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Review

Cardiorenal Crosstalk in Patients with Heart Failure

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Abstract: Worsening renal function is associated with poor outcomes in heart failure and often accompanies the initiation and up-titration of guidelines-directed heart failure therapy. This narrative review summarizes current evidence on immediate and long-term effects of pharmacological or device-based treatment in heart failure patients with reduced or preserved left ventricular ejection fraction.

Keywords: cardiorenal syndrome; heart failure; chronic kidney disease; worsening renal function

1. Introduction

Many patients with heart failure (HF) suffer from chronic kidney disease (CKD), which not only worsens prognosis but also complicates guidance of medical HF therapy [1,2]. Initiation or up-titration of guidelines-directed HF therapy often goes along with a decrease in renal function [3–7]. This interaction is unpleasant from a clinical point of view; however, HF therapies such as renin–angiotensin–aldosterone system (RAAS) antagonists largely improve the prognosis of HFrEF and slow the progression of renal dysfunction in the medium and long term.

Most pivotal randomized-controlled trials testing drugs for the treatment of HF with reduced ejection fraction (HFrEF) excluded patients with more severe chronic kidney disease (CKD). By consequence, evidence guiding implementation of HF drugs in patients with more severe CKD is limited (Table 1). Therefore, most clinicians are watchful when implementing HF drugs that interact with renal function, and are often inert with respect to increasing the guidelines-recommended drugs to the target dose. Figure 1 illustrates the mechanisms of heart failure and evidence-based treatments for renal function in HFrEF.

Table 1. Recommendation of drug dosing in HFrEF in patients without and with CKD, based on available evidence and the SWISS medicinal product licensing body (SWISSMEDIC).

Drug Class	Medical Therapy	Target Daily Dose in Heart Failure Clinical Trials	Drug Dose Recommendations in Advanced CKD
ACE inhibitors (ACEis)	Enalapril	20 mg BD	Maximum dose of 5 mg D for enalapril
	Lisinopril	50 mg D	Maximum dose of 5·mg D for lisinopril
	Captopril	75 mg BD	Maximum dose of 6.25 mg D for captopril
Angiotensin II Receptor Blockers (ARBs)	Candesartan	32 mg D	Candesartan untested in eGFR < 15 mL/min
	Valsartan	160 mg BD	Valsartan untested in eGFR < 10 mL/min

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Table 1. *Cont.*

Drug Class	Medical Therapy	Target Daily Dose in Heart Failure Clinical Trials	Drug Dose Recommendations in Advanced CKD
Angiotensin Receptor–Neprilysin Inhibitor (ARNI)	Sacubritril/Valsartan	200 mg BD	No adjustment recommended
Steroidal Mineralocorticoid receptor Antagonist (MRA)	Spironolactone	50 mg D	Contraindicated with eGFR < 30 mL/min
	Eplerenone	50 mg D	Contraindicated with eGFR < 30 mL/min
Nonsteroidal Mineralocorticoid Antagonist	Finerenon	10 mg D	Not recommended with eGFR < 25 mL/min
Beta-blockers	Carvedilol	50 mg BD	No adjustment recommended for carvedilol, cardvedilol, or bisoprolol
	Bisoprolol	10 mg D	
	Metoprolol	200 mg D	
Sodium–glucose cotransporter-2 inhibitor (SGLT2i)	Dapaglifozin	10 mg D	No adjustment recommended
	Empaglifozin	10 mg D	Not recommended with eGFR < 20 mL/min (results of the EMPA-Kidney pending)
Practice guidelines recommend up-titration of evidence-based medications at trial doses for all HF patients, as tolerated. Close monitoring of blood pressure, serum potassium and kidney function is recommended			

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor blocker–neprilysin inhibitor; BD, twice a day; CKD, chronic kidney disease; D, daily; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

This narrative review summarizes evidence on immediate, and mid- or long-term effects of HF drugs in patients with concomitant kidney dysfunction with or without diabetes mellitus. Given the particularities associated with HF with reduced or preserved ejection fraction (HFpEF), these entities will be discussed separately. Furthermore, this review will discuss the effect of treatment options for advanced HF on kidney function, particularly percutaneous mitral valve repair with the MitraClip, percutaneous intervention for moderate-to-severe tricuspid regurgitation using the TriClip, long-term mechanical circulatory systems (LT-MCSs) and orthotopic heart transplantation (HTx) [8].

