

Approaching the patient with CKD and associated comorbidities: how to choose the right treatment?

Chronic kidney disease (CKD) is among the leading causes of morbidity and mortality worldwide. Its prevalence in modern societies is rapidly increasing, this related to prolonged life span and more effective treatments of metabolic and heart disorders. Hence, nowadays CKD commonly occurs in individuals with coexisting comorbidities. The most common comorbid conditions associated with CKD are diabetes, hypertension and cardiovascular disease, which per se are already linked to adverse clinical outcomes. The co-occurrence of CKD and comorbidities with shared pathophysiology and/or pharmacological treatment prompts collaboration between different specialities, especially nephrologists, cardiologists and endocrinologists. These areas of expertise are often interconnected and the CKD population is an excellent example where different perspectives from these distinct fields interconnect for the ultimate benefit of the patient.

The right approach to a patient with CKD and hypertension, obesity or diabetes

The major treatment goal in CKD patients is to prevent disease progression and postpone dialysis. This is achieved by combining non-pharmacological and pharmacological interventions. The fundamental approach in all patients with CKD and diabetes, obesity and/or cardiovascular disease is focused on lifestyle modifications that simultaneously target all these conditions. Lifestyle interventions include optimizing one's diet, maintaining a healthy weight, promoting adequate physical activity, and encouraging cessation of tobacco consumption.

The mainstay of the pharmacological approach to CKD associated with diabetes and heart disease in the last decades has been renin-angiotensin-aldosterone (RAAS) inhibition. In this respect, the scenery has changed substantially with the recent introduction of sodium-glucose transporter 2 (SGLT2) inhibitors. The foremost metabolic effect of this class of drugs is modulating sodium-glucose transport proteins in the nephron to inhibit tubular glucose reabsorption and consequently lower glycaemia. Although originally designed for the treatment of diabetes, in large randomized clinical trials (RCT) these agents also displayed remarkable cardioprotective effects and soon became one of the main pillars of guideline-directed medical therapy in heart failure. Recently these medications also found their place in the nephrology and diabetes guidelines for slowing down the progression of diabetic kidney disease and the rate of cardiovascular events, and this seems to be, at least in part, independent of glycaemic control. Moreover, these agents were also shown to slow down the progression of estimated glomerular filtration rate (eGFR) decline in other kidney diseases.

Like SGLT2 inhibitors, glucagon-like-peptide-1 receptor (GLP1R) agonists are a class of medications initially utilized in the treatment of type 2 diabetes and obesity but were soon recognized to reduce the risk of all-cause mortality, cardiovascular mortality, and kidney failure, even regardless of their hypoglycaemic action. Hence, they are also indicated on the treatment of patients with type 2 diabetes and CKD or with atherosclerotic cardiovascular disease. Nevertheless, they should be cautiously used in older adults with type 2 diabetes in whom they can sometimes cause unintentional weight loss and aggravate frailty.

Finally, a novel non-steroidal mineralocorticoid receptor antagonist (MRA), which essentially regulate body fluid and electrolyte balance by antagonizing the aldosterone effects on renal tubules, also exhibited kidney and cardioprotective effects in large RCTs. These newer, selective, non-steroidal MRA may be associated with fewer adverse events as compared to traditional non-selective steroidal MRAs, spironolactone and eplerenone. These agents have now been introduced in multiple guidelines, including nephrology, endocrinology, and cardiology guidelines as well.

