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Novas terapêuticas farmacológicas no atraso da progressão e tratamento das complicações da Doença Renal Crónica
New pharmacologic therapies for delaying progression and treat complications of chronic kidney disease complications

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A. Abstract

Background: The prevalence of chronic kidney disease has increased over the past decade, leading to high morbid-mortality and socio-economic burden. Chronic kidney disease treatment primarily aims to improve patients' quality of life while delaying the loss of kidney function and end-stage renal disease. Recent research and multiple randomized clinical trials have demonstrated efficacy for novel therapeutic agents aiming to improve renal outcomes, including delaying progression and improving chronic kidney disease patients' quality of life.

Objectives: We present an extensive narrative review of the pathophysiology of chronic kidney disease progression and complications and the results of the most recent studies on new available agents, including SGLT2 inhibitors, selective mineralocorticoid receptors antagonists, HIF-PH inhibitors, novel potassium binders, and KOR agonists.

Methods: The following databases were extensively searched between September 2022 and March 2023: PubMed, EMBASE, the Cochrane Library and the website clinicaltrials.org, to include published randomized clinical trials, meta-analysis, and international guidelines, as well as registered on-going clinical trials.

Conclusion: In both diabetic and non-diabetic chronic kidney disease patients, SGLT2 inhibitors and selective mineralocorticoid receptors antagonists have successfully improved renal and cardiovascular outcomes. Several new drugs are arousing on the treatment of the most important complications of chronic kidney disease, including HIF-PH inhibitors, new potassium binders and new agents to improve pruritus. In comparison to current medications, new agents are more effective, present less adverse effects and might have a significant impact on patients' quality of life.

B. Keywords

Anemia; Chronic Kidney Disease; CKD progression; hyperkalemia; SGLT2 inhibitors; pruritus.

C. Introduction

Chronic kidney disease (CKD) is an increasingly prevalent disease with deleterious consequences in patients' morbidity and mortality and an important impact on socioeconomic and global health. With the increasing ageing of the world population, as well as a growing incidence of CKD risk factors worldwide, it is estimated that the prevalence of end stage renal disease (ESRD) will exponentially increase in the coming decades. [1]

Early detection of CKD is one the most important measures to decrease the incidence of ESRD, since it allows a precocious start of interventions that might prevent CKD progression. New drugs are arousing with promising results on delaying CKD progressions, and large guidelines, including American Society of Diabetes [2], European Heart Association [3], and the Kidney Disease Improving Global Outcomes (KDIGO) [4] are changing their treatment paradigms to include these new drugs. Also, in recent years several advances have been made in the drugs offered for CKD complications treatment, with a special focus on patients' quality of life (QoL).

In this review, we aim to describe the pathophysiology of CKD progression and CKD complications and present the new available agents, including the major clinical trials that have shown a positive effect in some of these comorbidities.

D. Methods

The following databases were searched between September 2022 and March 2023: PubMed, EMBASE, the Cochrane Library and the website clinicaltrials.org. We used free text and the MeSH terms, according to each chapter, in different types of combinations. For the included articles, we used the tools "reference lists" and "related articles" of PubMed to increase our search. There was no restriction on publication date but we only selected articles in English and Portuguese. When multiple reports describing the same sample were published, the most recent or most complete report was used.

E. Results

E.1. CKD prevalence and burden

CKD has a high prevalence worldwide, varying from 10 to 20% of the population, and large population studies predict that CKD incidence will significantly increase in the next decade. [1] Despite being more common in low and middle-income countries, its prevalence is rapidly increasing in developed countries because of an ageing population and the presence of risk factors such as obesity, hypertension, and diabetes mellitus. [5] In Portugal, CKD is an alarming health issue since the prevalence and incidence of dialysis dependent CKD is one of highest in Europe. [6] Unfortunately, the reason for the high prevalence of dialysis patients in Portugal is not fully understood but one proposed explanation is the increased incidence of CKD risk factors including sedentary lifestyle, obesity, diabetes mellitus and salt intake. [7]

CKD is associated with high morbidity and mortality. In 2017, a systematic review showed that deaths related to CKD or cardiac disease due to impaired kidney function accounted for 4.6% of overall mortality, making CKD the 12th leading cause of death that year. Additionally, when referring to disability-adjusted life-years, that accounts not only for mortality but also morbidity, it was estimated a loss of 35.8 million years lost due to CKD. [8] However, the main cause of death in CKD is cardiovascular disease (CVD), which includes heart attack, stroke, heart failure, peripheral artery disease. [9] Indeed, CKD is a risk factor for CVD, because of hypertension, hyperglycemia, and dyslipidemia. Also, inflammation, increased proteinuria and vascular calcifications can contribute to CVD in a CKD setting. [10] Moreover, CKD is associated with a high economical and socioeconomic burden, and it is estimated that in 2030, there won't be enough resources to support the increased number of patients needing renal replacement therapy. [11]

E.2. CKD definition and classification

CKD is usually detected in routine screening since most patients are asymptomatic or present with unspecific symptoms at diagnosis. Early detection is of utmost importance to rapidly start pharmacological and non-pharmacological strategies to slow the progression of CKD. [12]

The most recent guidelines on the evaluation and management of CKD are the from de KDIGO, published in 2012. [13] This group defines CKD as a progressive loss of kidney function or structural abnormality that is present for more than 3 months, has implications for health and that is usually irreversible. [14] They also propose an algorithm for the risk of CKD progression and outcomes according to a combination of

decreased glomerular filtration rate (GFR) and urinary albumin excretion (figure 1). [15] It is important to note that only patients that present with stage G3 or higher have a diagnosis of CKD; stage G2 in the absence of other kidney lesion markers does not define as CKD. [13]