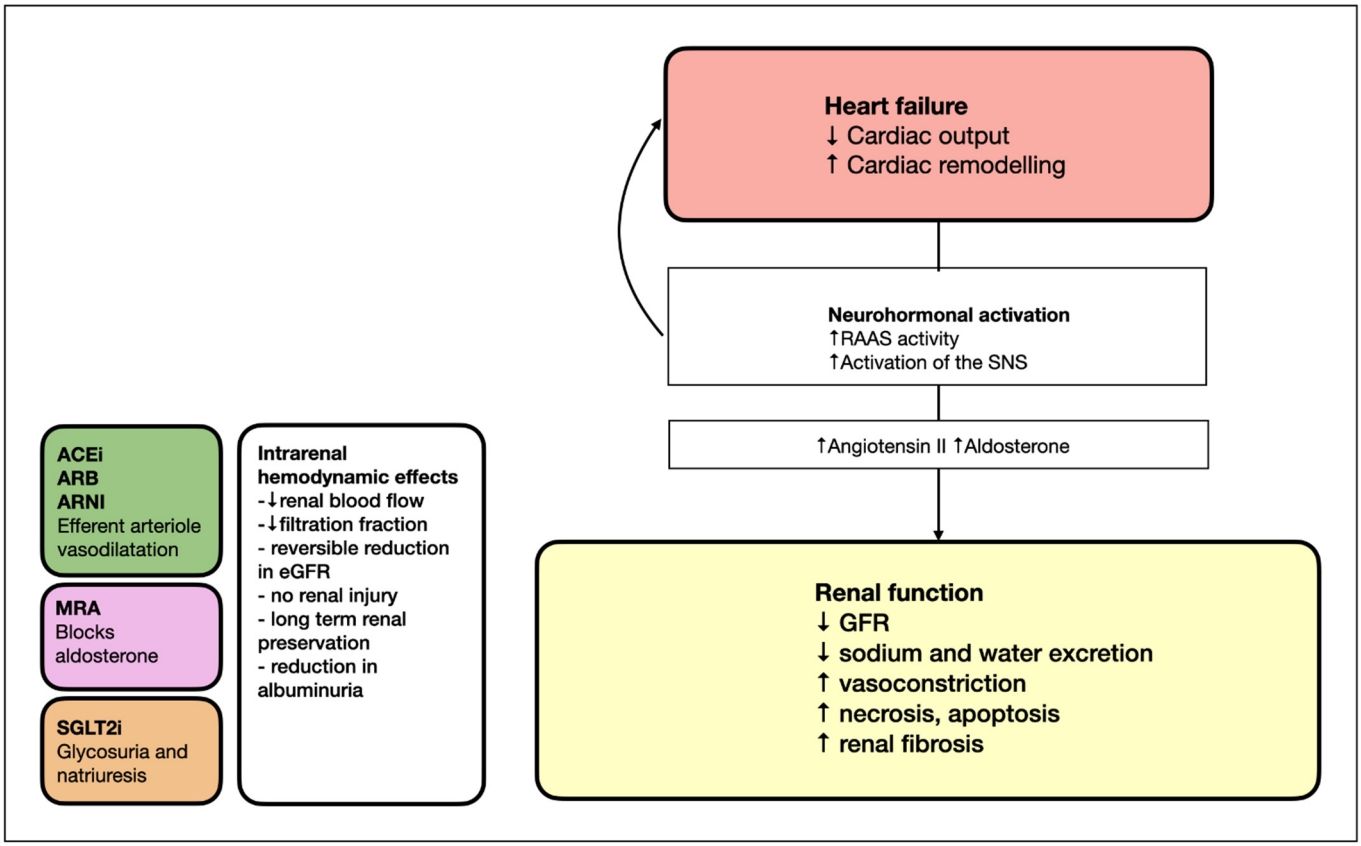

Figure 1. Mechanisms of heart failure and evidence-based treatments for renal function in HFrEF. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor blocker–neprilysin inhibitor; GFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; RAAS, renin–angiotensin–aldosterone system; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SNS, sympathetic nervous system.

2. Chronic Kidney Disease in Heart Failure—The Real-World Data

Chronic kidney disease (CKD) is the most prevalent comorbidity in HF and is associated with a high risk for all-cause mortality and HF hospitalization [5,9,10]. At least 60% of HF patients have mild renal dysfunction, and around 20% have moderate-to-severe kidney dysfunction [11]. In addition, CKD is a key risk factor of suboptimal use of guideline-directed medical therapy (GDMT) as shown in the in the CHAMP-HF registry (Change the Management of Patients With Heart Failure). CKD was the most frequent reason for the absence of evidence-based therapy up-titration in HFrEF patients in the BIOSTAT-CHF trial [12–14]. Furthermore, the TRANSLATE-HF trial recently showed that GDMT was applied less frequently with increasing severity of CKD. In fact, among patients with HFrEF, treatment with three classes of GDMT was used in only 15% and 5% when the estimated glomerular filtration rate (eGFR) was 30 to 44 mL/min/1.73 m^2 or <30 mL/min/1.73 m^2, respectively [15]. Patients with HFrEF and CKD are therefore at double risk of having an adverse prognosis.

Due to strict eligibility criteria for HF patients included in randomized controlled trials (RCTs), study results are often considered to be of limited applicability for real-world HF patients, while registry data are thought to map the typical HF patient more accurately. However, recent results obtained from a retrospective observational study including 17,106 de novo HFrEF patients indicate that higher treatment intensity is associated with lower mortality and lower rehospitalization risk [16]. Moreover, triple GDMT HF therapy at discharge was associated with a 32% decrease in the incidence of death or rehospitalization. These results extend the applicability of the RCT findings to HF patients with a more severe comorbidity burden, as 54% of the study participants had diabetes and 34% had CKD.

3. Definition of Worsening Kidney Function

Many HF studies have defined worsening renal function (WRF) as a decrease in the eGFR, but there is great variability in the definition of WRF, and the biomarkers used for grading severity of WRF vary (serum creatinine, cystatin C or estimated GFR). This inhomogeneity makes it difficult to compare studies with each other. For example, when WRF is defined by the increase in absolute creatinine, it inhomogeneously weighs the percentage of worsening of renal function between patients with mild and moderate-to-severe CKD. Nonetheless, there is a general consensus that WRF is an increase of 26.5 µmol/L of serum creatinine, as this increase is associated with a significant elevation in the risk of mortality and morbidity [17,18].

4. Antagonists of the Renin–Angiotensin–Aldosterone System (RAAS)

4.1. Angiotensin Receptor Blockers (ARBs)

4.1.1. ARB in HFrEF with Kidney Dysfunction

The multicenter Valsartan in Heart Failure Trial (Val-HeFT) study evaluated the effect of valsartan on the incidence of all-cause mortality and morbidity among patients with HFrEF (left ventricular ejection fraction (LVEF) < 40%) when added to standard-of-care HF therapy [19]. Valsartan treatment reduced the incidence of the primary combined endpoint by 13.2%, and this improvement was primarily due to a lower number of patients hospitalized for treatment of HF. HFrEF patients with a creatinine level > 220 µmol/L were excluded from study participation; however, in patients with renal impairment at baseline (n = 2346; 46.8% of the study participants), the benefit of valsartan treatment was even more pronounced, with a 24% reduction in the incidence of the primary endpoint (hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.66–0.88; p = 0.0002).

