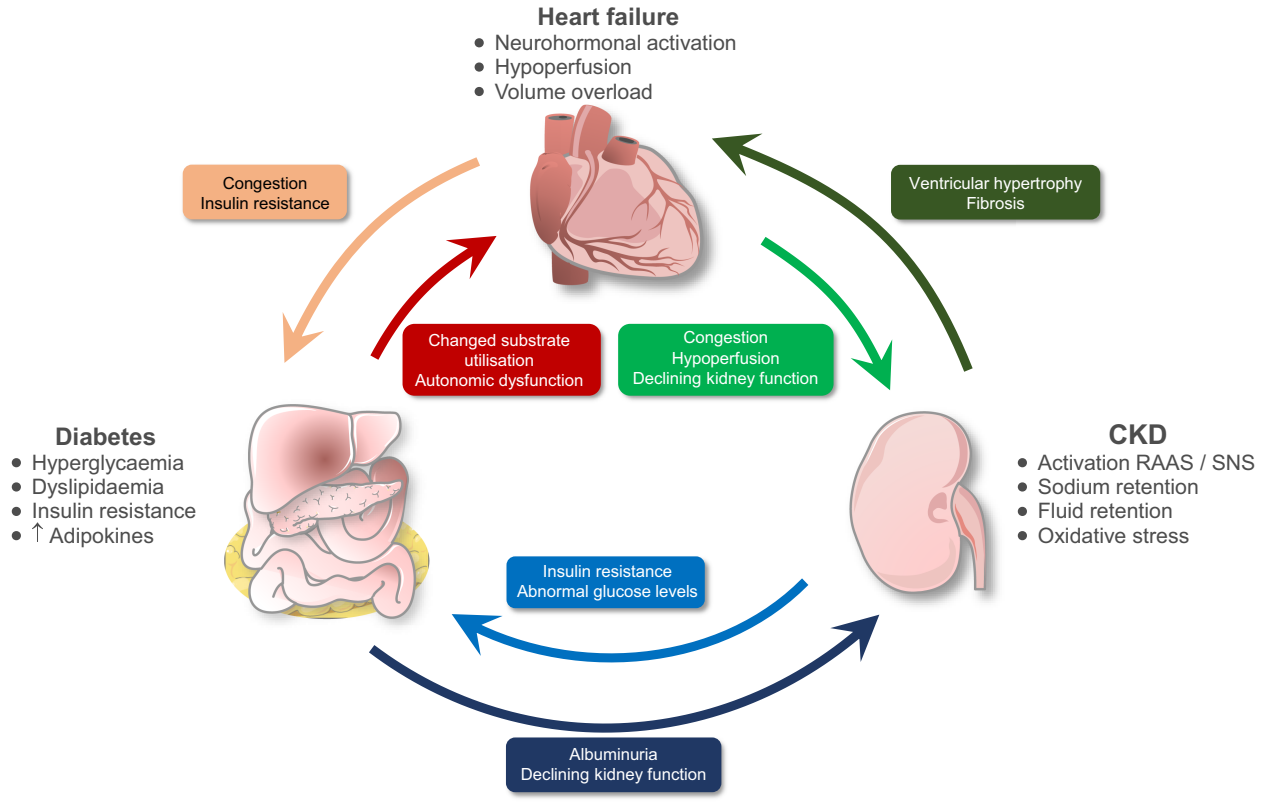

Figure 1 Cardio-renal-metabolic interaction. Various mechanisms in diabetes, heart failure, and CKD contribute to the progression of organ dysfunction and influence the prognosis of patients. Effects shown are an example and not exhaustive.

at least one elevated BNP reading and received more renin-angiotensin-aldosterone therapy. After a mean follow-up of 4.2 years, the primary endpoint of asymptomatic left-ventricular dysfunction with or without newly diagnosed HF was reduced in the intervention group [odds ratio (OR) 0.55; 95% confidence interval (CI) 0.37-0.88, $P = 0.01$].[19] Subsequent cost-effectiveness analysis suggested a high probability of cost-effectiveness.[20] The 2022 ACC/AHA HF guidelines provide a moderate strength recommendation that in those at risk of HF, natriuretic peptide-based screening followed by team-based care with optimized guideline-directed medical therapy can be useful to prevent the development of LV dysfunction or new-onset HF.[14] This is supported by the 2021 ESC HF guidelines.[16]