This new abundance of options to treat CKD, diabetes, and heart failure faced endocrinologists, cardiologists, and nephrologists with a predicament



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of whether to employ all these agents simultaneously from the very beginning of treatment or to exercise the traditional sequential approach. Experts agree that this decision should be patient-centred, and carefully weigh the risks and benefits in each case. Several currently ongoing clinical trials are exploring the effectiveness and safety of concomitant therapies and their result are expected to further elucidate this issue. In the CKD population, more advanced renal dysfunction and associated metabolic derangements preclude drug overuse and demand caution. The pragmatic approach in this specific group would probably rely on the careful introduction of new drugs on top of the RAAS blockade as eGFR declines. Post-hoc analyses suggest that the risk of hyperkalemia, as a much-feared side effect of RAAS inhibition and MRAs, can be potentially reduced by combining these agents with SGLT2 inhibitors, along with carefully tailored dietary restrictions and continuous patient education. Also, a noteworthy challenge is pill burden and the costs of these medications, which may hamper the desired course of action when choosing the optimal treatment approach.

The challenges in the assessment and management of patients with CKD, diabetes, obesity and hypertension

Overnutrition and obesity contribute to the development of interconnected maladaptive cardiovascular and kidney disease risk factors that include insulin resistance, hypertension, and dyslipidemia, constituting the Cardiovascular-Kidney-Metabolic Syndrome (CKS). The emerging pandemic of obesity in recent decades is accompanied by a steep rise in the number of patients with CKS. In this context, early identification of individuals at risk of developing CKS is becoming increasingly important as a tool to predict and timely address cardiovascular and renal issues and prevent complications.

SGLT2 inhibitors reduce body fat mass, including visceral fat, probably as a result of lipolysis in the adipose tissue due to the activation of gluconeogenesis. Nevertheless, initial hesitance in prescribing these agents to older frail adults has not been substantiated in clinical practice. More well-designed trials including representative cohorts of elderly patients and with long duration are still needed to elucidate the potential impact of SGLT2i on sarcopenia in older individuals. Meanwhile, based on the current knowledge, frailty should not necessarily limit the use of SGLT2i in the elderly population with T2DM.