Among study participants with WRF during the observation time, 8.6% had a decrease in the eGFR > 20% within 1 month after randomization while 91.4% had a decrease in the eGFR $\leq$ 20%. In study, for participants whose eGFR decreased while on valsartan therapy, the risk for the combined endpoint was significantly reduced (HR 0.83, 95%CI 0.75–0.92; p = 0.0005), and this benefit was also present in study participants whose renal function declined rapidly (HR 0.63, 95%CI 0.45–0.89; p = 0.0086). Altogether, valsartan decreased the incidence of the combined endpoint independent of pre-existing kidney dysfunction or WRF [4]. Nonetheless, patients with early worsening of renal function had a higher risk of cardiovascular (CV) death and hospitalization for HF compared with those without early worsening renal function (HR 1.44, 95%IC 1.21–1.71; p < 0.0001).

Corresponding observations were reported from the CHARM-Alternative trial testing in HFrEF patients the efficacy of candesartan for the reduction in the composite endpoint of cardiovascular mortality and hospitalizations for HF. Overall, candesartan reduced the incidence of the composite primary endpoint by 23% (HR 0.77, 95%CI 0.67–0.8; p = 0.0004) [20]. As in the Val-HeFT study, the incidence of the combined endpoint was increased in study participants with WRF (odds ratio (OR) 2.29, 95%CI 1.75–3.00; p < 0.001). However, the incidence of the combined endpoint was numerically less important in the candesartan treatment group (HR 1.29, 95%CI 0.96–1.73; p = 0.71) when compared to patients with WRF in the placebo group (HR 1.51, 95%CI 1.02–2.22; p = 0.039). In summary, results from the Val-HeFT as well as the CHARM-Alternative trials indicate beneficial effects of antagonist of the angiotensin II receptor in HFrEF patients with or without renal dysfunction at baseline or WRF during the course of the study.

4.1.2. ARB in HFpEF with Kidney Dysfunction

The CHARM-Preserved trial included 3023 HF patients in New York Heart Association (NYHA) Class II-IV with an LVEF $\geq$ 40% and previous hospitalization [21]; 64% of patients had hypertension, and 28% had diabetes mellitus. The difference in the primary outcome, a composite of cardiovascular death and hospitalization for HF, failed to reach statistical significance (HR 0.89, 95%CI 0.77–1.03; p = 0.12). The results nonetheless suggest that the use of ARBs reduces recurrent hospitalizations for HF; however, since the primary endpoint

of the study was not significantly changed, the statistical robustness of a hierarchical secondary endpoint remains questionable.

The Irbesartan in Heart Failure With Preserved Ejection Fraction study (I-PRESERVE) compared irbesartan versus a placebo in 4133 patients with HFpEF, of whom 88% had hypertension and 27% diabetes mellitus [22]. Unfortunately, I-PRESERVE lacked statistical power due to a high rate of study discontinuation (34%) and the concomitant use of ACE inhibitors in 39% of patients in the placebo group and 40% of patients in the irbesartan group. Therefore, a firm conclusion regarding the efficacy of irbesartan in patients with HFpEF is not possible. In this study, the incidence of WRF at 8 weeks was 6.4% (n = 229), and patients randomized to irbesartan treatment experienced WRF more often when compared with patients in the placebo group (8.4% vs. 4.3%, OR 2.07; 95%CI 1.56–2.75; $p < 0.001$). Worth noting is that WRF after initiation of irbesartan treatment in HFpEF patients was associated with excess risk in the unadjusted analysis but not in the adjusted analysis. This observation differed according to WRF in the test group of the Val-HeFT or the CHARM-Alternative trial, where candesartan lowered the risk when compared to WRF in the placebo group [23]. However, these results mandate thoughtful interpretation since the primary endpoint of the I-Preserve trial was negative, and the secondary endpoints therefore cannot claim a causal relationship.

Nonetheless, irbesartan showed beneficial effects in patients with diabetic kidney disease (DKD) as suggested by the Irbesartan Diabetic Nephropathy (IDN) trial. This trial included 1715 participants with type 2 diabetes, hypertension, urine protein excretion $\geq$ 0.9 g/day and mean serum creatinine of 150 micromol/L. Patients were randomly assigned to irbesartan (75 to 300 mg once daily), amlodipine (2.5 to 10 mg once daily) or a placebo [24]. At 2.6 years, the likelihood of a doubling of serum creatinine was lower in patients with irbesartan (17%) compared with study participants in the amlodipine (25%) or placebo groups (24%). In addition, irbesartan numerically reduced the incidence of end-stage kidney disease (ESKD) (14 vs. 18% for amlodipine and placebo, respectively). In this study, irbesartan was shown to be effective in protecting against the progression of nephropathy due to type 2 diabetes, independent of the action of blood pressure reduction. The IDN trial did not include patients with symptomatic HF, but type 2 diabetes mellitus and HF often coexist, with diabetes mellitus occurring in ≈25% of patients with chronic HF [25]. In fact, in the IDN trial, secondary endpoints, including the incidence of heart failure, did not differ between treatment groups, suggesting that this trial enrolled patients with asymptomatic stage B HF at baseline.

Altogether, these results indicate that irbesartan is appropriate for the management of DKD, like other RAAS-inhibiting molecules, and may not be harmful in patients with HFpEF.

4.2. Angiotensin-Converting Enzyme Inhibitors (ACEIs)

4.2.1. ACEI in HFrEF with Kidney Dysfunction

Angiotensin-converting enzyme (ACE) inhibitors are widely used for treatment of HF, and remain the cornerstone treatment for patients with HFrEF despite the availability of other vasodilator molecules. Among 6797 patients randomized to enalapril or a placebo in the Studies Of Left Ventricular Dysfunction (SOLVD) trial, 9.5% experienced early WRF [3]. Early WRF was associated with increased mortality in the placebo group (HR 1.2, 95%CI 1.0–1.4; p = 0.037) but not in the enalapril treatment group. Furthermore, a survival benefit was maintained with enalapril therapy in patients remaining on the study drug despite early WRF. This mortality benefit was also demonstrated in a post hoc analysis of SOLVD focusing on HF and more severe CKD [26]. In CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), 11% of patients assigned to enalapril experienced doubling of serum creatinine [27]. The doubling of serum creatinine occurred early in most study participants, and serum creatinine returned back to within 30% of baseline values in the majority of these patients [28]. Altogether, these observations provide consistent

evidence that ACEI in HFrEF patients preserves a beneficial effect even in the context of WRF.