Table 1 Biochemical diagnostic criteria for diabetes and pre-diabetes according to the World Health Organization (WHO) and the American Diabetes Association (ADA)

	WHO criteria (2019)[a]	ADA criteria (2021)[22]
Glycaemic marker	**Diabetes**	
FBG	≥7.0 mmoL/L (≥126 mg/dL)	
2hPG (OGTT)	≥11.1 mmoL/L (≥200 mg/dL)	
HbA1c	≥6.5% (≥48 mmoL/moL)	
RPG	≥11.1 mmoL/L (≥200 mg/dL)	
Glycaemic marker	**Pre-diabetes**	
FBG	6.1-6.9 mmoL/L (110-125 mg/dL)	5.6-6.9 mmoL/L (100-125 mg/dL)
2-h PG (OGTT)	7.8-11 mmoL/L (140-199 mg/dL)	
HbA1c	6.0-6.4% (42-47 mmoL/moL)	5.7-6.4% (39-47 mmoL/moL)

[a]World Health Organization. Classification of diabetes mellitus 2019.
2hPG, 2-h plasma glucose; FPG, fasting plasma glucose; IFG, impaired fasting glucose; HbA1c, glycated haemoglobin; RPG, random plasma glucose.

- Echocardiography: Echocardiography is essential to evaluate structural and functional abnormalities of cardiac function and structural changes in asymptomatic individuals with diabetes can have prognostic implications.[21] However, routine echocardiography in asymptomatic people with diabetes has not been recommended by any organization at this time. In the presence of any symptoms though, echocardiography is recommended for assessment and perhaps in the future, if the provision of echocardiography can be made more accessible at a lower cost, screening in asymptomatic individuals with diabetes may be justified.

Screening for diabetes in HF

Given the high prevalence of diabetes in HF patients, screening for diabetes and pre-diabetes is recommended in HF patients for diagnostic and prognostic

reasons.[14,16] The 2021 ESC HF guidelines recommend routine fasting glucose and HbA1c testing in all patients with chronic HF (suspected or confirmed).[16] The diagnostic criteria for pre-diabetes and diabetes are shown in *Table 1*.

Screening for CKD in diabetes

CKD is defined as abnormalities of kidney structure or function for >3 months with GFR < 60 mL/min/1.73 m^2 and/or markers of kidney damage including UACR ≥3 mg/mmoL (30 mg/g) (*Figure 2*).[23] In diabetes, CKD is the most frequent first cardiorenal disease manifestation and is associated with increased mortality.[12] Routine annual screening for CKD is recommended for all adults living with diabetes with spot urine sample UACR testing as well as serum creatinine testing to determine GFR.[23,24] Despite this recommendation being long-standing and consistent around the world, urinary ACR testing continues to be underperformed resulting in delayed diagnoses and missed opportunities to prevent progression and complications.[25]

Therapy for HFrEF among patients with diabetes or CKD

Current therapeutic options in HFrEF patients are largely based on cardiovascular outcome trials (CVOTs), which assessed the effect of both medical as well as interventional therapies to reduce morbidity and mortality. Though clinical trials in patients with HfrEF trials included varying percentages of patients with diabetes and/or CKD, patients with advanced CKD have been excluded in most HF studies. Thus, management recommendations for these patients often have to be extrapolated from subgroup analyses.

Current HF guidelines from ESC as well as ACC/AHA recommend four foundational therapies in patients with HfrEF to reduce cardiovascular morbidity and mortality: ACEi/ARNIs, beta-blockers, mineralocorticoid receptor anatgonists (MRAs), and SGLT2 inhibitors (SGLT2i).[14,16]

