Review Article

Contemporary use of antiarrhythmic drugs: practical messages for clinical cardiologists from the EHRA compendium.

Silvia Palomo-Piñón, Francisco J. Ramos-Carrillo.

Grupo de Expertos en Hipertensión Arterial México (Group of Experts on Hypertension from Mexico) (GREHTA).

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ABSTRACT

Chronic kidney disease is a global public health problem characterized by high prevalence, underdiagnosis, and substantial morbidity and mortality, primarily driven by cardiovascular outcomes. It is currently recognized as a major independent risk factor for both atherosclerotic and non-atherosclerotic cardiovascular disease, with risk increasing in parallel with declining glomerular filtration rate and rising albuminuria. This association is explained by the synergistic interaction between traditional cardiovascular risk factors and non-traditional pathophysiological mechanisms that are highly prevalent in chronic kidney disease. These include mineral and bone disorder, anemia, volume overload, uremic toxins, oxidative stress, chronic inflammation, dysbiosis, and overactivation of the renin–angiotensin–aldosterone system and the sympathetic nervous system. Collectively, these processes promote endothelial dysfunction, accelerated atherosclerosis, and maladaptive cardiac remodeling, ultimately contributing to the high cardiovascular morbidity and mortality observed in this population.

INTRODUCTION

The cardiorenal metabolic continuum (CRM) favors cardiovascular risk (CVR), and chronic kidney disease (CKD) is part of it.[1] It is defined by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2 and/or structural anomalies and/or functional anomalies of the kidney for a time ≥3 months, with implications for health. It is classified in 5 stages according to eGFR and stratified in three categories of albuminuria *(Table 1)*. The contribution of CKD to the continuum is complex, and there are mechanisms participating, related to the uremic milieu produced by a decrease in glomerular filtration (GF), where the effect of uremic toxins on the CV system is early.

In this review, we show the contribution of CKD to CVD in the CRM continuum, through a poor adaptation of initially adaptive mechanisms in the kidney in an attempt to maintain homeostasis. These internal changes are unique to patients with CKD and have devastating consequences.

THE SIGNIFICANCE OF CKD IN THE CONTINUUM

1) It is a CVR amplifier

Type 2 diabetes (T2D) and hypertension (HTN) are the most prevalent causes of CKD and both increase CVR. However, there is an equally increased CVR in primary glomerular diseases, regardless of nephrotic syndrome and the extent of albuminuria. The estimated probability of a CV event in this population is 1.38

Renal and cardiovascular risk according to the CKD classification

Category of GFR (glomerular filtration rate in ml/min)	Category of albuminuria (in mg/g) A1 Normal < 30	A2 Moderate 30–300	A3 Severe > 300
G1 > 90 Normal	Low risk	Low risk	Low risk
G2 60–89 Mild	Low risk	Moderate risk	High risk
G3a 45–59 Moderate	Moderate risk	High risk	Very high risk
G3b 30–44 Moderate	High risk	High risk	Very high risk
G4 15–29 Severe	High risk	Very high risk	Very high risk
G5 < 15 Renal failure	Very high risk	Very high risk	Very high risk