4.2.2. ACEI in HFpEF with Kidney Dysfunction

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study with its 850 study participants remains the largest trial to date investigating the use of ACE inhibitors in HFpEF. The trial included patients older than ≥70 years with an LVEF ≥ 45% [29]. The study failed to meet sufficient power for its primary endpoint, which was a composite of all-cause mortality and HF hospitalization due to a lower event rate than expected. However, the PEP-CHF study showed a significant reduction in HF hospitalization within the first year, but this beneficial result was not maintained for the entire duration of follow-up. Only 25% of the study participants had a serum creatinine level > 110 µmol/L because patients with a serum creatinine level > 200 µmol/LL were excluded from study participation. Given the relatively small number and the overall neutral effect of perindopril treatment, it remains unclear whether there is a benefit of ACEIs in HFpEF patients with kidney dysfunction.

4.2.3. ACEI in Diabetic Kidney Disease

The best data supporting ACEI in patients with type 1 diabetes come from a trial including 409 adult participants with a mean urine protein excretion ≥ 500 mg/day and a serum creatinine level ≤ 221 micromol/L [30]. Patients were randomly assigned to captopril (25 mg three times daily) or a placebo. At 3 years, captopril reduced the rate of death or ESKD (11% vs. 21%) and reduced the likelihood of doubling of serum creatinine (12% vs. 21%).

4.3. Angiotensin Receptor–Neprilysin Inhibitor (ARNI)

4.3.1. ARNI in HFrEF with Kidney Dysfunction

In the PARADIGM-HF study (Prospective Comparison of ARNi with angiotensin-converting enzyme inhibitor to Determine the Impact on Global Mortality and Morbidity in), sacubitril–valsartan, an angiotensin receptor–neprilysin inhibitor, was shown to be superior to enalapril in reducing the incidence of the primary composite endpoint of hospitalization for CV mortality and hospitalization for worsening HF. All-cause mortality and a decline in renal function, among others, were prespecified secondary endpoints [31]. On the basis of the results of the PARADIGM-HF study, it is recommended that an ACE-I (or ARB) is replaced by sacubitril–valsartan in ambulatory HFrEF patients when patients remain symptomatic on ACEI or ARB treatment. Symptomatic HF was essentially defined by elevated brain natriuretic peptide (BNP) concentrations, and patients with an eGFR < 30 mL/min/1.73 m^2 were not included. In a prespecified subgroup analysis of PARADIGM-HF, treatment with sacubitril–valsartan slowed the decrease in the eGFR both overall and in patients with CKD while modestly increasing albuminuria [32].

4.3.2. ARNI in HFpEF with Kidney Dysfunction

In the PARAGON-HF trial (LVEF ≥ 45%; n = 4796), treatment with sacubitril–valsartan compared with valsartan was associated with a numerically modest but nonsignificant reduction in the composite primary endpoint total hospitalizations for HF and cardiovascular death (RR 0.87; 95% CI 0.75 to 1.01; p = 0.06). A prespecified analysis of patients enrolled in this trial showed that the combined endpoint of serious adverse renal outcomes (defined as either a ≥50% reduction in the estimated glomerular filtration rate (eGFR) or progression to end-stage renal disease) was reduced by sacubitril–valsartan regardless of baseline renal function [33]. In addition, a subgroup analysis showed that addition of sacubitril–valsartan rather than valsartan alone appears to slow progress of renal dysfunction when added to mineralocorticoid receptor antagonist (MRA). Moreover, this combination was not associated with an increase in severe hyperkalemia. These data support the potential added

value of sacubitril–valsartan in combination with MRA in patients with HFpEF, but again, caution is needed in interpreting this result because of the neutral primary outcome [34].

4.3.3. ARNI in Diabetic Kidney Dysfunction

Sacubitril–valsartan blocks the RAAS and inhibits neprilysin, a ubiquitous vasopeptidase enzyme breaking down >50 vasoactive peptides, including the biologically active natriuretic peptides, bradykinin, angiotensin I and II, endothelin 1, glucagon, glucagon-like peptide-1 and insulin-B chain. There is some evidence to suggest an improvement in glucose metabolism through inhibition of the renin–angiotensin system, although this effect is most likely modest, whereas there are a number of potential mechanisms by which inhibition of neprilysin may lead to improved glycemic control. Because these mechanisms are not fully understood, detailed mechanistic studies, as well as large randomized clinical trials in patients with DM, are needed to further clarify beneficial metabolic properties of sacubitril–valsartan [35].

4.4. Mineralocorticoid Receptor Antagonist (MRA)

4.4.1. MRA in HFrEF with Kidney Dysfunction

Complete suppression of the RAAS axis with the help of an MRA in addition to recommended HF therapy has a beneficial impact in more severely symptomatic HFrEF patients, as first demonstrated in the Randomized Aldactone Evaluation Study (RALES) [36]. The RALES study compared the effect of 25 mg of spironolactone with a placebo on all-cause mortality in severe heart failure patients in NYHA functional class IIIb and IV on standard therapy. The mean follow-up was 24 months. A post hoc analysis of the RALES trial showed that the incidence of the composite endpoint of all-cause mortality and the secondary endpoint combining all-cause death or HF hospitalization was not increased in study participants with an eGFR < 60 mL/min/1.73 m^2 in the placebo arm [37]. In the spironolactone treatment arm of the RALES, the eGFR declined more often during the first 4 weeks when compared with the placebo group (17% vs. 7%), and the eGFR remained reduced thereafter. However, while WRF was associated with an increased adjusted risk of death in the placebo arm, no such change was observed in study participants with WRF in the treatment group.

