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EDITORIAL

Chronic kidney disease and vascular risk - what's new?

Enfermedad renal crónica y riesgo vascular. ¿Qué hay de nuevo?

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Chronic kidney disease (CKD) will be a major challenge for the healthcare system in the years to come, as it is one of the most important contributors to morbidity and mortality from non-communicable diseases.[1] CKD affects 10%-12% of the population worldwide and is the third fastest growing cause of mortality.[2] CKD affects 10%-15% of the Spanish population[3,4] and was the eighth leading cause of death in 2016, and the second fastest growing cause between 2006 and 2016, after Alzheimer's disease.[5] CKD is also the second fastest growing cause of diseases involving living with a disability and disability-adjusted life years in Spain.[5]

There is a clear two-way epidemiological relationship between CKD and cardiovascular disease (CVD). On the one hand, CVD increases the risk of CKD.[6] CVD is more frequent in patients with CKD and is the leading cause of mortality in these patients. And on the other hand, population-based studies show that CKD is associated with a progressive increase in the risk of fatal and non-fatal vascular events as glomerular filtration rate decreases or albuminuria increases,[7] both key indicators of kidney damage. CKD is an independent risk factor for the development of atrial fibrillation,[8] heart failure, ischaemic heart disease, and cerebrovascular disease,[9] and worsens the prognosis following a vascular event.[10]

The new European Guidelines for the Prevention of Cardiovascular Disease[11] confirm CKD as an independent prognosis modulator, on a par with familial hypercholesterolaemia (FH), diabetes mellitus (DM), and established atherosclerotic cardiovascular disease (ASCVD). Therefore, patients with moderate CKD are classified as patients at high risk of vascular events, as are patients with FH with poorly controlled cholesterol levels or patients with DM with no prior vascular disease or target organ damage. Patients with severe CKD are classified in the same risk group (very high) as patients with DM2 with severe target organ damage, or patients with ASCVD (Tables 1 and 2). This has important clinical implications, as patients with CKD should be given the same degree of vascular care and protection as patients with DM or ASCVD.

This risk of vascular events in patients with CKD is partly mediated by the association with classical vascular risk factors (CVRF).[4] Therefore, it is essential to control these CVRFs to reduce the risk of events. Thus, in patients with CKD, in addition to lifestyle changes of known effectiveness in the prevention of CVD,[12] adequate blood pressure control with renin-angiotensin-aldosterone system blockade and lipid metabolism control are recommended, the target being to reduce LDL-cholesterol to below 70 mg/dl or 55 mg/dl in patients at high or very high vascular risk, respectively. With respect to DM, the sodium-glucose cotransporter 2 inhibitors (SGLT2i) canagliflozin,[13,14] empagliflozin,[15] dapagliflocin,[16,17] and glucagon-like peptide 1 receptor agonists (GLP-1RA)[18] have shown beneficial effects in reducing vascular and renal events (Table 3). These findings have meant that SGLT2i and GLP-1RA are considered key drugs in improving cardio-renal prognosis in the European Guidelines for the Prevention of Cardiovascular Disease[11] and in the American Diabetes

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Table 1 Cardiovascular risk stratification. Modified from FLJ et al..[11] ASCVD: Atherosclerotic Cardiovascular Disease, CKD: Chronic Kidney Disease, DM: Diabetes Mellitus, FH: Family Hypercholesterolaemia.

Situation	Classification of risk		
	Low risk	High risk	Very high risk
People without ASCVD, DM, CKD, or FH	10-year cardiovascular risk estimation with SCORE2 (people < 70 years) or SCORE2-OP (people >= 70 years)		
People with FH	—	Elevated cholesterol levels	—
People with CKD without DM or ASCVD	—	Moderate CKD	Severe CKD
People with DM	—	DM2 without ASCVD or severe target organ damage	DM2 with established ASCVD or severe target organ damage
People with established ASCVD	—	—	ASCVD documented clinically or unequivocally on diagnostic imaging techniques

Table 2 Definitions of clinical conditions modifying vascular risk. Modified from Visseren FLJ et al.[11] eGFR: Estimated glomerular filtration rate. uACR: Urine albumin-creatinine ratio.

Associated clinical condition	Definition
Moderate CKD	eGFR 30-44 ml/min/1.73m2 and uACR < 30 mg/g
	eGFR 45-59 ml/min/1.73m2 and uACR 30-300 mg/g
	eGFR >=60 ml/min/1.73m2 and uACR >300 mg/g
Severe CKD	eGFR <30 ml/min/1.73m2
	eGFR 30-44 ml/min/1.73m2 and uACR > 30 mg/g
Severe target organ damage	Microvascular complications in at least 3 different sites
	uACR > 300 mg/g
	eGFR 45-59 and uACR 30-300 mg/g
	eGFR < 45 ml/min/1.73m2 independently of uACR
Clinically documented ASCVD	Previous acute myocardial infarction
	Acute coronary syndrome
	Coronary revascularisation and other arterial revascularisation procedures
	Cerebrovascular accident and transient ischaemic attack
	Aortic aneurysm
	Acute pulmonary oedema
ASCVD on diagnostic imaging techniques	Atheroma plaque on coronary angiography
	Atheroma plaque on carotid ultrasound