Low risk | Moderate risk | High risk | Very high risk

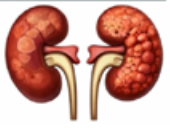
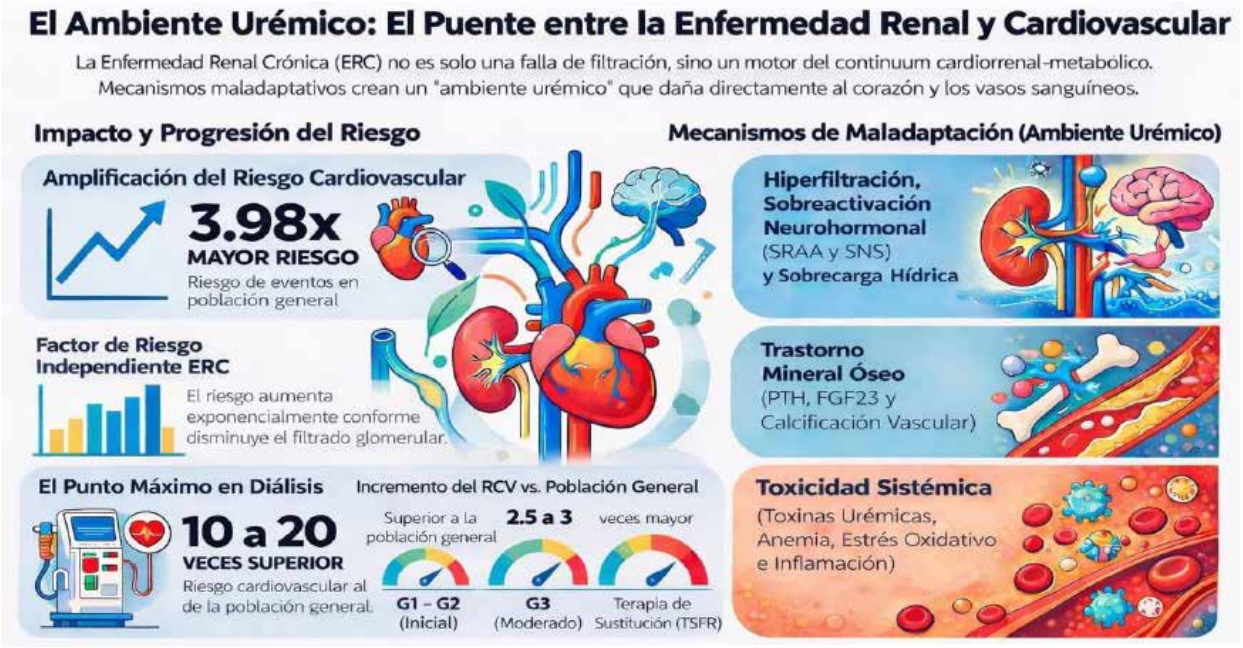


TABLE 1.
Categories of glomerular filtration (KDIGO 2024)

Corresponding author's address: **Dra. Silvia Palomo-Piñón.** Calle Retorno del Escorial No. 13, colonia Residencial El Dorado, Municipio Tlalnepantla de Baz, Estado de México, CP: 54020, México. *e-mail:* silvia-palomo@hotmail.com



CENTRAL FIGURE

to 3.98 greater than in the population without CKD of the same age and sex.[2] This CVR is not static, but increases exponentially as GF decreases, and it reaches its peak in kidney failure replacement therapy (KFRT). Patients in stages G1-G2 present a CVR greater than the one observed in the general population, due to alterations in the CV system due to GF decrease.[3] In the G3 stage, it increases 2.5 and 3 times, while in G4-G5 it may be up to 3.4 times greater in comparison with G1. During KFRT, it reaches values between 10 and 20 times more than in the general population, considering that 40%-50% of patients start this stage with CVD already established. After renal transplant, CVR is around 3.5% and 5%; nonetheless, it is still approximately 50 times more than the general population.[4]

2) It is an independent factor of CVR

Just as with T2D, plenty of studies have concluded that the association between CKD and CVD is synergic, strong, bidirectional, interdependent, of positive feedback loop and causal on multiple levels. Renal patients present atherosclerotic CVD (CAD, stroke and peripheral arterial disease) and nonatherosclerotic disease equally (heart failure, arrhythmia and sudden cardiac death), decreasing life expectancy.[5,6]

CONTRIBUTION OF CKD TO THE CARDIORENAL-METABOLIC CONTINUUM

Progressive decrease of GF is the trigger of multiple adaptive mechanisms that attempt to maintain homeostasis of the internal milieu. Hemodynamic, hormonal, metabolic and structural adaptations have been described throughout the nephron, becoming widespread. The problem starts when they become "maladaptive" and accelerate GF drop, harming different organs and systems *(central figure)*. The level of evidence of these data is high (1A and B).