The risk of hyperkalemia was higher in the spironolactone treatment group when compared to the placebo group, particularly in study participants with an eGFR < 60 at baseline (OR 3.7, 95% CI 2.5–5.7) or those with WRF (OR 3.8, 95% CI 1.2–6.4). Thus, spironolactone treatment was significantly more often reduced or discontinued in study participants with an eGFR < 60 (OR 2.3, 95% CI 1.2–4.7) but not in study patients with an eGFR $\geq$ 60. MRAs are therefore more commonly underused in patients with impaired kidney function.

A recent Cochrane meta-analysis including 44 studies suggests that an aldosterone blockade may reduce proteinuria and kidney function when added to ACEis or ARBs [38]. However, treatment effects did not prevent progression of CKD towards kidney failure, and did not reduce major cardiovascular events or all-cause death. Furthermore, this Cochrane analysis suggested that aldosterone antagonists in combination with ACEis or ARBs (or both) increase the risk of hyperkalaemia, similar to result from the RALES.

This increased risk may relate to the substantial change of pharmacokinetic properties of spironolactone in patients with moderate-to-severe kidney dysfunction as suggested by the AMBER randomized trial, in which spironolactone (25 to 50 mg/d) was administered for 12 weeks as an add-on therapy in patients with resistant hypertension and moderate CKD (eGFR of 25–45 mL/min per 1.73 m^2) [39]. After stopping treatment, more than half of the initial blood pressure reduction remained sustained for another 2 weeks after drug discontinuation, which suggests accumulation of active metabolites of spironolactone in the circulation of these patients. This can also explain why discontinuation of spironolactone treatment for hyperkalemia may not restore normokalemia immediately.

Since discontinuation of spironolactone is associated with an increased risk for all-cause mortality or the composite endpoint of all-cause mortality or heart failure hospitalization, the DIAMOND (Patiromer for the Management of Hyperkalaemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure) trial assessed if treatment of hyperkalemia with patiromer could maintain a lower risk for cardiovascular death or cardiovascular hospitalization [40]. The results of the study were presented at the ACC congress 2022. The multicenter trial initially screened 1642 patients with HFrEF and either a history of hyperkalemia or current hyperkalemia related to RAASi use. The median follow-up was 27 weeks. Although the study was double-blinded, clinicians monitored patients' K^+ levels over time and were able to adjust RAASi doses accordingly. As a result, many clinicians decreased the dose of RAASi for patients in the placebo group. Despite receiving higher doses of RAASi, patients who continued to take patiromer still had lower K^+ levels on average compared with those taking a placebo, meeting the study's primary endpoint. The relative risk of the total number of hyperkalemia events was reduced by 35%.

4.4.2. MRA in HFpEF with Kidney Dysfunction

The Treatment of Preserved Cardiac Function with an Aldosterone Antagonist Trial (TOPCAT) randomized 3445 symptomatic high-risk HFpEF patients, characterized by elevations in natriuretic peptide levels or HF hospitalization within the previous year, to receive spironolactone (mean dose of approximately 25 mg; targeted dose: 45 mg) or a placebo [40]. Patients were generally older (age > 50 years) with relatively preserved renal function (eGFR > 30 mL/min) and serum potassium levels (K^+ < 5.0 mmol/L). After a mean follow-up period of 3.3 years, there was no difference in the composite primary endpoint of cardiovascular death, aborted cardiac arrest or HF hospitalization between groups (HR 0.89, 95% CI 0.77–1.04; $p = 0.14$). Beldhuis et al. used data from the TOPCAT to explore the effects of spironolactone on renal function in people with HFpEF [41]. The overall median eGFR was 57.9 mL/min/1.73 m^2, and WRF was associated with increased risk of the primary endpoint regardless of the treatment (HR 2.04, 95%CI 1.52–2.72). Although there was no statistical interaction between treatment assignment and WRF, spironolactone-associated WRF (17.8% of patients in the spirololactone group) was associated with a lower risk of cardiovascular death and all-cause mortality when compared to placebo-associated WRF, similar to observations from the RALES trial.

4.4.3. MRA in Diabetic Kidney Dysfunction

MRAs are highly efficacious for further reducing albuminuria when added to ACE-Is or ARBs in DKD, however, at the risk of worsening hyperkalemia [42].

Recent clinical trials have demonstrated efficacy of the novel, selective, nonsteroidal MRA finerenone in slowing progression of kidney and cardiovascular disease, including HF, in patients with CKD and type 2 diabetes. Barkis et al. demonstrated in a phase II trial that the addition of finerenone resulted in an improvement in the urine albumin-to-creatinine ratio in patients with diabetic nephropathy when compared with the placebo [43]. The FIDELIO-DKD trial further demonstrated a favorable effect on cardiorenal outcomes in T2DM patients with predominantly CDK stage 3 and 4 [44]. Finally, the FIGARO-DKD trial, which randomized 7437 patients to finerenone or a placebo, showed beneficial effects of finerenone on CV outcomes among patients with T2DM and CKD. This beneficial effect was mainly driven by a reduction in the incidence of hospitalization for HF [45].

5. Overall Consideration of RAAS Antagonists

A large meta-analysis of ≈29,000 patients analyzed results from randomized, placebo-controlled trials of RAAS antagonists [7]. WRF was associated in all patients with increased mortality and a higher risk of hospitalization for HF. WRF occurred more frequently in patients on RAAS antagonist treatment when compared with the placebo (13% vs. 9%). Consistent with previous study results, the magnitude of the impact of WRF on mortality was lower in HFrEF patients on RAAS inhibition when compared to the placebo control

group. In contrast, in patients with HFpEF randomized to RAAS inhibitors, WRF was associated with an increased mortality (RR 1.78, 95% CI 1.43–2.21; $p < 0.001$).

