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Practical Approaches to the Management of Cardiorenal Disease beyond Congestion

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Abstract

Background: The coexistence of heart and kidney diseases, also called cardiorenal syndrome, is very common, leads to increased morbidity and mortality, and poses diagnostic and therapeutic difficulties. There is a risk-treatment paradox, such that patients with the highest risk are treated with lesser disease-modifying medical therapies. ***Summary:*** In this document, different scientific societies propose a practical approach to address and optimize cardiorenal therapies and related comorbidities systematically in chronic cardiorenal disease beyond congestion. Cardiorenal programs have emerged as novel models that may assist in

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delivering coordinated and holistic management for these patients. ***Key Messages:*** (1) Cardiorenal disease is a ubiquitous entity in clinical practice and is associated with numerous barriers that limit medical treatment. (2) The present article focuses on the practical approaches to managing chronic cardiorenal disease beyond congestion to overcome some of these barriers and improve the treatment of this high-risk population.

Introduction and Magnitude of the Problem

How Do We Define Cardiorenal Disease?

Patients with chronic kidney disease (CKD) are at high risk of developing cardiovascular disease (CVD) with its atherosclerotic and non-atherosclerotic acute and chronic manifestations. On the other hand, patients with CVD are prone to develop CKD and acute kidney injury. The co-occurrence of kidney and heart disease results from complex pathophysiological interactions between the two organs, leads to increased morbidity and mortality, and poses diagnostic and therapeutic difficulties [1]. Prognosis of CKD varies according to the categories of glomerular filtration and albuminuria (Fig. 1). In addition, the coincidence of kidney and heart diseases has been classified into five clinical phenotypes (also called cardiorenal syndromes 1–5) based on the understanding and primary driver of organ disease [2]. While this classification scheme helps provide a theoretical framework for conceptualizing cardiorenal patients, it is often difficult to identify the primary driver of organ dysfunction in clinical practice, and there is a spectrum of diseases with considerable overlap between these categories [3]. Therefore, the current view is that cardiorenal disease represents the interplay among metabolic risk factors, CKD, and the cardiovascular system, leading to the emerging concepts of "chronic cardiovascular and kidney disorder" or "cardiovascular-kidney-metabolic health," in which coordinated and specific diagnostic and therapeutic approaches are needed to improve cardiorenal disease care (central figure) [4–7].

Is Cardiorenal Disease a Common Pathology in Clinical Practice?

To date, the estimated prevalence of CKD in patients with heart failure (HF) ranges between 26% and 45% [8]. In a recently published study of a cohort of contemporary chronic HF patients, we found the highest reported prevalence of CKD in a stable HF with a total of 70% of the patients suffering some degree of kidney failure population [9]. On the other hand, the prevalence of CVD in patients with CKD varies according to the CKD stage, increasing from 63% in patients with CKD stages G1–2–75% in patients with CKD stages G4–5 [10].

Do Cardiorenal Disease Patients Receive Adequate Treatment for Heart Failure?

The 2021 European Society of Cardiology guidelines for HF give a Class I recommendation for the use of renin-angiotensin-aldosterone system inhibitors (RAASi), beta-blockers, and sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with HF with reduced ejection fraction (HFrEF) [11]. Despite this strong recommendation, contemporary registries reveal that prescription rates and adherence to these life-saving drugs remain disappointingly low, especially among individuals with concurrent CKD [9, 12]. Moreover, since these patients benefit from RAASi, recent data do not support the discontinuation of these agents, even in patients with more advanced CKD [13].

Pharmacological Treatment of Heart Failure

Heart Failure with Reduced Ejection Fraction

When and How Should We Start Pharmacological Treatment in Patients with Cardiorenal Disease?

While guidelines suggest caution in the use of some of these medications for patients with advanced CKD (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2), they make no distinction for milder stages of CKD severity (eGFR 30–60 mL/min/1.73 m^2) [11]. Therefore, quadruple therapy with angiotensin receptor-neprilysin inhibitors (ARNi), beta-blockers, mineralocorticoid-receptor antagonists (MRAs), and SGLT2i should be generally initiated and up-titrated as soon as possible in patients with eGFR ≥30 mL/min/1.73 m^2 [14]. In some clinical scenarios, such as eGFR <30 mL/min/1.73 m^2, hyperkalemia, or low blood pressure (BP), the expert's opinion of this document suggests starting treatments in a graduated manner and with low doses. In the case of patients with eGFR between 20 and 29 mL/min/1.73 m^2, initial therapy with SGLT2i and beta-blocker should be attempted as they have the best safety profile [15]. Given the cardiovascular benefit and the frequent oscilant trajectory of eGFR, we suggest using ARNi instead of other RAASi in eGFR between 15 and 29 mL/min/1.73 m^2. Although patients with advanced renal impairment (eGFR <30 mL/min/1.73 m^2) were excluded in the PARADIGM-HF trial, accumulating evidence indicates no significant safety concerns associated with its use in this population [16–18] (Fig. 2).