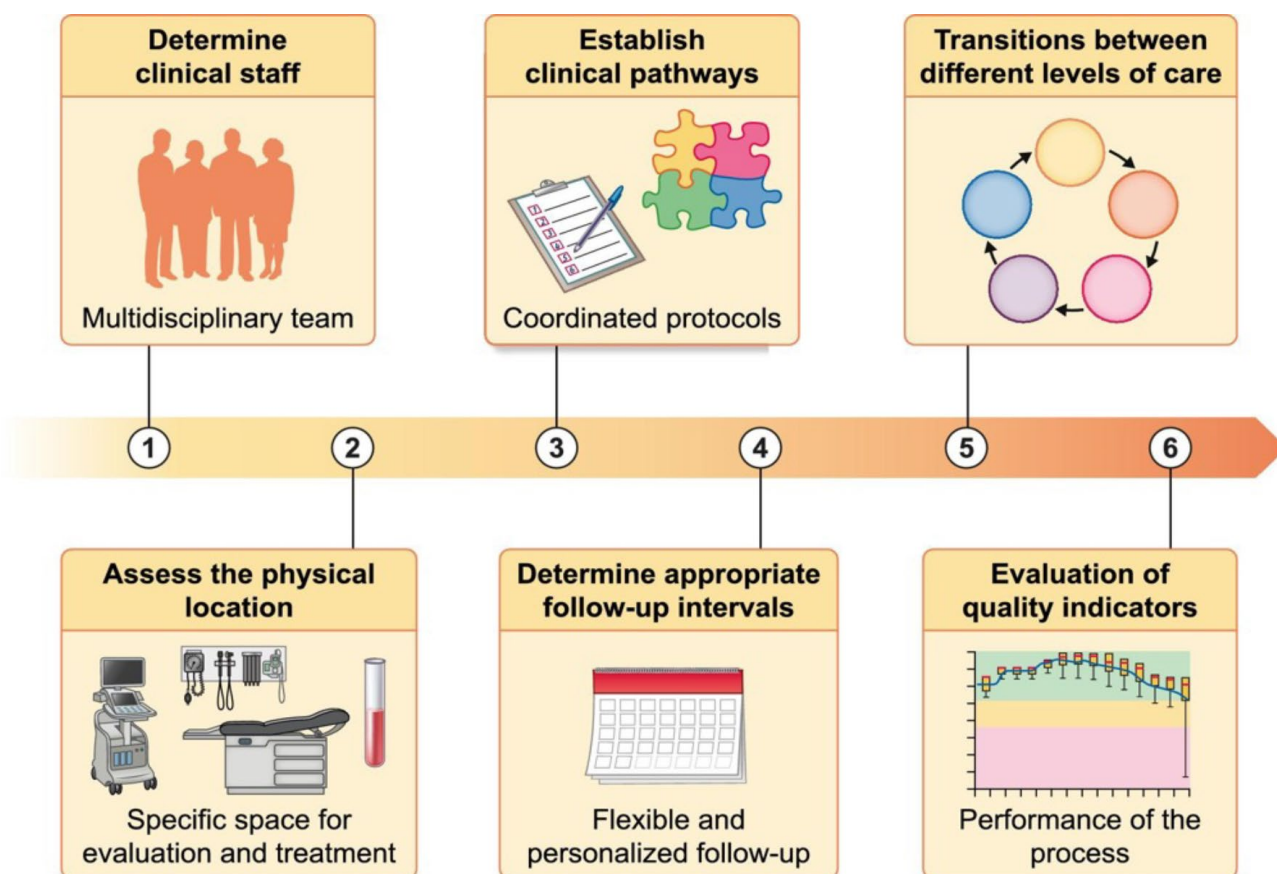


Figure 1.
Practical approach to establishing a cardiorenal unit

Patient education has become an integral part of effective disease management in all chronic diseases, especially in individuals with CKS. Cooperation from the patients and caregivers in adjusting their lifestyle to the new circumstances is essential for the outcome, but also a major challenge in the treatment process. There is a range of barriers preventing widespread implementation of comprehensive patient education, such as limited human resources, lack of time, limited health literacy and lack of readiness to learn and implement necessary changes. While modern technologies might help both health professionals and patients to track their engagement, building a trustful relationship between these two parties is still the cornerstone of achieving effective results.

Close collaboration is necessary among primary care providers or family physicians and the different specialists involved in the treatment of patients with multiple morbidities. There is a significant overlap in therapeutic goals and therapeutic strategies employed by nephrology, cardiology and endocrinology, and an organized team approach could improve patient care and satisfaction, and strive for optimal outcomes. At the same time, a joint approach could enable health professionals to learn from each other's expertise and optimize the utilization of healthcare infrastructure and resources. A recently published work by de la Espriella et al. presents a set of detailed practical points in the process of building up a facility for integrated cardiorenal care. The experiences from the Cardiorenal Unit in the University Hospital in Valencia and cardio-renal-metabolic clinics in the USA speak in favour of prioritizing such a multidisciplinary, coordinated and structured approach in the treatment of diabetic patients with CKD and cardiac disease. The recent published Cardiovascular-Kidney-Metabolic Health Advisory from the American Heart Association also addresses many of the points discussed above.

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All the speakers reviewed and approved the content*

KEY POINTS

- 1** The cardiovascular, kidney and metabolic systems are intricately linked.
- 2** Several new classes of drugs, including SGLT2 inhibitors and GLP-1 receptor agonists, are changing the landscape for the treatment of diabetes, obesity, heart failure and CKD.
- 3** Polypharmacy and patient education and adherence to therapy remain the challenges in the treatment of patients with cardiovascular-kidney-metabolic morbidities.
- 4** A coordinated institutionalized multidisciplinary approach to treatment of patients with coexisting metabolic, cardiovascular and kidney morbidity improves the effectiveness of care and patient outcomes.

Further readings

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5. Ndumele CE, Rangaswami J, Chow SL, et al. American Heart Association. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. *Circulation.* 2023 Oct 9. doi: 10.1161/CIR.0000000000001184.
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