Although evidence is lacking for a definite benefit of RAAS inhibitors in patients with HF with a preserved ejection fraction (HFpEF), these therapies are frequently prescribed, most often for blood pressure control.

It is difficult to speculate on the specific underlying mechanisms that cause the apparent difference in outcomes associated with RAAS-inhibitor-induced WRF in both subtypes of HF. One obvious reason could be that the detrimental outcome associated with WRF in HFpEF is not counteracted by the positive effects of RAAS inhibition and that the findings are merely a reflection of the lack of benefit of these compounds in HFpEF. Whether the pathophysiology of renal dysfunction differs between HFpEF and HFrEF remains to be determined. However, clustering of HFpEF patients on the basis of latent class analysis suggests that renal dysfunction in HFpEF is associated with obesity, diabetes and hypertension. These comorbidities are associated with a systemic inflammatory state and secondary endothelial dysfunction [46], which is not taken care of when applying RAAS inhibition.

In daily practice, treatment with RAAS blockers should not be discontinued with a small-scale decrease in the GFR in HF patients. According to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, an increase in creatinine of >50% above baseline, or 266 µmol/L creatinine, or an eGFR < 25 mL/min/1.73 m^2, whichever is the smallest, is acceptable [47]. In this case, the patient should be evaluated thoroughly, and the assessment should exclude renal artery stenosis, excessive hyper- or hypovolemia, concomitant medication and hyperkalemia. If the creatinine level remains elevated despite adjustment of concomitant medications, the dose of RAAS inhibitors should be halved and blood chemistry re-checked within 1–2 weeks. Serum creatinine, BUN and serum potassium should be rechecked frequently (at least weekly) until levels have stabilized.

6. Beta-Blockers in HFrEF with Kidney Dysfunction

Beta-blockers have been evaluated in numerous HF RCTs showing that most beta-blockers significantly reduce mortality and morbidity in HFrEF. Contrary to RAAS inhibitors, beta-blockers do not interact with the progression of kidney disease, as evidenced by the equal slope of eGFR decline in the beta-blocker treatment groups when compared to controls. This observation is also valid for patients with moderate or moderately severe renal impairment at baseline. Likewise, the incidence of adverse renal events was not different when beta-blocker treatment groups were compared with placebo groups. WRF during follow-up was associated with higher mortality over a median follow-up of 1.3 years, and a decrease in the GFR was independently associated with mortality, with a 12% higher risk of death for every 10 mL/min/1.73 m^2 decrease in the eGFR (95%CI 10–15; $p < 0.001$). Overall, in 13,861 patients in sinus rhythm, beta-blockers reduced mortality when compared with the placebo: adjusted HR 0.73 for eGFR 45 to 59 mL/min/1.73 m^2 (95% CI 0.62–0.86; $p < 0.001$) and 0.71 for eGFR 30 to 44 mL/min/1.73 m^2 (95% CI 0.58–0.87; $p = 0.001$) [48].

Concordant results were observed in the Metoprolol Controlled Randomized Intervention Trial in Chronic HF (MERIT-HF) study including 3991 patients with NYHA class II to IV HF and an LVEF < 40%. A prespecified secondary analysis investigated the effect of metoprolol versus a placebo across eGFR ranges of >60, 45–60 and <45 mL/min/1.73 m^2. A significant benefit was observed across all subgroups [49]. In accordance with this result, the Swedish Heart Failure Registry showed that β-blocker therapy improves survival in HFrEF patients with concomitant advanced chronic kidney disease. Likewise, it also reduces the risk for the composite outcome of cardiovascular death and HF hospitalization (adjusted HR 0.87, 95% CI 0.77–0.98) [50].

These benefits were not observed in patients with HF with a midrange ejection fraction or HF with preserved ejection fraction and advanced chronic kidney disease, although these findings afford careful evaluation since respective studies suffer from limited power.

7. Sodium–Glucose Cotransporter 2 Inhibitors (SGLT2)

7.1. SGLT2 Inhibition in HFrEF Patients with Kidney Dysfunction

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are new oral blood-glucose-lowering agents demonstrating consistent cardiovascular and renal benefit in HFrEF patients with or without type 2 diabetes. In addition to their diuretic and antidiabetic effects, these molecules have other favorable properties, as they reduce sympathetic activity, preserve potassium balance, lower the risk of acute renal injury and decrease the level of serum uric acid.

The DAPA-HF trial enrolled patients with HFrEF with or without type 2 diabetes and an eGFR $\geq$ 30 mL/min/1.73 m^2. Patients with HFrEF (irrespective of diabetes status) were randomized to dapagliflozin 10 mg daily (n = 2373) versus a placebo (n = 2371).

Over time, dapagliflozin slowed the progression of kidney dysfunction and consistently reduced the primary composite outcome of cardiovascular death or worsening HF in all patients independent of the baseline eGFR. Of note, the absolute risk reduction was more important in patients with a lower eGFR [51]. In the EMPEROR-Reduced trial, patients were randomized in a 1:1 fashion to either empagliflozin 10 mg (n = 1863) or a matching placebo (n = 1867) [52]. The results of this trial indicate that empagliflozin is superior to the placebo in improving HF outcomes among patients with symptomatic stable HFrEF (EF $\leq$ 40%) on the best GDMT, irrespective of diabetes status. Corresponding results were obtained in a meta-analysis combing the study populations of the DAPA-HF and the EMPEROR-Reduced study [53].

The exact mechanism of the favorable effects of dapagliflozin on the eGFR is unclear, but the reduction in intraglomerular pressure due to enhanced tubuloglomerular feedback is considered to play a central role. In fact, initiation of SGLT2i therapy is associated with an immediate decrease in the eGFR of 4 mL/min/1.73 m^2) [51,52]. However, over the mid-term, preservation of the eGFR in the treatment group resulted in a slowed rate of decline in the eGFR with either SGLT2 inhibitor in patients and independent of the presence or absence of type 2 diabetes mellitus.