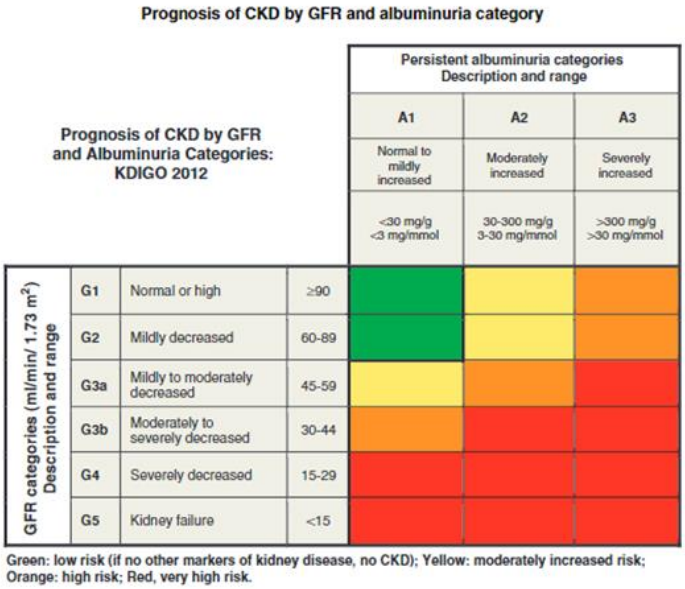

Figure 1 | Prognosis of CKD by GFR and albuminuria category. Green indicates low risk, yellow indicates moderate risk, orange indicates high risk and red indicates very high risk. Modified by KDIGO from Levey et al. 2011 [15]

E.3. CKD complications

The complications that emerge from CKD affect morbidity and mortality and vary according to different stages of CKD. The main complications include anemia, arterial hypertension, mineral bone disorder, hyperphosphatemia, hyperparathyroidism, and hypoalbuminemia. The frequency of these complications differs with the stage of CKD and GFR (table 1).

CKD complications	**G1**	**G2**	**G3a**	**G3b**	**G4-G5**
Anemia	4.0%	4.7%	12.3%	22.7%	51.5%
Acidosis	11.2%	8.4%	9.4%	18.1%	31.5%
Hyperphosphatemia	7.2%	7.4%	9.2%	18.1%	31.5%
Hypoalbuminemia	1.0%	1.3%	2.8%	9.0%	7.5%
Hyperparathyroidism	5.5%	9.4%	23.0%	44.0%	72.5%
Hypertension	18.3%	41.0%	71.8%	78.3%	82.1%

Table 1 | Prevalence ratio of different CKD complications by stage in KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [13]

Patients frequently report fatigue, poor appetite, nausea, vomiting, weight loss, pruritus, dyspnea, peripheral edema, and even changes in mental status in the late stages of CKD. [16] Unfortunately, advanced CKD complications are not fully treated with renal replacement therapy and these patients, even on dialysis, have a high burden of pharmacological therapy, with important side effects, not always efficient and for many patients influencing negatively their QoL.

Until recently, erythropoietin stimulation agents (ESA) were exclusively intravenous or subcutaneous and demanded a tight control of hemogram levels in order to prevent serious adverse events. [17] Potassium and phosphorus binders are usually needed in more than 2 pills a day and cause important gastrointestinal side effects. [18] Pruritus is a common complication of advanced CKD, often undervalued by the assistant physician. [19] All these complications of advanced CKD are associated with higher morbi-mortality, and an important impairment of QoL.

E.4. Delaying CKD progression

E.4.1. Physiopathology

CKD progression is defined as a decline in GFR category, a drop in GFR ≥25% from baseline or, a sustained decline in GFR of more than 5 ml/min/1.73 m2 /year (rapid progression). [13] CKD-patients are prone to have more acute kidney injury (AKI) episodes, leading to kidney damage and consequently CKD progression (AKI-to-CKD transition). [20] Progression is a consequence of several mechanisms including hypoxia, chronic activation of the renin-angiotensin system (RAS), changes in cell phenotypes and functions, epigenetic changes, and cell cycle arrest, that culminates in chronic inflammation, interstitial fibrosis, and tissue senescence. [21]

Podocyte loss induces misdirected filtration and liquid extrusion, which promotes inflammation and fibrosis with consequent adhesion between the glomerular tuft and Bowman's capsule and tubular degeneration. All these mechanisms contribute to proteinuria, one of the most important markers of CKD progression. [22, 23]

The proximal tubule is another important location of initial injury. Proximal tubule cells are responsible for the active transport of numerous substances, needing larger numbers of mitochondria and relying on oxidative phosphorylation as a way of producing energy. For this reason, these cells are vulnerable to injury. [24] Abnormal renal perfusion, a common finding in AKI and CKD, is associated with vascular endothelial growth factor deficiency. [25] This creates a relative hypoxia stress and damage of proximal tubular cells that leads to cell-cycle arrest at G2/M phase of the cell cycle, resulting in the release of profibrotic and proinflammatory molecules. [26]

One of the most important cells in the physiopathology of CKD progression are fibroblasts. Fibroblasts are responsible for sensing hypoxia and have a major role on erythropoietin (EPO) production. [27] However, in the presence of injury, fibroblasts differentiate into myofibroblasts, who produce high levels of collagen that contribute to interstitial fibrosis and lose their capability of hypoxia sensing. In addition, this fibrotic environment destabilizes peritubular capillary vessels, leading to regression and capillary rarefaction. [28]

Persistent inflammation has negative consequences in kidney cell differentiation. Macrophages are the cells that are most important in the progression from inflammation to fibrosis. M1 phenotype macrophages are often pro-inflammatory, whereas M2 phenotype macrophages are reparative macrophages. As a result of multiple cytokines - interleukin 4, 10, 13, and transforming growth factor (TGF) β - present in an inflammatory environment, a change from the macrophage phenotype M1 to M2 may occur. Extracellular matrix and tubulointerstitial fibrosis are developed because of these