ARNIs/ACEi

ARNIs promote natriuresis and reduce blood pressure, contributing to renoprotection in patients with diabetes. In pre-clinical studies, ARNI manifested its renoprotective effects by improving natriuresis, ameliorating inflammation, oxidative stress, and renal dysfunction, and slowing down glomerulosclerosis and tubulointerstitial injury of kidney, but its effect on proteinuria is still controversial. Beneficial effects of ARNIs on blood glucose regulation and glycometabolism have also been reported. In the PARADIGM-HF trial, the ARNI LCZ696 significantly reduced the primary endpoint of CV-death and HF hospitalization compared with enalapril. Of the 8399 patients randomized in the PARADIGM-HF study, 8274 had a measurement of HbA1c at baseline. A total of 2907 patients (35%) had a known history of diabetes. In the remaining 5367 patients, analysis of HbA1c measurements indicated that 26% were normoglycemic, 25% were pre-diabetic and 13% were considered to have undiagnosed diabetes. The rates of both the primary composite outcome and all-cause death were lowest in the normoglycemic group, significantly higher in the pre-diabetes category, and highest in individuals with undiagnosed and known diabetes. Renal impairment and hyperkalemia were more common in patients with diabetes. The incidence of hypotension adverse events was similar regardless of the glycemic status.[4]

In addition, sacubitril/valsartan lowered the decline in eGFR, and this favourable effect in patients with diabetes was twice as large as in those without diabetes, mainly due to the increase of cGMP.[26] Sacubitril/valsartan showed a trend towards reduction in worsening renal function, especially in patients with CKD. The rate of renal function decline doubled with coexistence of Type 2 diabetes with HFrEF vs. HFrEF without diabetes. The magnitude of benefit from sacubitril/valsartan on renal function was larger in HFrEF patients with diabetes vs. those without diabetes. The renal composite outcome and cardiovascular outcome occurred significantly less frequently in patients assigned to sacubitril/valsartan, despite a modest increase in the UACR compared with enalapril.[26] Of note, eGFR <30 mL/min/1.73 m^2 at screening, end of enalapril run-in or randomization, or $a > 35\%$ decrease in eGFR between screening and end of enalapril run-in or between were exclusion criteria.

Precautions for use of sacubitril/valsartan in patients with HFrEF and renal impairment need to be implemented. If patients experience tolerability issues (SBP ≤95 mmHg, symptomatic hypotension, hyperkalemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration, or if tolerability issues persist, discontinuation of sacubitril/valsartan is recommended. No dose adjustment is required in patients with mild (eGFR 60–90 mL/min/1.73 m^2) renal impairment. A starting dose of 24 mg/26 mg twice daily should be considered in patients with moderate renal impairment (eGFR 30–60 mL/min/1.73 m^2). In view of very limited clinical experience in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), sacubitril/valsartan should be used with caution, and a starting dose of 24 mg/26 mg twice daily is recommended.[27]

The use of sacubitril/valsartan is not recommended in patients with ESRD, as there is no experience in this group of patients. ACE inhibitors have been shown to reduce morbidity and mortality in numerous large randomized trials. A clear benefit of ACE inhibitors in patients with CKD Stages 1–3 has been suggested, but few data are available in patients with advanced CKD stages.

Beta-blockers

No dedicated clinical trials have assessed the effect of betablocker treatment in HFrEF patients with diabetes. However, a meta-analysis of large betablocker trials in HF demonstrates for the group of patients with diabetes (24.6%) a significant benefit compared with placebo, suggesting that beta-blockers are equally effective in the treatment of HFrEF in patients with and without diabetes.[28] Similarly, a meta-analysis assessing the effect of beta-blockers on overall mortality in subjects HF and CKD Stages 3–5 demonstrated a significant 28% risk reduction.[29]

MRAs

Spironolactone and eplerenone improved the prognosis of HFrEF patients, and this therapy is effective in patients