7.2. SGLT2 Inhibition in HFpEF Patients with Kidney Dysfunction

The EMPEROR-Preserved trial indicates that these molecules may also be beneficial in patients with an LVEF > 40% [54]. In patients with HFpEF, with NYHA class II to IV HF symptoms and elevated NT-proBNP levels, the SGLT2-i empagliflozin was associated with a 21% lower relative risk (HR 0.79, 95% CI 0.69–0.90) of the composite endpoint of cardiovascular death or hospitalization for heart failure. This significant effect was primarily related to a 29% lower risk of HF hospitalization in the treatment group. When the interaction between the study drug and the primary endpoint was evaluated in prespecified subgroups of LVEFs, empagliflozin reduced the rate of the composite primary endpoint more significantly in patients with an LVEF between 40 and 49% (HR 0.71, 95%CI 0.57–0.88) and less significantly in HFpEF patients with an LVEF 50–59% (HR 0.80, 95% 0.64–0.99) while the effect was attenuated in patients with an EF $\geq$ 60% (HR 0.87, 95%CI 0.69–1.10). Nearly half of the patients had diabetes, and about half had an eGFR of <60 mL/min/1.73m^2, providing further evidence that the effect of empagliflozin is not limited due to patients' diabetes or renal dysfunction since, again, the rate of decline in the eGFR was slower in the empagliflozin group when compared with the placebo group ($-$1.25 vs. $-$2.62 mL/min/1.73 m^2 per year; $p < 0.001$).

Furthermore, compared with patients in the placebo group, fewer patients in the empagliflozin group presented outpatient intensification of diuretics (482 versus 610; HR 0.76, 95% CI 0.67–0.86; $p < 0.0001$). Patients assigned to empagliflozin were 20% to 50% more likely to improve their NYHA class, with significant effects already present after 12 weeks of treatment, and this beneficial effect was maintained for at least 2 years. Last but not least, the decrease in heart failure hospitalizations was similar in patients with an LVEF of >40% to <50% and 50% to <60%, but was more attenuated at higher ejection fractions [55].

However, the prespecified analysis of the composite endpoint did not demonstrate a beneficial effect of empagliflozin treatment on major renal outcomes when compared with the placebo (HR 0.95, 95%CI 0.73–1.24) [56]. This neutral effect of empagliflozin on kidney outcomes was similar across the prespecified ejection fraction subgroups of 41–49%, 50–59% and ≥60 [38] The EMPEROR trial's definition of major renal outcomes relied on a threshold of a sustained ≥40% decrease in the eGFR without including occurrence of renal death. To test whether the neutral effect of empagliflozine was related to this definition, the study data were re-analyzed by applying the meta-analysis-based definition of an eGFR decline ≥50% including renal death [53]. In patients with an LVEF of 41–49%, the hazard ratio was 0.41 (95% CI 0.20–0.85), an effect similar to that previously reported for patients with an ejection fraction of ≤40% (HR 0.52, 95%CI 0.29–0.92), a finding consistent with the principle that patients with an ejection fraction of 41–49% should be classified as having heart failure with a mildly reduced ejection fraction [57].

In contrast, in patients with an ejection fraction ≥ 60%, the hazard ratio was 1.24 (95% CI 0.66–2.33), indicating a neutral effect. Accordingly, the influence of the ejection fraction on renal outcomes (p-trend = 0.02) closely parallels the influence of the ejection fraction on heart failure hospitalizations (p-trend = 0.008), as shown above.

7.3. SGLT2 Inhibition in Patients with Diabetic Kidney Dysfunction

On the basis of present evidence, SGLT2 inhibition is recommended in combination with ACEis (or ARBs) in DKD patients with albuminuria [58]. Initiating SGLT2 inhibitors should generally be avoided among patients with an eGFR < 25 to 30 mL/min/1.73 m^2, although they could be continued safely among patients whose eGFR falls below 25 mL/min/1.73 m^2 [59].

8. Non-Pharmacological Treatment Options

8.1. Ultrafiltration

Despite optimal treatment of heart failure, some patients will progress towards advanced stage of renal failure. Resistance to diuretics, renal dysfunction and refractory congestion frequently complicates advanced heart failure. Ultrafiltration through hemodialysis or peritoneal dialysis can be alternative options to treat fluid overload. The UNLOAD trial demonstrated that ultrafiltration safely produces greater weight and fluid loss when compared with intravenous diuretics [60]. In these patients, especially when resistance to diuretic therapy develops, the initiation of ultrafiltration may be a salvage therapy to improve volume status and reduce the incidence of recurrent hospitalizations.

8.2. MitraClip Placement in HFrEF Patients with Kidney Dysfunction

Transcatheter edge-to-edge mitral valve repair has become an established treatment option for patients with HFrEF and concomitant severe mitral valve valvular disease. Of the two trials investigating this treatment option, the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation Trial) included patients with an LVEF of 20–50%, LV end-systolic diameter < 70 mm, systolic pulmonary pressure < 70 mmHg and absence of significant right ventricular dysfunction or hemodynamic instability. In this study population, MitraClip treatment demonstrated significant probability of postprocedural success (98% of technical procedural success) [61]. Therefore, fulfilling the criteria of this randomized-controlled multicenter study is recommended when considering this treatment option.

Preoperative renal dysfunction is a risk factor for mortality in patients undergoing mitral valve surgery [62]. One reason for this observation is the high prevalence of mitral annular calcification in renal disease, complicating surgical mitral repair or replacement. Moreover, mitral annular calcification is also associated with an increased risk of perisurgical complications [63].