M2 phenotype macrophages' subsequent promotion of fibroblast proliferation and activation. [29]

The renin-angiotensin system (RAS) is another crucial process underlying the progression of CKD. Angiotensin II (AngII) promotes vasoconstriction, adrenal aldosterone secretion, and renal salt absorption brought on by the activation of Ang II type I receptors. [30] These receptors are expressed in the smooth muscle cells of the kidneys and, by constricting the afferent and efferent glomerular arterioles, directly affect the glomerular filtration coefficient. Then, Ang II causes glomerular capillary hypertension, which results in glomerular injury by expanding capillaries, inflicting damage on the endothelium, and increasing protein filtration.[31] By the activation of Ang II type 1 receptors, Ang II is also implicated in enhancing the tubule glomerular feedback response. [32] Fibrosis itself is promoted intra-renally by Ang II. It has been demonstrated that signaling of type 1 AngII receptor results in the activation of kinases and transcription factors, oxidative stress, and the creation of cyclin. This results in the production of profibrotic mediators, proinflammatory mediators, and general cell damage, all of which are essential elements in the development of fibrosis in CKD. [33] TGFβ, which oversees extracellular matrix modulation and epithelial-mesenchymal transition, is one of the prominent cytokines that are elevated by AngII. [34]

In conclusion CKD progression occurs due to sustained damage to the kidney, resulting in an AKI to CKD progression. Tubule cell activation, that correlates with maladaptive regeneration, is a major trigger for chronic inflammation and fibrosis. The understanding of the pathophysiology behind these fibrotic mechanisms can be used to delay extracellular matrix deposition and prevent disease progression and ESRD.

E.4.2. First pharmacological agents to stop CKD progression – ACE inhibitors and ARB

RAS blockade agents: ACE (Angiotensin-converting-enzyme) inhibitors and angiotensin receptor blockers (ARB), are the first line agents in the treatment of arterial hypertension in CKD patients, especially if diabetic and/or proteinuric. [35–37] These agents work by stopping AngII production and blocking type 1 AngII receptor activation, respectively. [38] This effectively inhibits the intrarenal action of AngII and reduces glomerular hyperfiltration and proteinuria. Moreover, these agents antagonize tubule glomerular feedback effects and the inflammatory effects of Ang II. [39] Limiting further glomerular damage and proteinuria is an improvement for decreasing fibrotic processes in the kidney, and in that way delaying CKD progression. However, fibrosis regression with RAS inhibiting has only been observed in animal models. [40]

In 1997, one of the earliest studies that demonstrated RAS inhibition as a useful strategy for improving renal outcomes was published. Ramipril, an ACE inhibitor, or a placebo were administered to 117 non-diabetic patients with chronic nephropathies and proteinuria values of less than 3 g/24 hours. Participants on ramipril experienced significantly less GFR decline (0.53 vs. 0.88 mL/min) than those taking a placebo and proteinuria was inversely linked with GFR decline. The incidence of ESRD was significantly lower in the ramipril group (32% versus 65%). [41]

This first randomized clinical trials (RCT) were followed by several others that tested ACEI and ARB, all with the same beneficial results not only in renal but also cardiovascular (CV) outcomes. [42] These drugs are now the first line therapy for arterial hypertension in CKD, despite the presence of diabetes or proteinuria. [36]

E.4.3. SGLT2

SGLT-2 inhibitors are considered a breakthrough as novel therapeutic targets to delay CKD and especially diabetic kidney disease (DKD) progression. [43]

The sodium-dependent glucose cotransporters (SGLT) include various types, two of them are expressed in the kidney, SGLT1 and SGLT2. They are responsible for glucose reabsorption in the proximal tubule, especially SGLT2 which reabsorbs most of the urinary glucose. After reabsorption, glucose transporters type 2 facilitate its transport into the bloodstream. Thus, SGLT2 inhibitors are responsible for decreasing renal glucose reabsorption in the proximal tube, increasing glucose concentration in the urine, and decreasing glycemia. [44] One of the most important effects of SGLT2 inhibition is reducing glomerular hyperfiltration, and consequently reducing proteinuria and kidney damage over time. This is mainly due to sodium cotransport by these transporters which leads to a diminished delivery of sodium to the macula densa, and thereby increasing renal blood perfusion. Inhibiting SGLT2 prevents the tubular-glomerular feedback, and also prevents hypoxia damage by reducing Na+/K+ active transporter activity and oxygen demand. [43] These mechanisms are schematically represented in figure 2. Recently, a beneficial effect of SGLT2 inhibitors mitochondrial dysfunction has been showed. The use of SGLT2 inhibitors improved mitochondrial fusion and decreased reactive oxygen species (ROS) formation. These changes resulted in a decrease in albuminuria and renal fibrosis in rodent models. [45]

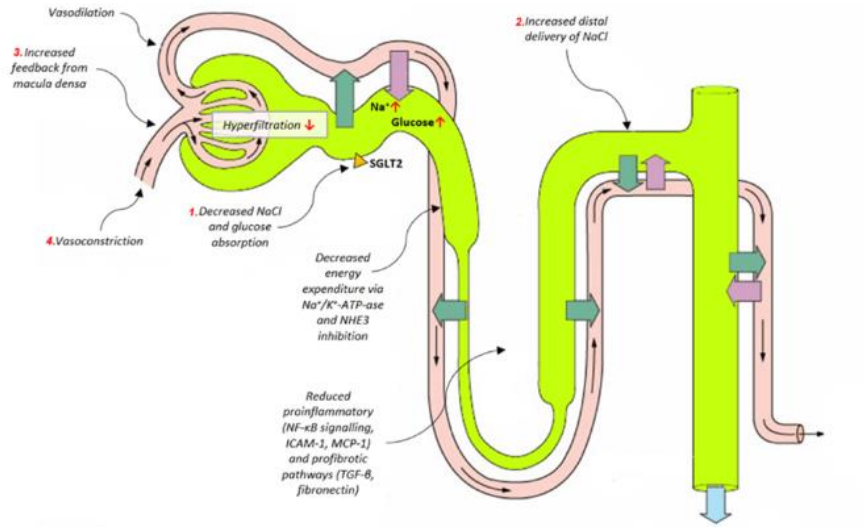

Figure 2 | Schematic representation of the mechanism of action of SGLT2 in the nephron. Adapted from Skrabic at al. 2022. [43]

Other extra-renal effects that might indirectly benefit renal outcomes are shown in table 2.