1) Intrarenal adaptations: glomerular hyperfiltration

Also known as compensatory hyperfiltration, it is the first mechanism to activate because of decrease in the number of functional nephrons. It occurs due to afferent arterioles dilatation and vasoconstriction of efferent arterioles, with the subsequent increase of intraglomerular filtration, but the effect of the rest of the simultaneous adaptations produces a sustained elevation of the glomerular capillary pressure that damages the podocyte structures and allows albumin to go through. Over time, the mentioned structures scar and stop working (progressive sclerosis).[7,8]

2) Renal and systemic neurohormonal adaptations

A) Overactivation of the renin-angiotensin-aldosterone system (RAAS)

At renal level, chronic vasoconstriction of efferent arterioles (that initially maintains GF) is the trigger to overactivate RAAS, as the macula densa perceives it as a chronic decrease in renal perfusion. Consequently, a reduction of effective intraglomerular pressure and overactivation of the systemic neurohormonal response occur, with retention of Na+ and H2O, expansion of extracellular volume and increase in systemic blood pressure. The strong vasoconstrictor effect of angiotensin II and Na+ and H2O retention stimulate nonhemodynamic mechanisms that favor vascular hypertrophy, cardiac fibrosis and endothelial function, which are enough per se to increase blood pressure and produce major CVD. Simultaneous overstimulation of aldosterone favors Na+ retention and pathological remodeling of cardiovascular tissues, contributing to progression of CVD and increase of adverse events. Over time, this mechanism ends with renal fibrosis, vascular stiffness, and alterations in cardiac remodeling, producing HF, arrhythmias and death.[8]

B) Overactivation of the sympathetic nervous system (SNS)

It is favored by the decrease in renal perfusion and the effective reduction of intraglomerular pressure previously described. This effect is initial, and over time it represents the main mechanism perpetuating cardiorenal damage, as it maintains a sustained increase in vascular tone, heart rate elevation, Na+ retention and increase in myocardial consumption of oxygen. These maladaptive changes generate fibrosis, vascular stiffness and alterations in cardiac remodeling. Sympathetic stimulation also favors renin release, further amplifying RAAS activation, and establishing a positive feedback loop that perpetuates cardiac and renal dysfunction.[9]

The combined effects of the RAAS and the SNS explain largely the high incidence of CVD, including left ventricular hypertrophy (LVH), HF, arrhythmias, CAD and sudden cardiac death. The therapeutic benefit of its pharmacological modulation has been documented with controlled clinical trials in populations with multimorbidity.[8]

3) Adaptations in the fluid and electrolyte balance: Na+ and H2O

The decrease in the number of functional nephrons and GF, along with neurohormonal overactivation, increase the excreted fraction of Na+ and H2O, and natriuresis occurs. This triggers the response of natriuretic peptides to favor natriuresis and vasodilation, in an attempt to restore fluid balance. As GF drop advances and volume overload exacerbates, there is resistance to the compensatory effect, in such a way that volume overload cannot be offset and filling pressure, hypertension disarray and arterial stiffness increase, thus contributing to LVH and HF. This condition has a poor outcome, particularly in patients in KFRT, as it is associated consistently with higher risk of CVD and mortality. Likewise, Na+ and H2O retention may worsen albuminuria, a situation that accelerates renal impairment progression.[10]

4) Adaptations in acid-base balance

Kidneys maintain pH stable faced with GF drop by three basic mechanisms: 1) increase in excretion of acid by nephron (ammoniagenesis by remnant nephron); 2) reduction in serum bicarbonate by increase in titratable acid excretion; 3) respiratory compensation that decreases partial pressure of carbon dioxide (pCO2). These mechanisms remain stable until the terminal stages of CKD, where the evident decrease in functional nephrons prevents fully compensating the acid load. Thus, chronic metabolic acidosis occurs, leading to stress and structural changes in the CV system, arterial stiffness, active chronic inflammation, instability of blood pressure and high risk of HTN, LVH, HF, CAD, strokes and death by CV origin.[11]