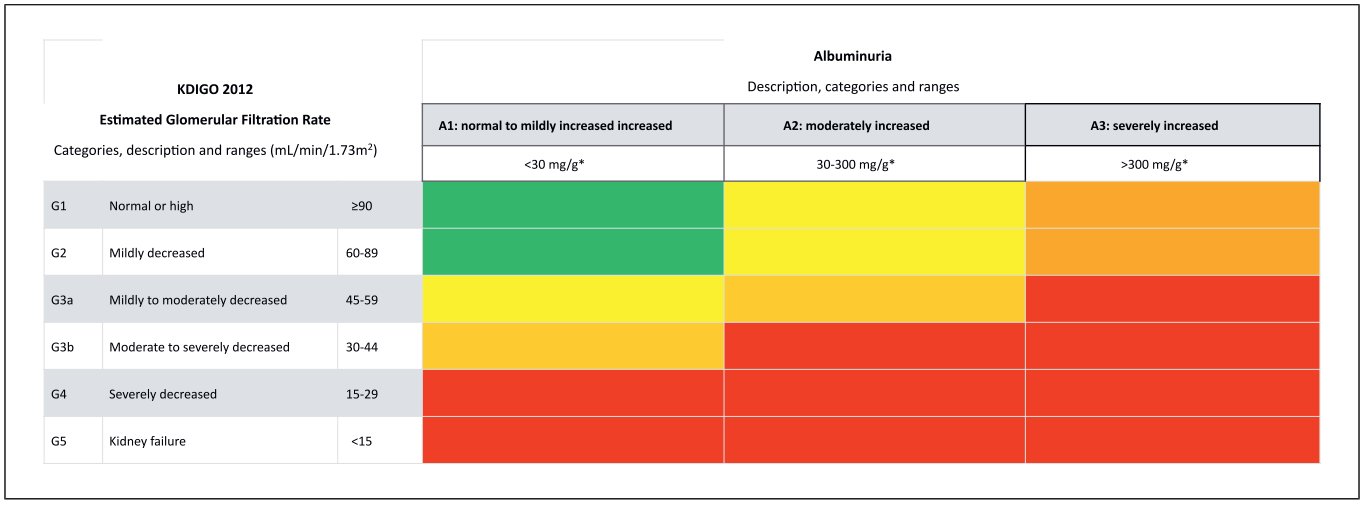

Fig. 1. Prognosis of CKD according to the categories of glomerular filtration and albuminuria. Risk categories of CKD according to 2012 KDIGO classification. Patients are categorized into each risk category based on eGFR value and severity of albuminuria. Green: low risk; yellow: moderately increased risk; orange: high risk; red, very high risk. KDIGO, Kidney Disease: Outcomes Quality Initiative; eGFR, estimated glomerular filtration rate. *Albuminuria is expressed as albumin/creatinine ratio mg/g in urine.

Beta-blockers' effectiveness in HFrEF patients with CKD has shown nuanced insights into their efficacy and safety. Metoprolol CR/XL and Bisoprolol significantly reduce mortality risk and worsen HF hospitalizations irrespective of renal function [19–20]. Furthermore, a comprehensive meta-analysis revealed that beta-blocker treatment substantially lowers all-cause and cardiovascular mortality in CKD patients with chronic systolic heart failure while also highlighting a heightened risk of bradycardia and hypotension [21].

Both RALES and EMPHASIS-HF trials demonstrated the clinical benefit of MRA regardless of baseline renal function. However, data on patients with advanced CKD are limited, as those with a serum creatinine >2.5 mg/dL or eGFR <30 mL/min/1.73 m^2 were excluded [22, 23]. MRA should be started at a lower dose (i.e., 25 mg on alternative days) if the eGFR is 30–49 mL/min/1.73 m^2 [23]. Current guidelines advocate using MRA in HFrEF patients with eGFR >30 mL/min/1.73 m^2 and potassium <5 mmol/L [11] (Fig. 3). The expert's opinion of this document estimates that selected patients with lower eGFR may benefit from MRA under close monitoring.

The VICTORIA trial showed the clinical benefits of vericiguat in HFrEF with an eGFR ≥15 mL/min/1.73 m^2 [24]. For the combined endpoint of cardiovascular death and HF hospitalization, there was no evidence of treatment/eGFR interaction. Notably, among patients with CKD stage 4 who participated in the trial, vericiguat did not show a higher incidence of adverse events, including renal events [25] (Fig. 3).

How to Optimize and Monitor Treatment?

We recommend slow titration and early monitoring in high-risk patients, such as those with eGFR <30 mL/min/1.73 m^2, potassium >5 mmol/L, or systolic BP <100 mm Hg. In other words, the patient should be reevaluated 1–2 weeks after the start or titration of any RAASi or beta-blocker, and we suggest waiting for titration at least 2–4 weeks. If the eGFR is 30–49 mL/min/1.73 m^2, the recommended daily dose of MRA is 25 mg [23]. Patients with repeated yeast infections or frequent urinary tract infections should be vigilant once SGLT2i is prescribed (Fig. 2).

When to Stop or Reduce Treatment?

Hypotension is of particular concern in cardiorenal patients. Nonessential vasodilators such as nitrates and calcium-channel blockers should be stopped, and reducing diuretic dose may be considered in the absence of congestion. If symptomatic hypotension persists, we recommend reducing/stopping beta-blocker or any RAASi (ARNi, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or MRA). In this clinical scenario, the adaptive mechanisms to renal hypoperfusion are exceeded and the glomerular perfusion pressure decreases, which implies a decrease in glomerular filtration rate [26].

After the start or titration of any RAASi, an increase in creatinine of up to 30–50% above the baseline or in potassium to ≤5.5 mmol/L is acceptable. If creatinine increases by >100%, the RAASi should be stopped [11, 27]. It would also be important to evaluate for other causes of