SGLT2 inhibitors extra-renal effects

Heart	↓ blood pressure
	↑ ketone and free fatty acids utilization
	↓ glucose utilization
	Reduced preload
Pancreas	↑ glucagon
	↓ insulin
Fat mass	↑ lipolysis
	↑ free fatty acid uptake
Liver	↑ hepatic glucose output
	↑ free fatty acid utilization
	↑ ketogenesis

Table 2 | Extra-renal effects of SGLT2 inhibitors that can relate to better renal outcomes. [46]

The beneficial clinical impact of SGLT-2 inhibitors was first proven in the EMPA-REG trial, published in 2015. This first trial, that included 7020 patients, was interrupted precociously due to a significant benefit in the intervention arm, with a significative reduction of major CV events (risk ratio of 0.78 when compared to the control group), fatal or non-fatal myocardial infarction (risk ratio of 0.79) and hospitalization due to heart failure (risk ratio of 0.80) in diabetic patients with arteriosclerosis. [47] A post-hoc review of the EMPA-REG data indicated significant renal consequences, including a decreased chance of nephropathy worsening, a doubled creatinine level, and a requirement for

renal replacement therapy. [48] More recently, renal outcomes in diabetic patients have been the target of several RCTs. (Table 3)

In 2023 the EMPA-Kidney was the first RCT to explore the effects of SGLT2 inhibitors in non-diabetic CKD patients. In total, 6609 people received empagliflozin or a placebo at random in this research. After a 2-year follow-up, 13.1% of patients receiving empagliflozin experienced CKD progression or died from CV causes, compared to 16.9% of patients receiving a placebo. In addition, the risk of hospitalization from any cause was decreased in the empagliflozin group compared to individuals who received the placebo, with a hazard ratio of 0.86. The risks of hospitalization (4% in empagliflozin vs. 4.6% in placebo) and death from any cause (4.5 in empagliflozin vs. 5.1% in placebo) did not differ significantly, though. [49]

The most common adverse effects of SGLT2 are genito-urinary infections, with three times increase in risk when compared to the general population. There has also been some relation with extra vertebral fractures, although there is not increased risk for fragility fractures. This side effect can be associated with dehydration and increased risk of falls in older population, but more studies are needed to assess if this effect is significant. Diabetic ketoacidosis was also reported as a consequence of insulin decrease because of the increased glucose loss. Additionally, SGLT2 inhibition is related to high ketone production. The increased risk of AKI, linked to volume depletion and glomerular hemodynamic changes, is easily prevented by monitoring kidney function. [50]

Nevertheless, the benefits of inhibiting SGLT2 have been proven to overcome side effects in renal protective properties. These effects are consistent in all CKD stages and heart failure severity [51] and SGLT2 inhibitors have revolutionized the treatment of patients with type 2 diabetes mellitus with established or at risk for atherosclerotic cardiovascular disease (ASCVD) and patients with CKD. [4]

Name	***Year***	***Population***	***Agent***	***Results***	***Additional***
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes [52]	2015	N = 7020 Patients with type 2 diabetes at high CV risk	Empagliflozin vs Placebo	Patients in empagliflozin group had a lower rate of CV outcomes such as nonfatal myocardial infarction, nonfatal stroke or death of any cause	Lower hospitalization rate for heart failure complications in the empagliflozin group
Canagliflozin Cardiovascular Assessment Study [53]	2018	N = 15494 Patients with type 2 diabetes at high CV risk	Canagliflozin vs Placebo	Patients in canagliflozin group had a reduced risk of sustained loss of kidney function, attenuation of GFR decline and reduction in albuminuria	Lower hospitalization rate for heart failure complications in the canagliflozin group
DECLARE-TIMI 58 [54]	2019	N = 17160 Patients with type 2 diabetes both with and without ASCVD	Dapagliflozin vs Placebo	Patients in dapagliflozin group had a reduce progression in kidney disease	Most patients preserved renal function
Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation [55]	2019	N = 4401 Patients with type 2 diabetes and CKD	Canagliflozin vs Placebo	Patients in canagliflozin group had a reduced risk of serious and nonserious kidney-related side effects	Reduced risk of ESRD evolution and lower serum creatinine concentration was described in canagliflozin group
Dapagliflozin And Prevention of Adverse outcomes in Heart Failure [56]	2020	N = 4742 Patients with chronic heart failure with reduced ejection fraction with or without type 2 diabetes	Dapagliflozin vs Placebo	Patients in dapagliflozin group had slower rates of GFR decline, including in non-diabetic patients	Mortality and morbidity because of underlying cardiac condition was the same in both groups

Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease	2021	N = 4304 Patients with CKD	Dapagliflozin vs Placebo	Patients in dapagliflozin group had a reduced risk of major adverse kidney and CV events and all-cause mortality, including non-diabetic patients	Reduced risk of ESRD and CKD progression in dapagliflozin group
Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Reduced Ejection Fraction [57]	2021	N = 3730 Patients with heart failure with reduced ejection fraction	Empagliflozin vs Placebo	Patients in empagliflozin group significantly improved CV and renal outcomes	
Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Preserved Ejection Fraction [58]	2022	N = 5988 Patients with heart failure with preserved ejection fraction	Empagliflozin vs Placebo	Patients in empagliflozin group significantly improved CV outcomes	
Empagliflozin in Patients with Chronic Kidney Disease [49]	2023	N = 6609 Patients with CKD at risk of progression	Empagliflozin vs Placebo	Patients in empagliflozin group have showed lower risk of progression of kidney disease and death from CV causes	These results present a median of a 2 year follow up