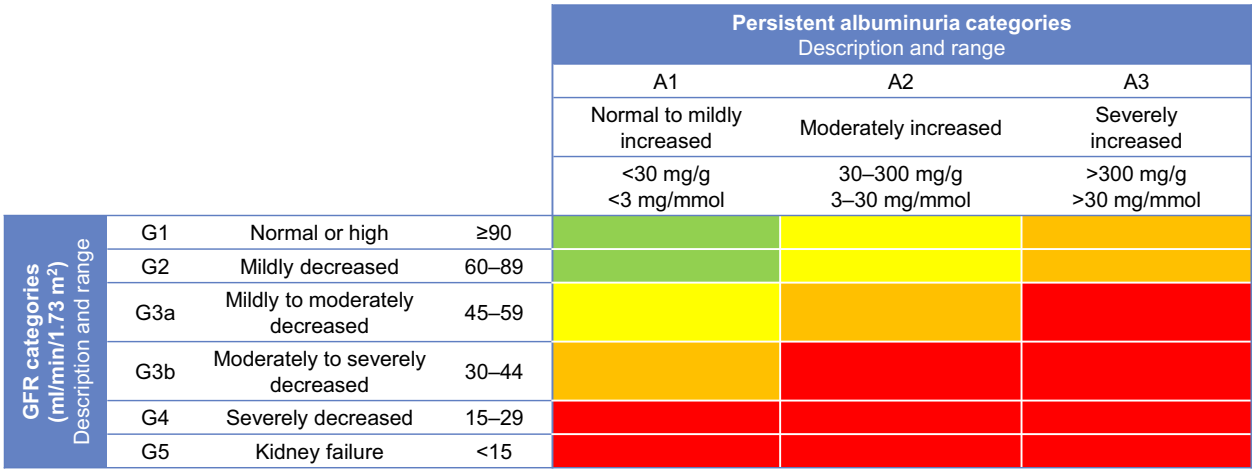

Figure 2 KDIGO CKD staging by GFR and UACR categories with colour charts for risk of initiation of maintenance renal replacement therapy. Green represents low risk, yellow represents moderately increased risk, orange represents high risk, and red represents very high risk. If no other markers of kidney disease, no CKD; GFR, glomerular filtration rate; UACR, urinary albumin to creatine ratio. Adapted from KDIGO (2020)[23].

with HF and diabetes as well as in HF patients with CKD Stages 1–3.[30,31] MRAs formally are still contraindicated in advanced CKD. The ongoing Aldosterone Antagonist Chronic HEModialysis Interventional Survival Trial (AL-CHEMIST trial) examines the effect of aldosterone on CV outcome (including HF) in chronic haemodialysis patients. Novel therapeutic strategies with potassium binders may provide an additional option for patients with hyperkalemia.

SGLT2 inhibitors

SGLT2i were initially granted regulatory approval for glycemic control among patients with Type 2 diabetes. However, in the relatively short time since the initial publication of the EMPA-REG Outcome trial in 2015, the regulatory label for SGLT2i has markedly expanded.[32] The medication class now includes approved indications to improve clinical outcomes across the spectrum of cardio-renal-metabolic disease, including HF, CKD, and T2D.

SGLT2i in patients with HFrEF and diabetes

With respect to the benefits of SGLT2i in HF patients, the hypothesis began in the initial large CVOTs of patients with Type 2 diabetes. Across these trials, while effects on major adverse cardiovascular events varied, SGLT2i therapy consistently decreased the risk of HF hospitalization by 27–39%.[33–36] Given that >85% of these patients did not have HF at baseline, this finding reflected primary prevention of incident HF.[37] As such, recently published HF guidelines now include a Class IA recommendation for use of SGLT2i to prevent incident HF in at-risk patients with Type 2 diabetes.[14,16]

Subsequently, these findings for HF prevention among patients with Type 2 diabetes spurred initiatives to test SGLT2i as a treatment for patients with established HFrEF, both with and without Type 2 diabetes. In their respective dedicated trials, both dapagliflozin in DAPA-HF and empagliflozin in EMPEROR-Reduced substantially improved cardiovascular outcomes, with no statistical evidence of heterogeneity in treatment effect between the two trials.[38–40] Particularly notable, the benefits on cardiovascular outcomes were consistent irrespective of Type 2 diabetes status, with a near identical magnitude of relative risk reduction for cardiovascular death or HF hospitalization among patients with [HR 0.74 (0.65–0.84)] and without [0.75 (0.65–0.87)] Type 2 diabetes.[40] Further, secondary analyses of each trial highlight how consistency in treatment effect by Type 2 diabetes status extends to kidney and patient-reported outcomes. For example, irrespective of Type 2 diabetes status, SGLT2i slowed the progression of renal disease and decline in eGFR.[11,41] Likewise, SGLT2i exert consistent benefits on Kansas City Cardiomyopathy Questionnaire score in patients with and without Type 2 diabetes.[42] A secondary analysis of DAPA-HF also showed that among patients with HfrEF without baseline diabetes, SGLT2i therapy reduced the relative risk of developing new-onset diabetes by 32%.[43]