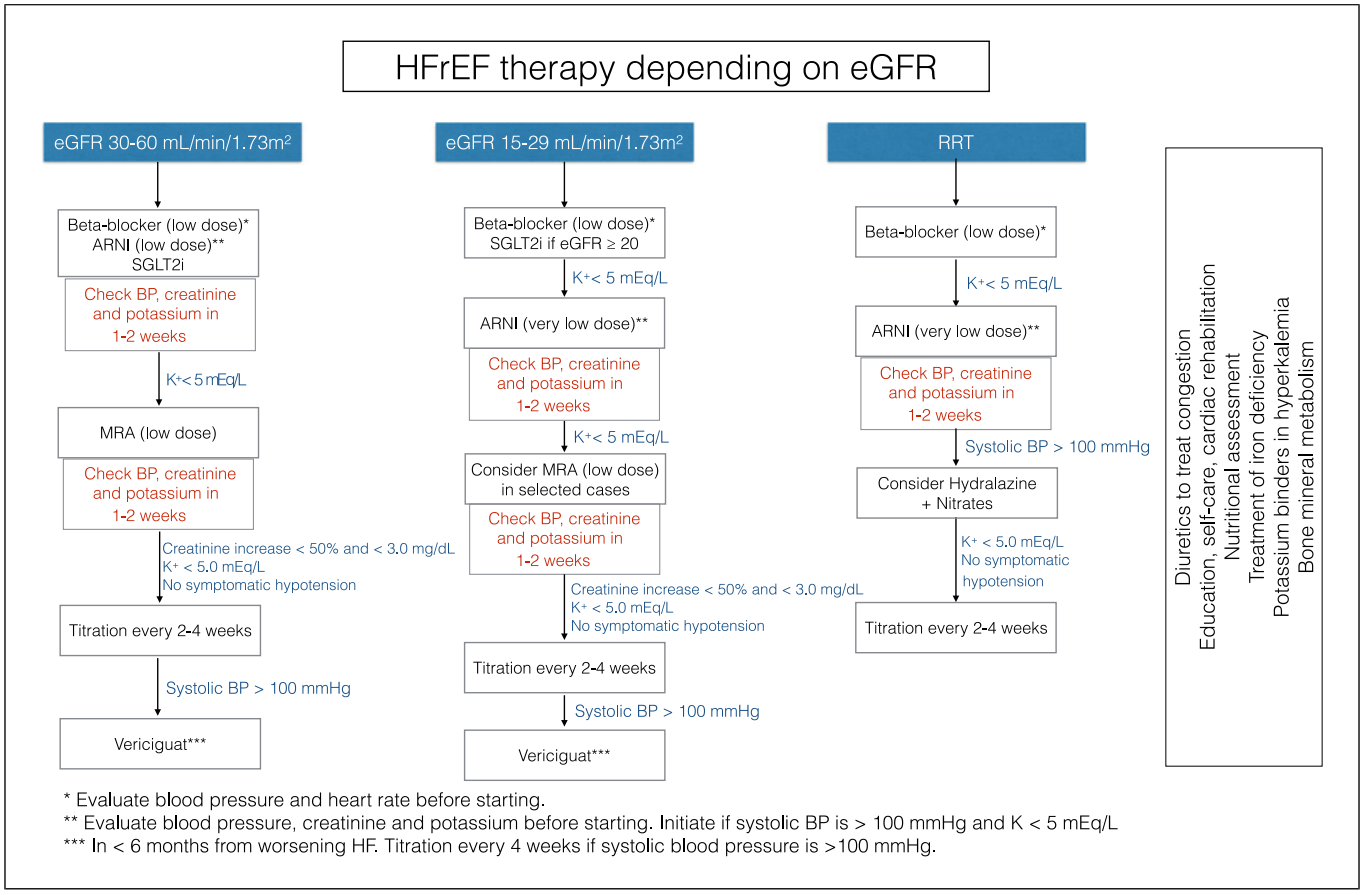

Fig. 2. HFrEF therapy proposed approach, depending on glomerular filtration rate. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; K^+, serum potassium; MRA, mineralocorticoid-receptor antagonist; RRT, renal replacement therapy; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

creatinine elevation, such as hypotension, volume depletion, and renal artery stenosis, as well as reevaluation of other prescribed treatments [28]. We suggest reducing the RAASi or adding potassium binders if potassium levels are between 5.6 and 5.9 mmol/L and stopping them in the case of potassium ≥6 mmol/L or electrocardiographic changes. However, treatment of chronic hyperkalemia is based on three pillars: normalizing bicarbonate levels (prescribing sodium bicarbonate [1–3 g/day] to achieve serum levels greater than 22 mEq/L), facilitating renal excretion with loop diuretics or thiazides (in patients with volume overload), and improving excretion through the gastrointestinal tract with potassium-binding agents. In any case, potassium binders should be considered in every patient with HFrEF and hyperkalemia. Likewise, we should be liberal when eGFR declines following SGLT2i initiation and only consider stopping after a significant decrease in renal function (>50%).

What Should Be the Pharmacological Approach in HFrEF Patients on Dialysis?

Randomized evidence supporting the use of the pharmacological treatment on dialysis is scarce [29]. Therapy with beta-blockers should always be attempted. A small-randomized trial with carvedilol showed decreased all-cause mortality, heart failure hospitalizations, and favorable effects in left ventricular remodeling [30]. An important aspect is that some beta-blockers are removed from the circulation by hemodialysis. In fact, treatment with "high dialyzability" beta-blockers like atenolol or metoprolol was associated with a higher risk of death compared to "low dialyzability" beta-blockers [31].

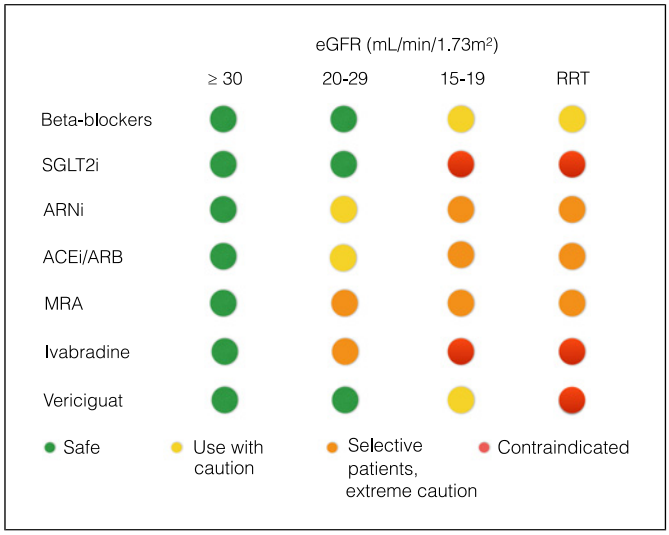

Fig. 3. Pharmacological treatment of heart failure in CKD. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid-receptor antagonist; RRT, renal replacement therapy; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Concerning angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, conflicting findings have been noted in observational studies, and current evidence does not provide reliable guidance [29]. ARNi has shown favorable effects in left ventricular remodeling and reducing cardiac biomarkers in observational studies, but safety and long-term efficacy are unknown [18, 32]. In the case of MRA, observational studies have shown conflicting evidence, but there was no increased risk of significant hyperkalemia in patients [29]. There is currently a lack of trial-level and observational evidence about the effectiveness of SGLT2i in patients on dialysis.

Heart Failure with Preserved Ejection Fraction

When and How Should We Start Pharmacological Treatment in Patients with Cardiorenal Disease?

Classic therapeutic goals of HF with preserved ejection fraction (HFpEF) were based on the management of comorbidities and congestion, but the 2023 Update of HF Guidelines recommends that all patients with HF should be treated with an SGLT2i regardless of left ventricular ejection fraction (LVEF) unless contraindications [14]. Furthermore, recent evidence confirms the efficacy of SGLT2i in nephroprotection in patients with CKD up to eGFR of 20 mL/min/1.73 m^2 [33].

There is less evidence to support the benefit of RAASi in patients with HFpEF. However, in those with an LVEF <60%, the use of an MRA, ARNi, or angiotensin II receptor blockers (when an ARNi is not feasible) may be considered [34, 35].

Anemia

How Do We Define Anemia and Iron Deficiency (ID) in Patients with Cardiorenal Disease?