Table 3 | Overview of RCT of SGLT2 inhibitors efficacy in improving CV and kidney outcomes. CKD: Chronic kidney disease; CV: Cardiovascular; ESRD: End stage renal disease

E.4.4. Mineralocorticoid receptor antagonists

There are several deleterious mechanisms of mineralocorticoid receptors (MR) that expand from their tubular role in sodium and water reabsorption. Many recent studies have demonstrated the role of aldosterone in modulating inflammation, collagen formation, fibrosis, and necrosis. Increasing evidence implicates overactivation of the MR as a major determinant of progression of CKD, despite continued and sustained renin-angiotensin blockade. MRs activation also has an important role in nonepithelial cells as it increases podocyte autophagy by downregulation of nephron, podocin and podoplanin; activates renal fibroblasts and stimulates fibronectin synthesis; promotes oxidative injury and impairs endothelial function. [59] This culminates in arterial stiffness, arteriosclerosis, metabolic syndrome, and promotion of CKD progression by multiple mechanisms. [60]

Considering these harmful effects, MRs blockade arises as an important therapeutic target to delay CKD progression. Firstly, animal studies have shown that selectively blocking aldosterone, without renin-angiotensin blockade, significantly decreased proteinuria and nephrosclerosis in hypertensive and partial nephrectomy rat models. [61, 62] Several studies were then performed in humans and a meta-analysis published in 2016, that included 19 trials, showed that the addition of MR antagonists (MRA) to RAS inhibition resulted in a significant reduction in blood pressure and an important decrease of mean protein/albumin excretion by 38.7 %. However, there was a decrease in glomerular filtration rate and a threefold higher relative risk of withdrawing from the trial due to hyperkalemia (HK). [63]

The development of a novel class of nonsteroidal, selective, MRA might overcome the deleterious side-effects of steroidal MRA. Non-steroidal MRA are as potent as spironolactone, but are much more selective to MRs, as they do not enter central nervous system nor have sexual side-effects (gynecomastia). Also, they have a shorter half-life (2-3 hours versus > 20 hours) and do not produce active metabolites. Their effect on blood pressure is less evident than spironolactone. [64]

Recently, finerenone, a non-steroidal MRA, was used in large RCT to understand its effect in reducing kidney failure risk and disease progression DKD (FIDELIO-DKD) and reducing CV mortality and morbidity in DKD (FIGARO-DKD). In the FIDELIO clinical trial, 17.8% patients given finerenone experienced kidney failure, a 40% reduction in GFR or death from kidney causes when compared to 21.1% of control patients. Additionally, 13% of patients in finerenone group experienced death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, compared to 14.8% of placebo patients. [65] However, finerenone showed an independent risk for HK, through routine potassium monitoring and management can

overcome this impact in clinical status. [66] The FIGARO-DKD trial showed that patients with established CKD and/or severely elevated albuminuria who were treated with finerenone had a 12.7% occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure, whereas the control group had a 14.4% incidence. A decrease of ≥ 57% of GFR or renal death were experienced in 5.5% of patients in the finerenone group vs 7.1%. [67]

These studies showed that finerenone can be part of the standard care of care in reducing the risk of clinically CV and kidney outcomes, delaying disease progression, and offering a better QoL to DKD patients. [68] The most recent guidelines on diabetic nephropathy include finerenone as a second-line therapy in diabetic nephropathy patients (Figure 3). [4]

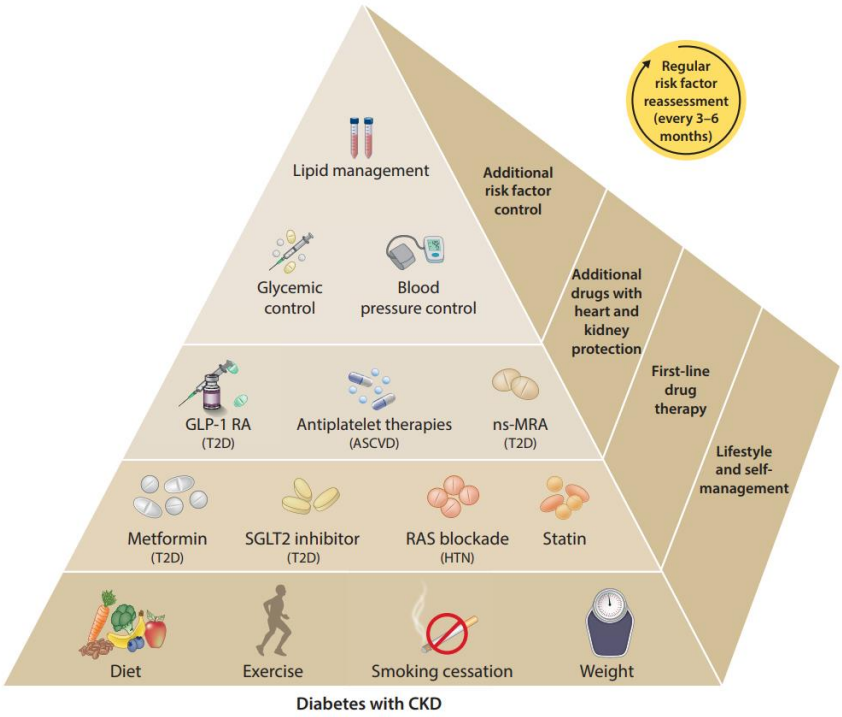

Figure 3 | Kidney and CV risk management in DKD recommendations included in KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease [4]