5) Adaptations in mineral and bone metabolism

Mineral and bone disorder (MBD) starts early in CKD, although biochemically is documented when GF is <60 ml/min/1.73 m^2.[12,13] It contributes to the presence of CVD by several interrelated mechanisms: 1) intact parathyroid hormone (PTH) elevation promotes hypertrophy, fibrosis and action by procalcific and proinflammatory pathways; its interaction with aldosterone contributes to endothelial dysfunction; 2) vitamin D2 and D3 deficiency favors the expression of renin and promotes inflammation and fibrosis, because it changes the vascular smooth muscle phenotype and fibroblast growth factor 23 (FGF23) signaling. These changes decrease the renal expression of Klotho (a protein that regulates phosphocalcic mechanism and inhibits vascular calcification), and produce LVH, HF, atrial fibrillation and CV death; 3) a reduction in phosphate excretion and uremic milieu favor vascular calcification in the intima (atherosclerosis) and media layers of vessels (arteriosclerosis); this makes them stiff, elevating systolic pressure, pulse pressure, increasing afterload and favoring LVH, which in turn affect subendocardial perfusion.[13,14,15]

6) Hematological adaptations: anemia

Anemia contributes to CV events by multiple interrelated mechanisms, based on tissue hypoxia. This state is associated to hemodynamic adaptations and cardiac remodeling, activating compensatory responses such as increase in cardiac output (tachycardia, systolic volume alteration) and peripheral vasodilation. Less O2 arterial content with greater myocardial demand leads to subendocardial ischemia, particularly in coronary arteries with coexisting atherosclerosis, predisposing to myocardial infarction or chronic angina. On the other hand, anemia worsens RAAS and SNS overactivation, systemic inflammation, increase in oxidative stress and loss in vasodilation mechanisms, damaging the endothelium and increasing atherosclerosis and thrombosis progression. It clinically worsens HTN and afterload, which is associated to LVH, as well as myocardial fibrosis.[16]

7) Systemic adaptations

There are several systemic compensatory mechanisms that end up maladapting to the uremic milieu. Their contribution to the CRM continuum is briefly described:

A) Loss of balance between the production of reactive oxygen species (ROS) and antioxidant systems of cells by uremic milieu and endothelial damage causing oxidative stress, characterized by excess of reactive species and reduction of antioxidant species (e.g.: superoxide dismutase, glutathione peroxidase). This exacerbates endothelial dysfunction, decreases bioavailability of nitric oxide, favors arterial stiffness, as well as activation of proinflammatory and proatherogenic pathways.[17]

B) The uremic milieu produces dysbiosis, favoring the production and absorption of toxic metabolites (such as p-cresyl sulfate and indoxyl sulfate), which increase systemic inflammation (increase of PCR, IL6, TNFα) and vascular lesion.[18]

C) The effect of more than a hundred uremic toxins on endothelial cells, cardiomyocytes and vascular smooth muscle cells promote fibrosis, calcification, thrombosis and metabolic alterations, accelerating atherosclerosis and LVH. Jointly, these processes constitute a vicious cycle that accelerates the progression of CKD and elevates global CV morbimortality.[19]

D) Finally, the convergence of the described mechanisms produces malnutrition, inflammation and accelerated atheroscle-

rosis syndrome (MIA syndrome). This complex phenotype is considered a multiplier of CVR, where early vascular ageing (EVA) is a preponderant characteristic. It is known that patients present CAD and stroke early. Malnutrition reduces the capacity of the body to repair tissue, increases susceptibility to infections, and thus, inflammation remains constant and active, promoting the mechanisms that favor atherosclerosis.[20]

CONCLUSION

The contribution of CKD to the CRM continuum lies in physiological mechanisms maladapting, which starts with an attempt to maintain homeostasis in the internal milieu. The uremic milieu makes its initial physiological effect unsustainable, and it favors endothelial damage by multiple phenomena at intrarenal and systemic level. The clinical consequence is CVD and premature death, regardless of the cause of the aggression. CVD is exponential and is directly related to a decrease in glomerular filtration and albuminuria. It is necessary to seek for renal damage in any patients with CRM continuum components and implement a treatment without delay.

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