In patients with HF, the definition of anemia is the same as for the general population (<12 g/dL in women and <13 g/dL in men) [36]. Ferritin is an acute phase reactant and may be increased in some individuals with comorbidities such as HF or CKD. Hence, higher cut-off values have been applied to define ID in these patients: serum ferritin <100 ng/mL or 100–299 ng/mL with transferrin saturation <20%. In addition, Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend higher thresholds (serum ferritin of 500 ng/mL and transferrin saturation of 30%) for adult CKD patients with anemia [37]. In cardiology field, there is emerging data suggesting transferrin saturation <20% may be the most accurate marker for defining ID in HF patients [38].

Which Studies Should Be Performed in Patients with Cardiorenal Disease and Anemia?

The presence of anemia should prompt evaluation for a specific diagnosis [36]. As the etiology of anemia in patients with HF is multifactorial and heterogeneous, its evaluation should consider etiologies related to HF as well as other causes (Table 1).

When Is Intravenous Iron Indicated?

Oral iron is not recommended as it is ineffective in iron repletion and does not improve exercise capacity in patients with HF [11, 39]. Based on recent trials and meta-analyses, intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose is recommended by the HF guidelines in symptomatic patients with HFrEF or HF with mildly reduced ejection fraction and ID to improve symptoms and quality of life and should be considered to reduce the risk of HF hospitalization [14, 40] (Table 2). There are two small-randomized trials with iron sucrose and one with ferric gluconate, but the evidence is insufficient to recommend their use [41].

When Are Erythropoiesis-Stimulating Agents Indicated?

Erythropoietic stimulating agents (ESAs) are approved for treating anemia due to CKD or chemotherapy-induced anemia. The available evidence does not support the use of ESA to treat anemia in patients with HF and suggests an increased risk of thromboembolic events [42]. ESA may be used in patients with HF who have other indications for an ESA, such as CKD. In this setting, it is recommended to consider initiating ESA when the hemoglobin level is <10 g/dL, individualizing dosing, and using the lowest sufficient dose of ESA to reduce the need for red blood cell transfusions

Table 1. Evaluation of anemia in patients with cardiorenal disease

Initial tests for diagnosis - Complete blood count (including red cell indices, reticulocyte count, and evaluation of the peripheral blood smear) - Iron studies: transferrin saturation and serum ferritin (testing soluble transferrin receptor may be appropriate when there is a strong suspicion of iron deficiency because it is not affected by inflammation) - Kidney function: creatinine and glomerular filtration rate - Assess for inflammation: C-reactive protein and erythrocyte sedimentation rate - Serum levels of vitamin B12 and folate - When hemolysis is suspected: unconjugated bilirubin and LDH (both increased) and haptoglobin (decreased)
Additional evaluations Patients with iron deficiency should be evaluated for the source of the deficiency - Dietary history - Menstrual history in females - History of gastrointestinal symptoms and gastrointestinal blood loss - Use of NSAIDs or anticoagulants - Testing the stool for occult blood in adults 50 years of age or older - Endoscopies for possible occult gastrointestinal blood loss are indicated for adults of all ages for whom a source of bleeding would be treated
In case of vitamin B12 deficiency, testing for autoantibodies to intrinsic factor is used to identify pernicious anemia
Bone marrow examination for possible myelodysplastic syndrome

[43] (Table 2). If there is ID, iron must be administered before; if the response to iron supplementation is adequate, ESA are not indicated. Although the optimal target of hemoglobin is not well defined, hemoglobin levels between 10 and 11.5 g/dL are usually recommended, whereas levels ≥13 g/dL are associated with adverse outcomes.

Hyperkalaemia

When Are Potassium Binders Indicated?

Potassium binders should be prescribed when plasmatic potassium levels are ≥5.0 mmol/L to prevent adverse events and to facilitate the implementation of optimal doses of RAASi [44]. There are three available potassium binders: calcium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate. First-line agents (patiromer and sodium zirconium cyclosilicate) present some differences regarding the mechanism of action and posology but with similar effectiveness [45–47] (Table 3).

Type 2 Diabetes Mellitus

What Should Be the Treatment in Patients with Cardiorenal Disease?

SGLT2i are an essential treatment for type 2 diabetes mellitus (T2DM) and cardiorenal disease since they are indicated in HF across the entire spectrum of LVEF [14, 48]. Apart from reducing glucose levels, they also have natriuretic and nephroprotective properties, making them the first-line therapy for cardiorenal patients with T2DM and eGFR ≥20 mL/min/1.73 m^2 [33].

If additional glucose control is needed, antidiabetic agents should be prescribed depending on individual comorbidities and functional status. Glucagon-like peptide-1 receptor agonists (GLP1-RA) are an option for T2DM patients at risk of/or with HF, especially those with obesity or high cardiovascular risk. They can result in significant weight loss, reducing the need for other antidiabetic drugs like insulin [49, 50]. Metformin can be used safely with SGLT2i but should not be prescribed when eGFR <30 mL/min/1.73 m^2. Dipeptidyl peptidase 4 inhibitors can also be considered for cardiorenal patients but cannot be combined with GLP1-RA. Finally, insulin should be the last option for glycemic control as its use has been associated with worse HF outcomes [51] (Table 4).

Dyslipidemia

When Should We Treat Dyslipidemia in Patients with Cardiorenal Disease?

The KDIGO guidelines recommend treating with statins adults ≥50 years with CKD and eGFR ≥60 mL/min/1.73 m^2 and with statins or statins/ezetimibe if eGFR <60 mL/min/1.73 m^2.

In adults with dialysis-dependent CKD, statins or statin/ezetimibe should not be initiated but maintained in patients

Table 2. Treatment of anemia in patients with cardiorenal disease

Iron deficiency treatment with ferric carboxymaltose			
Weight <70 kg		Weight ≥70 kg	
Day 1	Week 6	Day 1	Week 6
Hb < 10 g/dL: 1g	500 mg	Hb < 10 g/dL: 1g	1 g
Hb 10–14 g/dL: 1g	No dose	Hb 10–14 g/dL: 1g	500 mg
Hb 14–15 g/dL: 500 mg	No dose	Hb 14–15 g/dL: 500 mg	No dose

Iron deficiency treatment with iron sucrose
200 mg/per week
Based on Ganzoni formula: total iron dose (mg iron) = body weight (kg) × (target actual Hb) (g/dL) × 2.4 + iron for iron stores (mg iron)

Folate deficiency
Oral folic acid (1–5 mg daily) for one to 4 months or until there is laboratory evidence of hematologic recovery. For those with a chronic cause of folate deficiency, such as chronic hemolytic anemia, therapy may be given indefinitely