With regards to safety, both DAPA-HF and EMPEROR-Reduced showed SGLT2i to have a strong safety and tolerability profile, with similar numbers of total adverse events among patients receiving placebo than active therapy, and consistent safety among patients with and without Type 2 diabetes. Specifically, rates of glycemic adverse events in DAPA-HF and EMPEROR-Reduced were exceptionally low, with no excess risk of hypoglycaemia or diabetic ketoacidosis with SGLT2i, as compared with placebo.[11,42]

SGLT2i in patients with HFrEF and CKD

Among patients with HFrEF and CKD in the DAPA-HF and EMPEROR-Reduced trials, SGLT2i reduced the risk of CV-death and worsening HF regardless of baseline eGFR. In addition, both dapagliflozin and empagliflozin slowed the progression of kidney disease in patients with CKD and HF.[41,44] Dapagliflozin slowed eGFR decline and reduced the risk of doubling serum creatinine and serious adverse renal events, though there was no statistically significant difference in overall renal composite endpoint (≥50% sustained decline in eGFR, end-stage renal disease,

or renal death).[41] In EMPEROR-Reduced, empagliflozin slowed the decline in eGFR slope, while also reducing the risk of the composite kidney endpoint (dialysis initiation, kidney transplant, or sustained reduction in eGFR) by 50%, with consistent benefits across the spectrum of eGFR and UACR.[44]

With respect to renal safety, the SGLT2i trials in HFrEF permitted the inclusion of patients with severe kidney disease, a population often underrepresented or excluded from prior HFrEF trials. For example, patients with an eGFR as low as 20 mL/min/1.73 m^2 were eligible for EMPEROR-Reduced, with 54% of patients having CKD defined as eGFR <60 mL/min/1.73 m^2 or UACR >300 mg/g.[44] In both the DAPA-HF and EMPEROR-Reduced trials, there was no excess risk of renal adverse effects with SGLT2i compared with placebo, including among patients with baseline eGFR <60 mL/min/1.73 m^2.[41,44] Nonetheless, patients may experience a modest early decline in eGFR with SGLT2i therapy, with SGLT2i associated with >2-fold risk of >10% decline in eGFR within 14 days of medication initiation.[45] However, while such declines in eGFR are associated with excess clinical risk among patients not receiving SGLT2i, such early worsening in eGFR after SGLT2i initiation is paradoxically associated with reductions in cardiovascular death and worsening HF, without a greater risk of a long-term decline in GFR or excess adverse events.[45] Although prior data with ACEI and MRA have shown that declines in eGFR with the initiation of these therapies are not associated with excess risk, to our knowledge, SGLT2i are the first HF therapeutic where a decline in eGFR provoked by a therapy is associated with improved clinical outcomes, further supporting the strong safety and tolerability of SGLT2i in HFrEF.[46,47]

In addition to benefits towards slowing decline in eGFR and reducing kidney events, SGLT2i also reduce the risk of hyperkalemia among patients with HFrEF. These effects are particularly notable among patients concurrently receiving MRA therapy. For example, among patients treated with MRA at baseline, dapagliflozin reduced the relative risk of moderate/severe hyperkalemia >6.0 mmoL/L by 50% in DAPA-HF, while empagliflozin carried a 36% relative risk reduction in EMPEROR-Reduced.[48,49] These effects on reduced risk of hyperkalemia, without excess risk of hypokalaemia are consistent with effects seen with SGLT2i in T2D.[50] Moreover, given hyperkalemia persists as one of the most common reasons for intolerance to renin–angiotensin system inhibitors and MRAs, initiation of SGLT2i may indeed promote tolerance, adherence, and persistence with other key therapies for HFrEF.[24] For example, in EMPEROR-Reduced, among patients receiving MRA at baseline, empagliflozin reduced the relative risk of MRA discontinuation by 22% compared with placebo.[51]

Figure 3 (taken from Mullens *et al.*[52]) summarizes the initiation of HF drugs in relation to baseline CKD status.