Association's[19] recommendations for the management of patients with DM. SGLT2i is recommended in In patients with DM2 and CKD with glomerular filtration rates greater than 25 ml/min/1.73m^2 and urine albumin-creatinine ratio above 300 mg/g to reduce CKD progression and the risk of vascular events.[19] The beneficial renal and vascular protective effects of SGLT2i are maintained up to filtration rates of 30 ml/min/1.73m2 independently from the effect on metabolic control of DM.[20] A new aldosterone antagonist, finerenone, has shown beneficial effects on renal and vascular protection in this patient profile in the FIDELIO[21] and FIGARO[22] clinical trials (Table 3).

However, CKD is currently continuing to grow globally as a cause of mortality to a greater extent than other cardiovascular diseases.[23] This could be due to a lack of scientific evidence related to the management of CVD and CKD-

Table 3 Principal studies with SGLT2i and finerenone.

Reference	Study	Molecule	Principal conclusion
Zinman et al[15]	EMPA-REG OUTCOME	Empagliflozin	In patients with DM2 and high risk of CV events, empagliflozin reduced the risk of CV events and all-cause death.
Neal et al[13]	CANVAS	Canagliflozin	In patients with DM2 and high risk of CV events, canagliflozin reduced the risk of CV events and all-cause death.
Wiviott et al[16]	DECLARE-TIMI	Dapagliflozin	In patients with DM2 and high risk of CV events, dapagliflozin reduced cardiovascular mortality and the risk of hospitalisation due to heart failure.
Perkovic et al[14]	CREDENCE	Canagliflozin	In patients with DM2 and CKD, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group compared to placebo.
Heerspink et al[17]	DAPA-CKD	Dapagliflozin	In patients with CKD with or without DM2, dapagliflozin showed beneficial effects on CKD progression and renal or cardiovascular mortality, compared to placebo.
Bakris et al[21]	FIDELIO-DKD	Finerenone	Finerenone reduced the risk of CKD progression and vascular events in patients with DM2 and CKD, compared to placebo
Pitt et al[22]	FIGARO-DKD	Finerenone	?Finerenone improved cardiovascular prognosis in patients with DM2 and stage 2 to 4 CKD with moderate albuminuria or stage 1 and 2 with strong albuminuria, compared to placebo

related conditions, such as heart failure,[24] due in part to the few studies of cardiovascular protection in patients with CKD.[25,26] For many years, studies in patients with CKD have been slow to develop[26] and patients with CKD have been routinely excluded from large CVD specific clinical trials.[26] Moreover, the lack of uniformity in the definitions of renal prognostic variables has impeded valuable information on the effects of CVD-specific treatments on renal prognosis.[27] Fortunately, these issues and the complexity of the CKD and CVD patient is leading to measures to standardise the definition of renal prognostic variables,[28] increasing the number of clinical trials focussing on the CKD patient, and initiatives are being launched to directly address the problem of CKD and CVD in clinical care, research and education.[29–31]

Another characteristic of CKD is that that excess vascular risk may be related to non-classical risk factors specific to CKD,[32] such as phosphorus, inflammation and the influence of the microbiome and uraemic toxins, with recent new developments that could offer new therapeutic targets. Recent evidence shows how phosphorus, apart from the classical concept of development of vascular calcifications, could impact the development of CVD and progression of CKD, acting through lipid metabolism[33] and renal fibrosis processes.[34,35] CKD is also considered a situation of chronic inflammation with activation of cytokines and oxidative stress, which influences vascular damage and the risk of vascular events[36] and new therapies focussing on this aspect could provide additional benefits.[37] Finally, substances that are considered uraemic toxins are products of intestinal bacterial metabolism that pass into the bloodstream and are eliminated renally. As kidney function declines, these products accumulate,[38,39] which is associated with the development of CVD[40,41] and they are postulated as a treatment target to improve the vascular prognosis of patients with CKD.[42]

Finally, coordinated action for the early detection of patients with CKD is required to implement these measures. In this regard, the ''Information and consensus document for the detection and management of chronic kidney disease'' has recently been published by the Spanish Society of Nephrology together with 9 other Scientific Societies related to the care of patients with CKD and CVD.[43] This document includes and updates the key concepts of the definition and classification of CKD, as well as recommendations for the coordinated treatment and management of these patients.

In short, CKD confers a very high risk of vascular events in the same way as FH, DM, or the presence of previous vascular events. Although there have been many difficulties in building evidence in the management of patients with CKD and CVD, important recent therapeutic developments in the management of classical CVRFs are revolutionising the management of these patients. The complexity of patients with CKD and CVD means we need to deepen our understanding of the mechanisms that mediate the CKD-CVD relationship and generate more evidence to overcome knowledge gaps. Moreover, a multilevel approach and coordinated multidisciplinary follow-up are needed in routine clinical management.

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