Vitamin B12 deficiency
The recommended dose is 1,000 µg intramuscular weekly until the deficiency is corrected and then monthly (cyanocobalamin) or once every other month (hydroxocobalamin). In patients with normal absorption, oral dosing is equally effective as IM dosing when given at 1000 µg orally once daily. Some medications can interfere with vitamin B12 absorption (e.g., metformin and proton pump inhibitors), and its withdrawal must be considered

Erythropoiesis-stimulating agents
ESA (epoetin or darbepoetin, administered subcutaneously) are indicated in patients with CKD with Hb < 10 g/dL and transferrin saturation >20% and ferritin >200 ng/mL. If there is iron deficiency, iron must be administered before giving an ESA, and if the response to iron supplementation is adequate, ESA are not indicated
Doses
The lowest and most effective ESA doses are recommended: the initial dose for epoetin is approximately 50–100 units/kg/week. Darbepoetin is initiated with doses of 40-100 µg every two to 4 weeks. Higher doses have been associated with increased mortality and cardiovascular events independent of Hb level
Target Hb level
The optimal target Hb level is not well-defined
Hb levels between 10 and 11.5 g/dL are usually recommended
Hb levels ≥13 g/dL are associated with adverse outcomes

already receiving these therapies at the time of starting dialysis. Treatment with statin is recommended in adult kidney transplant recipients [52].

How Should We Stratify Risk in Patients with Cardiorenal Disease, and What Are the Low-Density Lipoprotein Cholesterol (LDLc) Goals?

In patients with CKD without diabetes or atherosclerotic CVD, we must evaluate eGFR and albumin-to-creatinine ratio (ACR) to stratify risk [53].

- High risk
  –LDLc goal <70 mg/dL (1.8 mmol/L)
  –eGFR 30–44 mL/min/1.73 m2 and ACR <30 mg/g
  –eGFR 45–59 mL/min/1.73 m2 and ACR 30–300 mg/g
  –eGFR ≥60 mL/min/1.73 m2 and ACR >300 mg/g.
- Very high risk
  –LDL goal <55 mg/dL (1.4 mmol/L)
  –eGFR <30 mL/min/1.73 m^2
  –eGFR 30–44 mL/min/1.73 m^2 and ACR >30 mg/g.

How Should We Treat Dyslipidemia in Patients with Cardiorenal Disease?

The different therapies for dyslipidemia are shown in Table 5. Beyond statins and ezetimibe, both alirocumab and evolocumab have demonstrated efficacy and safety in patients with CKD [54, 55]. In addition, treatment with bempedoic acid has been associated with a lower risk of cardiovascular events among statin-intolerant patients [56]. Finally, the pharmacodynamic effects and safety profile of inclisiran were similar in patients with impaired kidney function [57].

Table 3. Characteristics of the available potassium binders

	Calcium polystyrene sulfonate	Sodium zirconium cyclosilicate	Patiromer
Mechanism of action	Nonselective calcium-based ion exchange resins	Non-absorbed, non-polymer inorganic powder that captures K^+ in exchange for H^+ and Na^+ in the GI tract	Non-absorbed, cation exchange polymer that binds K^+ in the lumen of the GI tract
Posology	15 g/3–4 per day	Starting: 10 g/day Maintaining: 5–10 g/day	Starting: 8.4 g/day Maintaining: 8.4–16.8 g/day
Place of action	Colon	Intestine	Colon distal
Start of drug action	1–2 h	1 h	4–7 h
4-week effectivity	–	−0.8 a −1.2 mEq/L	−1.01 mEq/L
Drug interactions	Antacids, laxatives, digitalis, sorbitol, lithium, thyroxine	Separate 2-h medication with gastric pH-dependent bioavailability	Separate 3 h from other medication
Adverse effects	GI disorders Hypokalemia Hypercalcemia Intestinal necrosis	Hypokalaemia Edema GI disorders	GI disorders Hypomagnesemia

Fibric acid derivatives are not recommended in patients with CKD and hypertriglyceridemia. They could be considered for patients with CKD and markedly elevated triglycerides (411.3 mmol/L, 1,000 mg/dL). Fibric acid derivatives must be dose-adjusted for kidney function, and concomitant therapy with a statin is not recommended. Recently, icosapent ethyl has been shown to reduce ischemic events among patients with elevated triglyceride levels (135–499/dL) and eGFR >30 mL/min/1.73 m^2.

Arterial Hypertension

What Are the Goals of BP and What Should Be the Treatment of Arterial Hypertension in Patients with Cardiorenal Disease?

In accordance with the recommendations from the Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group, the target systolic BP (assessed using standardized clinic BP measurement) target is < 120 mm Hg for patients with CKD not submitted to kidney replacement therapy, <130–140 mm Hg for patients receiving dialysis, and <130 mm Hg for kidney transplant patients [28]. Although it seems reasonable to target diastolic BP of patients with CKD and diastolic hypertension to <80 mm Hg, the KDIGO Work Group is hesitant to recommend a diastolic BP target because of the lack of evidence of the risk-benefit ratios [28].

While the systolic BP target for patients with CKD not submitted to kidney replacement therapy is largely based on its cardioprotective, survival, and potential cognitive benefits, the evidence for its renoprotective benefits is almost nonexistent. Interestingly, there are certain subpopulations in CKD in which the risk-benefit ratios supporting the systolic BP target of <120 mm Hg are less certain [28]. This is the case of patients with diabetes mellitus, advanced CKD (G4 and G5 stages), those with significant proteinuria, patients with very low diastolic BP, patients with "white-coat" hypertension, or patients at extreme ages (younger or older).

The systolic BP target of <120 mm Hg is more intensive than the systolic BP target of <130 mm Hg proposed by the American College of Cardiology/American Heart Association Guideline and the European Society of Hypertension Guidelines [58, 59]. The KDIGO Work Group believes that patients should not be penalized for suboptimal clinical practice, and thus, clinicians should not rely on routine office BP to adjust BP-lowering therapy but on standardized clinic BP measurement [60].