Antihyperglycemic agents and HF safety signals in clinical trials

Different classes of antihyperglycemic agents are currently available for the treatment of Type 2 diabetes. Aside from SGLT2i, most other available antihyperglycemic agents seem to be neutral with respect to HF-related endpoints in large CVOTs. However, safety concerns exist for saxagliptin and thiazolidinediones (TZDs). Data from the SAVOR-TIMI 53 trial showed that treatment with saxagliptin compared with placebo leads to an unexpected increase in HF hospitalization[53] while no such an effect was observed with sitagliptin[54] and linagliptin.[55] Alogliptin was associated with a non-significant trend towards HF hospitalization.[56] Trials with TZDs (like pioglitazone or rosiglitazone) showed an increased risk of treated patients for HF hospitalization in trials such as PROactive[57] or RECORD.[58] Thus, saxagliptin and TZDs are not recommended in patients with HF in current guidelines.[16,59]

Finerenone

Finerenone is a novel, selective, non-steroidal MRA that has been investigated in dedicated trials in patients with CKD and T2DM. Previous experimental data had shown that finerenone exhibits anti-inflammatory and anti-fibrotic activities, thus exhibiting protective effects against progressive kidney disease and cardiovascular dysfunction in pre-clinical models (reviewed in Agarwal *et al.*[60]).

In the ARTS-HF, a Phase 2 study 1066 people with HF presenting to the emergency department with worsening HF and Type 2 diabetes mellitus, and/or CKD were randomized to one of five different finerenone groups: 2.5, 5, 7.5, 10, or 15 mg daily, with up-titration to 5, 10, 15, 20, and 20 mg, respectively, at 30 days vs. eplerenone 25 mg every other day, with up-titration to 25 mg daily at 30 days, and further up-titration to 50 mg daily at 60 days. The primary outcome was the percentage of individuals with a > 30% decrease in plasma NT-proBNP from baseline to Day 90. The reductions in this biomarker between eplerenone and finerenone were similar as was the risk for hyperkalemia. However, a key pre-specified secondary endpoint of all-cause death, cardiovascular hospitalizations, or worsening HF occurred least frequently in the finerenone 10 mg group vs. the eplerenone group (HR 0.56; $P = 0.016$). All-cause death ($P = 0.062$) and cardiovascular death ($P = 0.011$) occurred less frequently in the finerenone vs. eplerenone groups. This was despite the trial being of 90-day duration.[61]

Subsequently, two large Phase 3 cardiovascular outcome trials in patients with diabetes and CKD investigated the effect of finerenone vs. placebo on renal and cardiovascular outcomes. In both trials, patients with symptomatic HFrEF were excluded.

The FIDELIO-DKD trial randomized 5734 patients with Type 2 diabetes and an estimated eGFR ≥25 mL/min/1.73 m^2 and albuminuria (UACR ≥ 30 to ≤5000 mg/g) to finerenone 10 or 20 mg once daily vs. placebo and assessed the combined primary endpoint of time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death. At baseline, the mean eGFR was 44 mL/min/1.73 m^2 and the median UACR was 830 mg/g. Over a median follow-up of 2.6 years, finerenone significantly slowed CKD progression by 18% vs. placebo. In this study, the key secondary cardiovascular endpoint of CV-death, non-fatal MI, non-fatal stroke, or hospitalization for HF was significantly reduced by 14%

Table 4 Initiation of heart failure drugs in relation to baseline chronic kidney disease status

Drug	Evidence across GFR strata according to baseline eGFR enrolment criteria	Acute drop GFR	Impact on GFR slope in HF trial	CKD treatment interaction	Treatment effect with CKD
	ESKD 15–30 30–60 >60				
ACE-I/ARB	Moderate evidence if dialysis, weak evidence if not on dialysis	Yes	No (beneficial effect of around 1–2 ml/min/1.73 m^2 per year in CKD trials)	No	Relative benefit: ~ Absolute benefit: ↑
Beta-blockers		No	No	Yes (potentially but some conflicting results)	Relative benefit: ~ Absolute benefit: ↑
MRA		Yes	No	No	Relative benefit: ~ Absolute benefit: ↑
ARNI		Yes	Yes (around 0.5 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
SGLT2-i	>20	Yes	Yes (around 1–2 ml/min/1.73 m^2 per year)	No	Relative benefit: ~ Absolute benefit: ↑
Ivabradine		No	No	No	Relative benefit: ~ Absolute benefit: ↑
Vericiguat		No	No	No	Relative benefit: ~ Absolute benefit: ↑
Omecamtiv mecarbil		No	No	No	Relative benefit: ~ Absolute benefit: ↑