In a large retrospective study (n = 13,563) in the United States, baseline chronic kidney disease (CKD) was present in more than one-third of the study population undergoing transcatheter mitral valve repair (TMVR) [64] CKD patients undergoing TMVR had worse

outcomes when compared to no-CKD patients in terms of in-hospital mortality (OR 1.29, 95% CI 1.01–1.65; $p = 0.04$), acute kidney injury (OR 3.0, 95% CI 2.69–3.34; $p < 0.001$) or 30-day CHF readmission (OR 1.47, 95% CI 1.17–1.84; $p < 0.001$). These results are in agreement with a previously published study by Shah et al. showing that preprocedural renal disease is associated with increased risk for major adverse outcomes after TMVR. This is particularly true in the presence of KIDGO stage 4 or 5 renal disease where a >30% 1-year mortality was reported [65]. This adverse association is particularly strong in patients with acute kidney failure after TMVR, and acute kidney failure is significantly more frequent in patients with preintervention CKD when compared with MitraClip candidates without CKD at baseline.

These results may be surprising because the TMVR procedure is performed without contrast, and most often without major hemodynamic instability since mitral valve treatment improves severity of heart failure and renal dysfunction. This suggests that the procedure in itself carries a potential risk of WRF in patients with CKD, and while the pathomechanism is not completely clear, postoperatively worsened right ventricular function, bleeding and also worsening of concomitant comorbidity may play a role.

8.3. Tricuspid Clip

Tricuspid regurgitation (TR) is common in patients with left-sided valvular heart disease and is an important prognostic marker among HFrEF patients. Recently, minimal invasive catheter-based techniques have emerged as a feasible and effective option for TR treatment in selected high-risk patients who would clinically benefit from tricuspid valve repair.

The TRILUMINATE feasibility study showed promising results of the TriClip system in terms of TR reduction, low mortality, improvement in quality of life and right atrial and ventricular modeling [66]. The effect of this treatment on renal outcomes remains unclear; however, elevation of central venous pressure is an important risk factor for kidney dysfunction in acute heart failure as suggested by data from the ADHERE registry and the ESCAPE trial [67,68]. A curvilinear inverse relationship between the eGFR and central venous pressure was shown in 2557 stable patients with cardiovascular disease. Moreover, this study also indicated an independent association between central venous pressure and all-cause mortality [69]. Altogether, a reduction in right atrial pressure with a subsequent decrease in the central venous pressure should provide a beneficial effect on renal outcomes.

9. Long-Term Mechanical Circulatory Systems (LT-MCSs)

The LT-MCS is indicated in selected patients with advanced HF when symptoms persist despite optimal GDMT or when temporary MCS has not led to sufficient cardiac improvement. Left ventricular assist devices (LVADs) are used both as a bridge to a heart transplant or as a destination therapy in advanced heart failure, and have been shown to prolong survival and improve quality of life [70–72] regardless of the type of continuous-flow implantable device.

An analysis of patients with advanced HA with an INTERMACS level 1, which characterizes most severe HF, identified pre-existing renal dysfunction as an independent risk factor for 90-day mortality (OR 8.51, 95% IC 1.86–109.3; $p = 0.003$) [73]. In accordance with this result, Sandner et al. found that an eGFR < 60 mL/min/1.73 m^2 was a predictor of post-LVAD mortality at 6 months (OR 2.0, 95% CI 1.1 to 4.1; $p = 0.047$) [74]. Butler et al. reported that patients with an eGFR < 47 mL/min/1.73 m^2 were at a significantly higher risk of dying when compared with LVAD patients with an eGFR > 95 mL/min/1.73 m^2 (OR 1.95; 95%CI 1.14–3.63) [57]. These observations are based on the fact that pre-existing kidney dysfunction often requires postoperative hemofiltration, which prolongs the intensive unit care stay and its associated risks. These results indicate that LVAD implantation should be carefully considered for patients with end-stage heart failure and concomitant renal dysfunction. However, preoperative renal dysfunction may improve after LVAD implantation if the reason is primarily hemodynamic.

In line with this observation, in the United States, 155 patients with end-stage renal disease (ESRD) at the time of LVAD placement had a very poor prognosis with only 18.1% surviving until hospital discharge and a survival time < 3 weeks [75].

10. Orthotopic Heart Transplantation

Heart transplantation (HT) remains the most durable treatment for patients with end-stage heart failure refractory to medical treatment.

The incidence of CKD after heart transplantation is high, up to 80% [76]. Risk factors for the development of CKD after HTx include treatment with calcineurin inhibitors and pretransplant kidney dysfunction. Renal failure after HT is associated with increased mortality; therefore, in patients with more serve CKD, combined heart and kidney transplantation may be indicated, in particular when the eGFR is <40 mL/min/1.73 m^2 [77]. However, this strategy remains controversial because of the shortage of donor organs.

In a retrospective single-center study of 685 adult heart transplant patients, 121 patients developed ESRD after HT, 30 developed ESRD within the first 5 years, 58 between 5 and 10 years and 33 after 10 years [78]. Of importance, a higher eGFR before HT was associated with a later onset of ESRD. Heart failure etiology or the presence of diabetes mellitus before HT, however, were not associated with the timing of ESRD development.

Among 30,090 patients included in a large database in the United States, a pre-HTx eGFR < 60 mL/min/1.73 m^2 was associated with increased mortality after HTx [79]. On this basis, the actual recommendation for heart transplantation proposes heart–kidney transplantation if HTx candidates present with an eGFR < 40 mL/min/1.73 m^2 before HTx. However, this recommendation is limited to cases with kidney dysfunction due to important structural renal disease, such as HT candidates with long-standing arterial hypertension or diabetes mellitus. Listing for HT alone remains an option when reversibility of kidney dysfunction is likely, in the absence of structural changes.

11. Conclusions

Guidelines-directed drug treatment of heart failure has the potential to improve prognosis but may result in concomitant WRF. Since the beneficial effect of heart failure drug treatment is not present in all subtypes of heart failure, careful appreciation of the benefit and the risks related to application of drugs impacting renal function on an individual patient basis is afforded.

Future studies investigating epidemiology, pathophysiology and treatment strategies related to renal dysfunction in HFpEF are warranted in order to improve understanding of the complex interaction between HF treatment, kidney function and prognosis of patients suffering from heart failure with reduced or preserved LVEF.

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