There is limited evidence on the use of specific antihypertensive agents to treat high BP in CKD. Many people with CKD and BP who are at least 20 mm Hg above the target will need combinations of two or more antihypertensive drugs. Starting combination therapy in such people is, therefore, suggested [28]. There are, however, no randomized trials comparing different drug combinations in CKD, as there are no randomized trials on

Table 4. Dose adjustment of antidiabetic treatments according to estimated glomerular filtration rate

Drug	Comments
Biguanides	
Metformin	Dose adjustment is required when eGFR is between 30 and 60 mL/min/1.73 m^2 Not indicated when eGFR <30 mL/min/1.73 m^2
SGLT2i	
Dapagliflozin	Lose antidiabetic effectivity when eGFR is <45 mL/min/1.73 m^2 Not indicated when eGFR <25 mL/min/1.73 m^2
Empagliflozin	25 mg presentation is not recommended when eGFR is 30–60 mL/min/1.73 m^2 10 mg presentation can be used safely in patients with eGFR ≥20 mL/min/1.73 m^2 Not indicated when eGFR <20 mL/min/1.73 m^2
Canagliflozin	300 mg presentation is not recommended when eGFR is 30–60 mL/min/1.73 m^2 100 mg presentation can be used safely with eGFR >15 mL/min/1.73 m^2 Not indicated with renal replacement therapy
DPP4i	
Linagliptin	No dosage adjustment is required
Sitagliptin	Dose adjustment required with eGFR <45 mL/min/1.73 m^2 eGFR 30–45 mL/min/1.73 m^2: 50 mg per day eGFR <30 mL/min/1.73 m^2: 25 mg per day
Vildagliptin	Dose adjustment required with eGFR <50 mL/min/1.73 m^2 (50 mg per day)
Alogliptin	Dose adjustment required with eGFR <50 mL/min/1.73 m^2 eGFR 30–50 mL/min/1.73 m^2: 12.5 mg per day eGFR <30 mL/min/1.73 m^2: 6.25 mg per day
Saxagliptin	Dose adjustment required with eGFR <45 mL/min/1.73 m^2 (2.5 mg per day) Not indicated with renal replacement therapy
GLP1-RA	
Liraglutide (subcutaneous)	No dosage adjustment Limited data for severe CKD
Semaglutide (subcutaneous and oral)	No dosage adjustment Limited data for severe CKD
Dulaglutide (subcutaneous)	No dosage adjustment Use with eGFR >15 mL/min/1.73 m^2
Exenatide (subcutaneous)	Use with eGFR >30 mL/min/1.73 m^2
Lixisenatide (subcutaneous)	No dosage adjustment, Limited data for severe CKD, Not recommended with eGFR <15 mL/min/1.73 m^2
Tirzepatide* (subcutaneous)	No dosage adjustment Limited data for severe CKD
Insulin	No dosage adjustment is required

antihypertensive classes other than RAASi, beta-blockers, and calcium-channel blockers compared to placebo or each other. Any antihypertensive treatment algorithm in CKD, therefore, beyond monotherapy, is based on expert opinion, pathophysiologic or pharmacodynamic considerations, or extrapolation from findings in the general population or surrogate outcomes.

Obesity

Are GLP1 Receptor Agonists Useful in Patients with Cardiorenal Disease and Obesity?

GLP1-RA has demonstrated sustained weight loss and CVD prevention, including the risk of HF development in patients with obesity, with or without diabetes [61]. The STEP-HFpEF trial showed that treatment with once-

Table 5. Dose adjustment of lipid-lowering pharmacologic agents according to estimated glomerular filtration rate

Drug	Dose	Comments
Statins		
Fluvastatin	80 mg once daily	For patients with eGFR between G3a and G5, those on dialysis, or individuals who have undergone a kidney transplant, recommended doses are based on regimens that have demonstrated benefits in clinical trials conducted specifically within this patient population
Atorvastatin	20 mg once daily	
Rosuvastatin	10 mg once daily	
Simvastatin/Ezetimibe	20/10 mg once daily	
Pravastatin	40 mg once daily	
Simvastatin	40 mg once daily	
Pitavastatin	2 mg once daily	
Alirocumab (subcutaneous)	75/150 mg every 2 weeks or 300 mg SC monthly	No dose adjustment is required Limited data in patients with eGFR <30 mL/min/1.73 m^2. No indication on RRT or kidney-transplant recipients
Evolocumab (subcutaneous)	140 mg every 2 weeks or 420 mg SC monthly	No dose adjustment required in patients with advanced CKD or RRT.
Bempedoic acid	180 mg once daily PO	No dose adjustment required Limited data in patients with eGFR <30 mL/min/1.73 m^2 or RRT
Inclisiran (subcutaneous)	284 mg basal and at 3 months. Every 6 months afterward	No dose adjustment required Limited data in patients with eGFR <15 mL/min/1.73 m^2 or RRT.

weekly semaglutide (2.4 mg) in patients with HFpEF and obesity led to larger reductions in symptoms, greater improvements in exercise function, and higher weight loss than placebo [50]. In addition, semaglutide (2.4 mg) has recently shown a decrease in death and cardiovascular events in patients with CVD and obesity without diabetes [62]. The benefit in patients with CKD, reducing albuminuria, which is related to the progression of renal disease, is also well established [63]. This evidence suggests that the cardioprotective benefits of GLP1-RA also extend to cardiorenal patients. In addition, most GLP1-RA can be used in patients with eGFR up to 15 mL/min/1.73 m^2.

Atrial Fibrillation

What Options for Anticoagulation Do We Have in Advanced Kidney Disease?

Available data suggest that direct oral anticoagulants are generally safer and more effective than vitamin K antagonists in patients with CKD. This preference is based on their potential to reduce the risk of major bleeding events, vascular calcification, and anticoagulant-associated nephropathy. However, there is a lack of randomized controlled trials to guide clinical decision-making for individuals with CKD stages 4 and 5 [64]. In these patients, the choice of anticoagulation should be personalized and determined through collaboration between the physician and the patient. Given the elevated risk in this population, it is advisable to monitor renal function closely and continually reevaluate dosage adjustments, with a suggested frequency of at least every 6 months (Fig. 4).

Is Left Atrial Appendage Closure a Real Alternative in Patients with Cardiorenal Disease?

Left atrial appendage occlusion has become a feasible alternative to oral anticoagulants for individuals who may not be suitable candidates for long-term anticoagulation. Observational studies have shown the safety and efficacy of this device in end-stage renal disease patients undergoing dialysis, suggesting a clinical benefit over anticoagulation or no anticoagulant therapy [65].

Management of Mineral and Bone Metabolism Disorders

How Do We Assess the Mineral and Bone Metabolism in Patients with Cardiorenal Disease?