A decrease in eGFR over time does not automatically mean RAASi/SGLT2-i need to be downtitrated or discontinued

Dark green, strong evidence; light green, moderate evidence; red, not advised; light grey, no data. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease (eGFR <60 ml/min/1.73 m^2); eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2-i, sodium–glucose cotransporter 2 inhibitor.

Figure 3 Initiation of heart failure drugs in relation to baseline CKD status (obtained from Mullens *et al.*[52])

[HR 0.86 (95% CI 0.75–0.99), $P = 0.034$]. This reduction of the secondary endpoint translated into a number-needed-to-treat of 42 over 3 years.[62]

In the FIGARO trial of 7437 patients, a similar population was enrolled with a mean eGFR of 68 mL/min/1.73 m^2 and a median UACR of 308 mg/g. In this study the primary endpoint was a cardiovascular endpoint of CV-death, non-fatal MI, non-fatal stroke, or HF hospitalization; compared with a placebo, finerenone significantly reduced this endpoint by 13% with a number-needed-to-treat of 47 over 3.5 years.[63]

The pooled individual patient data meta-analysis of these two trials, called FIDELTY, showed in the overall population of patients with diabetes and CKD a 14% significant reduction of the composite cardiovascular outcome by finerenone with a number-needed-to-treat of 46 after 3 years; 1007 (7.7%) patients had a history of HF. This reduction was mainly driven by a significant reduction in HF hospitalization with a HR of 0.78 (CI: 0.66–0.92). The HR for cardiovascular death was 0.88 (0.76–1.02). Finerenone led to a placebo-corrected change in mean systolic blood pressure of −3.7 mmHg at 4 months. Hyperkalemia occurred in 14% of the finerenone and 6.9% in the placebo group while permanent discontinuation due to hyperkalemia was necessary for 1.7% of the finerenone and 0.6% in the placebo group. Interestingly, the cardiovascular benefits of finerenone were consistent regardless of baseline eGFR or UACR and the use of SGLT2i or GLP-1 receptor agonists.[64] These data suggest that finerenone in patients with diabetes and CKD Stages 2–4 and moderately increased albuminuria or CKD Stages 1–2 with severely increased albuminuria significantly reduced the risk of cardiovascular morbidity and mortality and that this benefit was mainly driven by a reduction of hospitalization for HF. Importantly, in these trials, patients with HFrEF were excluded. Still, of the 5674 patients in FIDELIO-DKD, 436 (7.7%) had a history of HF. Over a median follow-up of 2.6 years, the effect of finerenone compared with placebo on the composite CV outcome was consistent in patients with and without a history of HF [HR 0.73 (95% CI 0.50–1.06) and 0.90 (95% CI 0.77–1.04), respectively; interaction $P = 0.33$] suggesting that finerenone improved CV outcome in patients with CKD and Type 2 diabetes irrespective of baseline HF history.[65] Thus, finerenone provides a novel tool to reduce HF-related endpoints in patients with CKD and diabetes. An ongoing study, FINEARTS-HF is currently investigating the effect of finerenone vs. placebo on CV-death and HF hospitalization in patients with a diagnosis of HF and NYHA Classes II–IV and an LV ejection fraction ≥ 40% (NCT04435626).

Conclusion

The growing incidence of patients with HFrEF and CKD/and or diabetes as well as the implications on the prognosis if these comorbidities coexist underscore the necessity to screen patients for the presence of HF, CKD, and diabetes. In particular, in high-risk patients with HFrEF and CKD individualized treatment strategies need to be implemented and further research is required to develop novel options to reduce CV risk in multimorbid patients.

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Data availability

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

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