Chronic kidney disease is no longer a 'non-traditional' cardiac risk factor: a call to action for cardiovascular-kidney-metabolic health

In their renowned text *Clinical Examination*, Talley and O'Connor[1] state that '*the cardiovascular system… is believed by cardiologists to be the most important system in the body*'. Patients with chronic kidney disease (CKD) would concur. Cardiac events are the most common cause of death in dialysis patients in Singapore.[2] At the same time, they face an accelerated mortality risk; for instance, a 30-year-old on dialysis has an annual mortality rate equivalent to that of an 85-year-old in the general population.[3] Severe cardiac dysfunction also impairs tolerance of life-sustaining dialysis therapy and disqualifies patients from the kidney transplant waitlist.

The increase in cardiovascular risk begins early in CKD. Even at a normal estimated glomerular filtration rate (eGFR) of 60–89 mL/min/1.73 m^2, a urine albumin–creatinine ratio (UACR) >1 g/g, compared to no albuminuria, increases cardiovascular mortality by 3.2 times. The combination of reduced eGFR 15–29 mL/min/1.73 m^2 and UACR >1 g/g increases mortality by 6.5 times, as compared to a patient with normal eGFR 60–89 mL/min/1.73 m^2 and no albuminuria.[4] In patients with CKD, the risk of cardiac death often exceeds that of end-stage kidney disease (ESKD); in the FLOW study, among patients with diabetes mellitus (DM) and a mean glomerular filtration rate of 47 mL/min/1.73 m^2, the risk of cardiac death was 1.6 times that of dialysis initiation (8.26% and 5.29%, respectively, over a median follow-up period of 3.4 years).[5]

Historically, CKD was considered a non-traditional cardiovascular risk factor[6] and omitted from major coronary risk scores.[7] In 2008, the relationship between cardiac and kidney dysfunction was first christened 'cardiorenal syndrome',[8] emphasising the bidirectional interaction between cardiac and kidney dysfunction. While it is an important first step from organ-specific management towards integrated holistic care, the concept of cardiorenal syndrome is usually only invoked when end-organ dysfunction occurs; it does not promote early intervention to prevent organ failure.

With the impetus for upstream intervention and with increasing understanding that CKD is a key pathway by which metabolic risk factors lead to cardiovascular disease,[9] in 2024, the American Heart Association issued a presidential statement on cardiovascular-kidney-metabolic (CKM) syndrome,[10] which conceptualised the mechanistic progression from dysfunctional adiposity (stage 1 CKM) to metabolic risk factors, including hypertension, DM, metabolic syndrome or CKD (stage 2), and then to subclinical (stage 3) and clinical (stage 4) cardiovascular disease. Chronic kidney disease was included as a cardiovascular risk factor in stage 2 CKM, and stage 4–5 CKD was deemed a cardiovascular disease equivalent. The accompanying PREVENT (Predicting Risk of cardiovascular disease EVENTs) equations included eGFR and UACR in the risk models for prediction of atherosclerotic cardiovascular disease and heart failure.[11]

Cardiovascular-kidney-metabolic syndrome highlights the complex pathophysiology leading to multiorgan dysfunction, including haemodynamic processes (e.g. volume expansion, neurohormonal activation), inflammatory and metabolic stressors (endothelial dysfunction, vascular calcification) and progressive fibrosis (myocardial remodelling, renal tubulointerstitial fibrosis).[12] While being imperfect — notably downplaying non-metabolic causes of CKD, such as glomerulonephritis and inherited kidney disease — CKM syndrome represents a major paradigm shift in promoting integrated care of CKM disease and early intervention targeting common pathophysiological pathways.

What can be done to mitigate the adverse consequences of CKM syndrome? Firstly, screen for CKD early, especially in patients with dysfunctional adiposity, metabolic risk factors or cardiovascular disease. The World Kidney Day 2025 theme, 'Are Your Kidneys OK? Detect Early, Protect Kidney Health', underlines this need.[13] Screening for CKD should include both eGFR and UACR,[14] as eGFR is relatively preserved in the hyperfiltration state of early CKD and UACR is independently associated with adverse outcomes. Greater awareness of combined testing is essential, as a large registry study of patients with type 2 DM (i.e. stage ≥2 CKM) identified that 48% of patients failed to receive guideline-recommended eGFR and UACR testing.[15] More recently, it has been suggested that expanding CKD screening to the general population above 35 years of age may be cost-effective.[16]