Chronic kidney disease-mineral and bone disorder (CKD–MBD) is the term used to define the changes (laboratory abnormalities, bone abnormalities, and extra-skeletal calcifications) secondary to CKD. Secondary hyperparathyroidism (SHPT) results from CKD-MBD dysregulation and consists of hyperphosphatemia,

eGFR ml/min/1.73m^2	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
>50	150 mg twice daily	5 mg twice daily	20 mg once daily	60 mg once daily
30-49	110 mg twice daily	5 mg twice daily	15 mg once daily	30 mg once daily
15-29	Not recommended	2.5 mg twice daily Or if ≥2 of the following: -Cr ≥1.5 mg/dL -Age ≥80 years - Body weight ≤60 kg	15 mg once daily	30 mg once daily Or if ≥1 of the following: - Body weight ≤60 kg - Verapamil/Dronedarone or Quinidine
<15	Not recommended	Not recommended	Not recommended	Not recommended

Fig. 4. Dose adjustment of direct oral anticoagulants according to estimated glomerular filtration rate in atrial fibrillation. eGFR, estimated glomerular filtration rate; Cr, creatinine.

hypocalcemia, low active vitamin D, and high parathyroid hormone (PTH). Although the assessment of active vitamin D is not available in clinical practice, 25-(OH)-vitamin D (calcidiol) can be measured to detect suboptimal levels. The consequences of uncontrolled SHPT include soft tissue calcifications and calciphylaxis, which are directly linked to increased cardiovascular morbimortality [66].

What Are the Targets and What Drugs Should Be Used?

Although the optimal PTH level remains controversial, treatment of CKD-MBD in stages 3–5 should aim to normalize phosphorus and calcium. There are several therapeutic options available to manage CKD-MDB. We propose a practical algorithm based on the expert's opinion of the document (Fig. 5).

Phosphorus regulation is essential for an accurate PTH control. Approved phosphate binders (lanthanum carbonate, sevelamer carbonate, and iron-based) are safe and effective in controlling hyperphosphatemia, and no major differences exist between them. In selected cases (i.e., hypocalcemia with normal/low calcium), calcium-based phosphate binders can be considered.

In patients with elevated PTH despite calcium and phosphorus correction, selective activation of vitamin D receptor (paricalcitol) and/or native vitamin D may be indicated unless hypercalcemia is present. In cases of increased PTH and hypercalcemia, calcimimetics (cinacalcet [oral] and etelcalcetide [parenteral]) are the preferred agents (especially for dialysis patients or those with primary or autonomous hyperparathyroidism) (Fig. 5) [67]. Parathyroidectomy may be considered in severe SHPT (PTH >1,000 pg/mL despite optimal treatment) or tertiary hyperparathyroidism.

Nutrition and Sarcopenia

Which Tools Do We Have to Evaluate Nutritional Status in Patients with Cardiorenal Disease?

There is no consensus on the best method to evaluate the nutritional status of patients with HF or CKD. Body mass index (BMI) is a standard tool, but it does not distinguish weight attributable to excess fluid versus lean and/or fat mass, and patients with malnutrition but with volume overload may be classified as having falsely normal or high BMI. Serum albumin, prealbumin level, lymphopenia, and low serum cholesterol have been proposed as biomarkers for nutritional status in HF. However, these biomarkers are difficult to interpret as they are affected by comorbidities, medications, inflammation, and volume status.

For these reasons, it is recommended to use multidimensional tools that allow a global assessment of nutritional statuses, such as the Mini Nutritional Assessment (MNA), which assesses dietary intake, mobility, and BMI

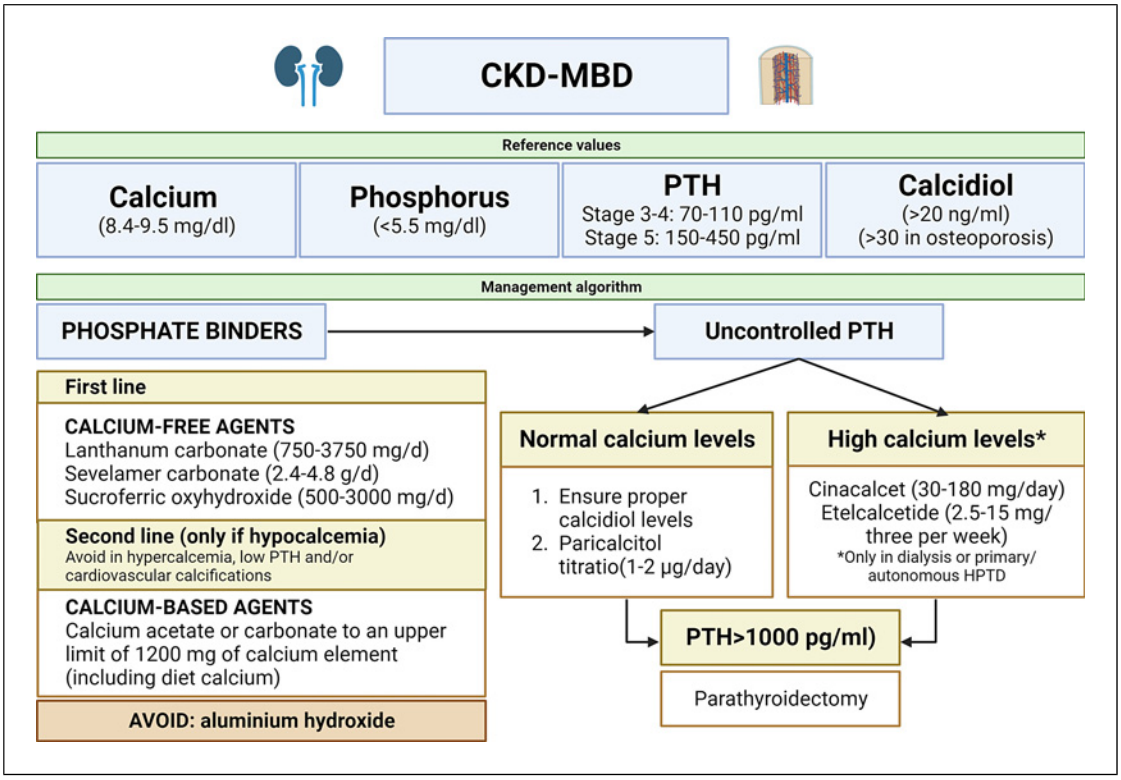

Fig. 5. Proposed algorithm for the management of chronic kidney disease-mineral and bone disorder (CKD-MBD). Created by "BioRender." All these considerations are opinion-based by several clinical guidelines. No level 1 grade evidence (suggestions). CKD-MBD, chronic kidney disease-mineral and bone disorder; PTH, parathormone; HPTD, hyperparathyroidism.