More studies are being recently developed in non-diabetic CKD patients to evaluate the potential benefits of selective MRA in a larger CKD population. [69, 70]

E.4.5. GLP1-receptor agonists

Besides SGLT2 inhibitors and MRs selective antagonists, other antidiabetic drugs are showing remarkable results in controlling CKD progression. Glucagon-like peptide 1 (GLP1) is an antihyperglycemic agent that has shown impact in reducing microalbuminuria and reducing the decline in GFR in diabetic CKD patients. GLP1 is an incretin involved in different regulation pathways of appetite and carbohydrate

metabolism. Its main function is to stimulate insulin secretion and reduce glucagon levels, thus decreasing plasma glucose. [71] GLP1 receptor agonists are efficient antidiabetics, but also have an important action in the kidney. They have an important role in inducing natriuresis and decreasing glomerular hypertension. GLP1 promote the vasoconstriction of the afferent arteriole in response to activation of tubule-glomerular feedback because of augmented sodium afflux to macula densa and promote vasodilation of efferent arteriola release of nitric oxide and natriuretic peptide. This is like SGLT2 inhibitors mechanism, which conveys a diminished GFR to prevent glomerular hyperfiltration and more kidney damage. Secondly, the natriuretic effect that involves the inhibition of sodium-hydrogen exchangers in the proximal tubule, leads to lower plasma renin activity, thus improving blood pressure values, and consequently reducing microalbuminuria. [72] Another important effect is GLP1 receptor agonists' capacity to modulate inflammatory response, one of the known causes for fibrosis development in CKD. [73] These agents also offer protection from oxidative stress damage by activating the cyclic adenosine monophosphate-protein kinase A pathway which can reduce ROS production in the kidney. [71, 74]

Moreover, GLP1 receptor agonists have indirect effects on CKD progression by aiding patients in losing weight, controlling their blood sugar levels, and lowering their blood pressure - conditions that affect prognosis in CKD by impairing kidney function or raising CV risk. [72]

These effects show a possibility in using these agents as possible therapeutic adjuvants in CKD, delaying its progression. The SUSTAIN and PIONEER trials have demonstrated that semaglutide, a GLP1 receptor agonist, leads to body weight loss and decrease systolic blood pressure, important factors in CKD morbidity and mortality. [75] However, when compared to SGLT2 inhibitors, GLP1 receptor analogues did not significantly lower the risk for CV or renal endpoints but showed better numeric results. Also, SGLT2 has shown a better action in reducing the risk of renal events when compared to GLP1. [76]

E.5. CKD complications – New pharmacological targets

E.5.1. Anemia

Erythropoiesis stimulating agents (ESA) are the main drugs available for treating anemia in CKD. The first available was epoetin alfa, approved by the US the Food and Drug Administration (FDA) in 1989. The development and establishing of ESA as a viable and effective option led to the development of other agents, darbepoetin alfa and methoxy polyethylene glycol-epoetin. All ESA have the same mechanism of action: activating the EPO receptor. [77] The main benefit of ESA is reduction of red blood cells transfusions, improve anemia symptoms and QoL. However, overcorrection to full hemoglobin (Hb) concentration normalization is accompanied by significant CV, thrombotic and neoplasia risks. [78, 79] The reason for an increased thrombotic risk with ESA treatment to normal Hb targets is unclear but might be related to increased blood viscosity or vascular endothelial wall stress. Also, the very high ESAs doses required to normalize Hb concentrations might have detrimental off-target effects. [80] The FDA recommends using the lowest ESA dose required to achieve therapeutic benefit, but individualization of the Hb target may be considered based on patient characteristics. The 2017 *Manual das Boas Práticas em Diálise* recommends that for patients under ESA Hb values should be between 10-12g/dL. [81]

Before initiating ESA treatment, iron status should be assessed and iron deficiency corrected, which might delay the onset of ESA or allow the use of lower doses.

A major handicap of ESA therapy, in addition to the previously discussed side effects is the intravenous or subcutaneous route. Especially in non-dialysis patients, this is an important limitation of ESA agents that decreases patients QoL. [82]

A new class of pharmacological agents that has been researched as a viable option to treat anemia in CKD are Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors. These agents are responsible for stabilizing the HIF-complex, simulating a hypoxic state, which stimulates endogenous EPO production even in ESRD patients. [77] They also stabilize HIF-2α, which is responsible for increasing intestinal iron absorption and limiting hepcidin transcription in the liver. These can contribute to treat functional iron deficiency related anemia, a common anemia mechanism in CKD. [83] There are currently 5 HIF-PH inhibitors being used in clinical practice: Daprodustat, Roxadustat, Vadadustat, Molidustat and Enarodustat. [84] A 1.75 g/dL Hb increase was seen in patients receiving Roxadustat in a 2021 study with 2781 CKD non-dialysis dependent patients, compared to 0.40 g/dL in the control group. Roxadustat also decreased red blood cells transfusion risk by 63%. [85] Other RCT have shown this

agent’s class efficacy (Table 4). This led to Roxadustat approval by the European Medicines Agent for the treatment of CKD anemia in 2021.