Secondly, institute antiproteinuric therapy in patients with CKD to reduce the risk of both renal and cardiovascular adverse outcomes. The four pillars of CKD management in the CKM era are: an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (but not both due to the increased risk of hyperkalaemia and acute kidney injury associated with combination therapy),[17] a sodium–glucose cotransporter-2 inhibitor, a nonsteroidal mineralocorticoid receptor antagonist (in patients with DM) and a glucagon-like peptide-1 receptor agonist (in patients with DM) [Table 1]. Other aspects of care include

Table 1. Pillars of CKD management in a cardiovascular-kidney-metabolic health era.

Pillar	Indications	Renal benefit	Cardiac and survival benefit
1. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (but not both) (e.g. lisinopril, losartan)	*DM or non-DM, with CKD*: albuminuria (UACR >30 mg/g), hypertension or heart failure. No GFR cut-off if able to tolerate	↓ GFR decline and ESKD,[21,22] even in advanced CKD[23]	↓ Mortality, hospitalisation for heart failure and myocardial infarction[24]
2. Sodium–glucose cotransporter-2 inhibitor (e.g. empagliflozin)	*DM or non-DM, with CKD*: eGFR ≥20, any UACR (stronger recommendation if albuminuric)	↓ Composite of death, ESKD and GFR decline[25,26]	↓ Mortality, hospitalisation for heart failure[27]
3. Nonsteroidal mineralocorticoid receptor antagonist[a] (e.g. finerenone)	*DM with CKD*: eGFR >25, UACR >30 mg/g[b], and K^+ <4.8 mmol/L *Non-DM with CKD*: off-label[a]	↓ Composite of death, ESKD and GFR decline[28]	↓ Composite of cardiac death, cardiac event, hospitalisation for heart failure[29]
4. Glucagon-like peptide-1 receptor agonist (i.e. semaglutide)	*DM with CKD*: eGFR >50+ UACR >300 mg/g or eGFR 25–50+ UACR >100 mg/g[b] *Non-DM with CKD*: consider for obesity	↓ Composite of death, ESKD and GFR decline[5]	↓ Major adverse cardiovascular event, mortality[30]

[a]Steroidal mineralocorticoid receptor antagonist (spironolactone) is indicated in patients with resistant hypertension or heart failure with reduced ejection fraction, with or without DM, and replaces nonsteroidal mineralocorticoid receptor antagonist. [b]On optimised doses of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. CKD: chronic kidney disease, DM: diabetes mellitus, eGFR: estimated glomerular filtration rate (mL/min/1.73 m^2), ESKD: end-stage kidney disease, GFR: glomerular filtration rate, UACR: urinary albumin/creatinine ratio

blood pressure control (target standard office systolic blood pressure <120 mmHg, regardless of DM status),[18,19] lipid-lowering therapy, weight management, physical activity, diet modification and smoking cessation.[14] Unfortunately, multiple patient, physician and system barriers hinder optimal CKD management; this is a wicked problem requiring complex interventions and policy decisions to unravel.[20]

Thirdly, individualise cardiac care in patients with CKD/ESKD. Avoid therapeutic nihilism ('renalism')[31] simply because of a patient's ESKD status. For instance, primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction demonstrated a comparable mortality benefit, regardless of dialysis dependence.[32] In contrast, upfront PCI in stage 4–5 CKD patients with stable coronary artery disease and moderate–severe ischaemia on stress testing failed to reduce the risk of death or myocardial infarction compared to a conservative strategy, but increased the risk of death or dialysis initiation.[33] Hence, careful patient selection is essential to optimise the balance between risks and benefits of certain treatments. In addition, prophylactic anticoagulation for atrial fibrillation has not been demonstrated to reduce thromboembolic risk in dialysis patients, but instead significantly increases bleeding complications,[34] violating *primum non nocere* and underscoring the caution warranted when extrapolating evidence from the general population to patients with ESKD.

Singapore has the second highest prevalence of ESKD on dialysis in the world,[35] highlighting a disproportionately high local burden of kidney disease. Early detection of CKD in patients with cardiac risk factors holds great promise to improve CKM health. Optimising and individualising evidence-based care would reduce the burden of CKD on our patients, our healthcare system and our nation. Happy World Kidney Day 2025!

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