[68]. According to MNA, patients are classified according to the score in normal nutritional state (12–14 points), malnutrition risk (8–11 points), and malnutrition (0–7 points). In hospitalized elderly patients, the nutritional risk index is a good predictor of complications [69]. Other scores incorporating laboratory data like albumin, such as the geriatric nutritional risk index, can also be helpful in malnutrition identification.

How Do We Treat Malnutrition and Sarcopenia?

Sarcopenia is a progressive skeletal muscle disorder involving muscle mass, together with a decrease in muscle strength and poor physical performance. Treatment of patients with this condition includes resistance exercise training, an individualized nutrition plan, and a goal protein intake of 1–1.5 g/kg/day. Pharmacologic treatment, including anabolic compounds like testosterone or growth hormone, has been evaluated in small studies, increasing exercise capacity and muscle strength. Still, no data are showing a favorable impact of sarcopenia treatment on outcomes. In addition, protein and caloric nutritional supplements could be considered in patients at risk of or with established malnutrition in whom previous dietary recommendations do not improve nutritional status.

Prevention of Contrast-Associated Acute Kidney Injury

Contrast-associated acute kidney injury (CA-AKI) prevalence in CKD patients is estimated to be between 1.3% and 11.1% [70]. It is higher in CKD patients requiring arterial contrast administration, where the risk may be increased by 10–30% [71].

When Should Prophylaxis Be Given?

It is necessary to consider the use of pre-contrast media prophylaxis in patients with risk factors for developing CA-AKI. Mehran et al. constructed a score using these risk factors [72]. The score found that patients older than 75 years, with diabetes mellitus,

Table 6. Steps for the prevention of CA-AKI

Steps for the prevention of CA-AKI
1. Avoid "renalism": do not delay a procedure if the benefit is well established.
2. Explore non-contrast diagnostic techniques like intravascular ultrasound, dextran-based optical coherence tomography, or fractional flow reserve/instantaneous wave-free ratio
3. Discontinue nephrotoxic drugs (non-steroidal analgesics, metformin)
4. Minimize risk with normal or low-osmolarity iodinated contrast media, using the smallest volume required and avoiding repeated administration in a short period
5. Evaluate individual AKI risk after contrast administration for each patient
6. Implement preventive strategies for moderate or high-risk patients (age >75 years, diabetes mellitus, eGFR: <40 mL/min/1.73 m^2), anemia, hypotension, balloon pump, and high contrast requirements)
7. Assess volume status and appropriateness of hydration when considering pre- and post-hydration for CA-AKI prevention
8. Choose normal saline over sodium bicarbonate if volume expansion is appropriate[a].
a. Outpatient: Administer 1 L of water 4 h before and after contrast administration
b. Inpatient: Administer 1 mL/kg/h for 6–12 h pre-procedure and postprocedure
9. Refrain from using unproven strategies like acetylcysteine, oral salt loading, diuretics, mannitol, etc.
10. Monitor kidney function 48–72 h after contrast administration
11. Consider nephrological assessment for kidney transplant or dialysis patients

[a]Evidence review for preventing contrast-induced acute kidney injury. NICE guideline NG148. December 2019.

eGFR <40 mL/min/1.73 m^2, anemia, congestive HF, hypotension, and the need for a balloon pump or large volumes of contrast (>100 mL) are at the highest risk of developing CA-AKI and eventually requiring dialysis. Preventive strategies are crucial for moderate or high-risk patients (Table 6).

What Is the Best Strategy to Avoid CA-AKI in Patients with Cardiorenal Disease?

Several strategies have been proposed to prevent the development of CA-AKI beyond the administration of crystalloids, which can be harmful in patients with fluid overload. These include avoiding high-osmolar contrast media, hypovolemia, and other nephrotoxic drugs. Devices such as DyeVert PLUS, Renal Guard, or Impella, as well as avoiding ventriculograms, minimizing the use of contrast media with intravascular ultrasound, and preferring radial to femoral access, have been shown to be effective [73].

Conclusions

The presence of concomitant heart and kidney disease is associated with a poorer prognosis and a significant decline in quality of life. The effective management of cardiorenal disease requires ongoing efforts to provide a specialized and multidisciplinary approach, with the goal of optimizing cardiorenal disease care.

In this document, different scientific societies propose a practical approach to systematically address and optimize cardiorenal therapies and related comorbidities in chronic cardiorenal disease. Cardiorenal programs have emerged as novel models that may assist in delivering coordinated and holistic management for these patients.

Conflict of Interest Statement

Zorba Blázquez-Bermejo reports consulting and lecture fees from Novartis, Rovi, Bayer, AstraZeneca, Novo Nordisk, Amgen, Lilly, and Boehringer Ingelheim Pharmaceuticals. Borja Quiroga reports honoraria for conferences, consulting fees, and advisory boards from CSL Vifor, Astellas, Amgen, Bial, Ferrer, Novartis, Astra-Zeneca, Sandoz, Esteve, and Otsuka. Jesus Casado reports consulting and lecture fees from Vifor, Astra-Zeneca, Lilly, and Boehringer Ingelheim Pharmaceuticals. Rafael de la Espriella reports personal fees or advisory boards from Astra-Zeneca, Boehringer Ingelheim, Bayer, Novartis, Novo Nordisk, Pfizer, Rovi, and Vifor CSL. Joan Carles Trullàs has no conflicts of interest to declare. Gregorio Romero-González reports personal fees from Astra-Zeneca, Vifor CSL, Bayer, and Diaverum. Jorge Rubio-Gracia reports consulting and lecture fees from Novartis, Bayer, Astra-Zeneca, Rovi, Esteve, and Boehringer Ingelheim Pharmaceuticals. Javier Díez has no conflicts of interest to declare. Julio Núñez reports personal fees or advisory boards from Alleviant, Astra-Zeneca, Boehringer Ingelheim, Bayer, Novartis, Novo Nordisk, Pfizer, Rovi, and Vifor CSL. Patricia de Sequera reports honoraria for conferences, consulting fees and advisory boards from Vifor Pharma, Amgen, GSK, Fresenius, Nipro, Astra-Zeneca, Bial, Astellas, Braun, and Baxter. Alejandro Recio-Mayoral reports personal fees from AstraZeneca, Novartis, Boehringer Ingelheim, Janssen, Bayer, MSD and Vifor Pharma, and support for attending meetings from Bayer,

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