HIF-PH inhibitors have been described as having a higher efficacy than ESA, with similar or inferior major adverse events. They can be taken orally, which provides a major advantage for the patient’s well-being. A recent meta-analysis, HIF-PH inhibitors demonstrated a 1.02 and 1.06 risk ratio of cardiac adverse events in comparison to a placebo or ESAs, respectively, in a recent meta-analysis. Moreover, there was no discernible difference in kidney-related side effects as compared to placebo. However, it was found that utilizing HIF-PH inhibitors vs a placebo resulted in risk ratios of 1.35 for hypertension and 1.25 for HK. [86]

Reference	*Agent*	*Study type*	*Study group*	*N*	*Comparator*	*Results*	*Conclusions*	*Side effects*
Singh et al. 2021 [87]	Daprodustat	Phase 3, randomized	DD-CKD, Hb between 8.0g/dL and 11.5g/dL	2964	ESA	The daprodustat group had a Hb change between weeks 28 through 52 of 0.28g/dL and the ESA group of 0.10g/dL	Daprodustat showed significant superiority in Hb change when compared to ESA therapy	Similar CV safety
Singh et al. 2021 [88]	Daprodustat	Phase 3, randomized active-controlled	NDD-CKD	3872	Darbepoetin alpha	The daprodustat group had a Hb change between weeks 28 through 52 of 0.74g/dL and the darbepoetin alpha group of 0.66g/dL	Daprodustat showed significant superiority in Hb change when compared to darbepoetin alpha	Similar CV safety
Fishbane et al. 2021 [85]	Roxadustat	Randomize Phase 3 Study	NDD-CKD, Hb < 10g/dL	2781	Placebo	There was a 1.75g/dL baseline change in Hb concentration in Roxadustat group versus 0.40g/dL in the placebo group	Roxadustat increases Hb effectively	Similar adverse effects were registered in both groups
Fishbane et al. 2022 [89]	Roxadustat	Phase 3 study	DD-CKD	2133	Epoietin alfa	There was a 0.77g/dL baseline change with roxadustat versus 0.68g/dL with epoetin alpha	Roxadustat showed superiority in Hb increase when compared to epoetin alpha	The adverse effects profile was similar in both groups
Eckart et al. 2021 [90]	Vadadustat	Randomized Phase 3 Study	DD-CKD	3923	Darbepoetin alfa	There was a change of -0.31g/dL at 24 to 36 weeks and -0.07g/dL at 40 to 52 weeks in the incident group versus -0.17g/dL at 24 to 36 weeks and -0,18g/dL at 40 to 52 weeks in the prevalent	Vadadustat showed better results in Hb concentration maintenance than with darbepoetin alpha	Vadadustat group showed less incidence of serious adverse effects than darbepoetin alfa group
Nangaku et al. 2021 [91]	Vadadustat	Randomized Phase 3 Study	NDD-CKD Japanese	304	Darbepoetin alfa	Square mean changes were 11.66 and 11.93 with roxadustat and erythropoietin, respectively	Vadadustat showed similar results in Hb increase when compared to darbepoetin alfa	Adverse effects were similar between groups

Table 4 | Overview of RCT of HIF-PH inhibitors efficacy in improving anemia markers and CV and overall safety. CV: Cardiovascular; DD: Dialysis dependent; Hb: Hemoglobin; NDD: Non-dialysis dependent.

E.5.2. Hyperkalemia

Nonpharmacological measures are the first step in the treatment of HK. Changing cooking techniques, avoiding hidden potassium sources, such as dietary additives and reviewing patient's prescriptions should be the first therapeutic action. If there is a metabolic acidosis background, alkaline medications can be helpful in reversing the etiology of HK. Diuretics can also be helpful because they induce kaliuresis. [92] Pharmacological treatment is required if potassium levels don't improve.

Potassium binders, like sodium polystyrene sulfonate (SPS), increase fecal potassium excretion. They work by exchanging sodium for calcium, ammonium, and magnesium in addition to potassium in the distal colon through cation exchange. Because of this, SPS is not particularly selective in excreting potassium, which could result in hypocalcemia and hypomagnesemia. [93] Patients with CKD who have moderate HK have shown success with SPS. According to a randomized clinical trial, SPS treatment resulted in normokalemia in 73% of patients with potassium blood levels between 5 and 5.9 mEq/L compared to 38% of patients who received a placebo. However, it was also noted that the SPS group experienced more electrolytic problems and gastrointestinal side effects. [94] Significant gastrointestinal side effects are described in a 2013 systematic review, with transmural necrosis being the most frequent. A 33% mortality incidence from gastrointestinal damage was also recorded. [95] Additionally, patients with ESRD appear to respond ineffectively to SPS, with no improvement beyond placebo. [96]

New potassium binders have just received FDA approval. They act by trapping potassium ions, which are then excreted in the feces. Colic ion transporters are unaffected.

Patiromer comprises of spherical beads made of a calcium ion-rich polymer that dissociates in the distal colon to absorb potassium ions. [93] To determine the efficacy of this novel binder, 105 patients with HF or CKD were randomized to receive patiromer or a placebo in the PEARL-HF trial. After four weeks, the potassium serum differential between the CKD patients in the patiromer group and the placebo group was -0.52 mEq/L, and the incidence of HK was 6.7% as opposed to 38.5% in the placebo group. There were mostly mild to moderate gastrointestinal side effects that were recorded and no severe adverse effects were reported. [97] Comparable outcomes were noted in the OPAL-HK trial, which used patiromer to treat 237 CKD patients who were on RAS inhibitors and had HK of 5.1 to 6.5 mmol/L. After four weeks, 76% of patients had achieved normokalemia (between 3.8 and 5.0 mmol/L), with the mean change in serum potassium being approximately -1.01 mmol/L. Subsequently, 107 patients were chosen at random and given either patiromer or a placebo. At the end of 8 weeks, 15% of patients

in the patiromer group experienced a recurrence of HK, compared to 60% of patients in the placebo control group. Mild to moderate constipation was the most typical adverse effect, with 11% of patients experienced. [98]

Another incredibly specific potassium binder is sodium zirconium cyclosilicate (ZS9). 753 individuals with HK and CKD, HF, or diabetes were given ZS9 in a range of doses (1.25g, 2.5g, 5g, and 10g) or a placebo in a multicenter, two-stage, double-blind, phase 3 trial. In contrast to the placebo and 1.25g groups, which had a mean reduction of 0.3 after 48 hours, patients in the 2.5g and 5.0g groups experienced a mean drop of 0.5 mmol/L and 0.7 mmol/L, respectively. Patients who received 5g and 10g of ZS9 throughout the course of the next 14 days maintained kalemia levels of 4.7 mmol/L and 4.5 mmol/L, as opposed to > 5 mmol/L in the placebo group. In the first 48 hours, 12.9% of patients in the ZS-9 group and 10.8% in the placebo group experienced side effects; throughout the maintenance phase, these numbers were 25.1% and 24.5%, respectively. In both groups, diarrhea was the most typical complication. [99] These findings were supported by the Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance - HARMONIZE experiment.

E.5.3. Pruritus

The lack of effective therapy options for CKD associated pruritus (CKD-aP) is mostly due to the underdiagnosis and undertreatment of the condition, as well as the incomplete understanding of its pathogenesis. [100]

Initial therapy with glycerol and paraffin emollients are the principal treatment options in this situation. [101] Topical steroids and topical immunosuppressants like tacrolimus were once also used to lessen itching, however due to a lack of evidence, these medications are only recommended in few clinical settings. [102] Gabapentinoids are a systemic alternative that can help reduce neural sensitization by altering calcium channels involved in itch pathways. [103] Indeed, when compared to placebo, studies have shown that gabapentin or pregabalin significantly improved clinical outcomes. [102] Antihistamines are also frequently used, although their effectiveness in treating CKD-aP appears to be limited. [104]

An innovative therapeutic target in CKD-aP appears to be opioid imbalance and elevated expression of kappa-opioid receptors (KOR). Difelikefalin has recently been proven to be beneficial in treating CKD patients' pruritus. This substance targets peripheral sensory neurons with strong KOR sensitivity and has immunomodulatory actions by lowering pro-inflammatory cytokines. [105] When compared to other KOR agonists, it has a better safety profile since its blood-brain barrier transit is constrained. As a result, it has little impact on the central nervous system and has no sedative or

respiratory depressant effects. [106] Furthermore, because of its strong selectivity, mu-opioid receptor types are unaffected, which results in a low addiction risk. [107] A 2020 RCT that randomly assigned 174 hemodialysis patients to difelikefalin at different doses (0.1, 1.0, or 1.5 microgram/kg) or placebo, demonstrated that 64% of patients in the 0.5 microgram group and 67% of patients in the 1.5 microgram group experienced a reduction of 3 or more points in the Worst Itching Intensity Numerical Rating Scale (WINRS) scale, compared to 29% of patients in the placebo group. Patients who received difelikefalin also reported an improvement in their QoL. However, 78% of patients utilizing difelikefalin reported experiencing side effects because of their treatment, such as diarrhea, dizziness, nausea, somnolence and falls (the most frequent). [108] Similar findings came from a subsequent RCT in which 247 hemodialysis patients were randomly assigned to receive difelikefalin in various doses (0.25 microgram, 0.5 microgram, or 1.0 microgram) or placebo. In comparison to 50% of patients in the placebo group, it was observed that 3 or more points were dropped off the WINRS in 53% of patients receiving 0.25 micrograms, 60% in 0.5 micrograms, and 57% in 1.0 micrograms. The effect on QoL was likewise favorable, with a reduction of 27.79 Skindex-16 points in the 0.5 microgram group compared to a reduction of 24.04 in the placebo group. The Skindex-18 questionnaire showed a lesser drop in the 0.25 microgram and 1.0 microgram groups, at 24,25 and 22,69 points, respectively. The reported side effects had an overall incidence of 72% in the 0.25 microgram group, 77% in the 0.5 microgram group, and 85% in the 1.0 microgram group compared to 67% in the placebo group, mirroring the results of the previous trial. [109]. Difelikefalin has currently received approval by FDA and is administered intravenously at the end of a dialysis session at a dose of 0.5 micrograms per kilogram. [110]

F. Conclusion

CKD is a chronic condition that is rising globally, leading to poor QoL, high morbidity and mortality risk and a huge socioeconomic impact. In the last decade, the increased knowledge of CKD progression and complications physiopathology have led to the development of new drugs that are changing the paradigm of CKD treatment. New guidelines are now including novel therapeutical approaches that focus on kidney outcomes but also on general risk factors and comorbidities. The SGLT-2 inhibitors were the first drug class to be included in the most recent KDIGO guidelines on diabetic CKD but also the American Heart Association, The European Society of Cardiology and the American Association of Clinical Endocrinology. Selective MR antagonists, like

finerenone, are also considered as a second-line therapy in DKD and new promising results are arousing for non-diabetic CKD.

Regarding CKD complications, the available recommended drugs are associated with several adverse effects and an important impact on patients' QoL. The investment in new drugs with better tolerability and similar efficacy provide a new hope for polimedicated CKD patients.

G. List of abbreviations

ACE	Angiotensin-converting-enzyme
AKI	Acute kidney injury
AngII	Angiotensin II
ARB	Angiotensin receptor blockers
ASCVD	Atherosclerotic cardiovascular disease
CKD	Chronic kidney disease
CKD-aP	CKD associated pruritus
CV	Cardiovascular
CVD	Cardiovascular disease
DD	Dialysis dependent
DKD	Diabetic kidney disease
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GLP1	Glucagon-like peptide 1
Hb	Hemoglobin
HIF-PH	Hypoxia-inducible factor prolyl hydroxylase
HK	Hyperkaliemia
KDIGO	Kidney Disease Improving Global Outcomes
KOR	Kappa-opioid receptors
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonists
NDD	Non-dialysis dependent
QoL	Quality of life
RAS	Renin-angiotensin system
RCT	Randomized controlled trial
SGLT	Sodium-glucose cotransporter
SPS	Sodium polystyrene sulfonate
TGF	Transforming growth factor
WINRS	Worst Itching Intensity Numerical Rating Scale
ZS9	Sodium zirconium cyclosilicate

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