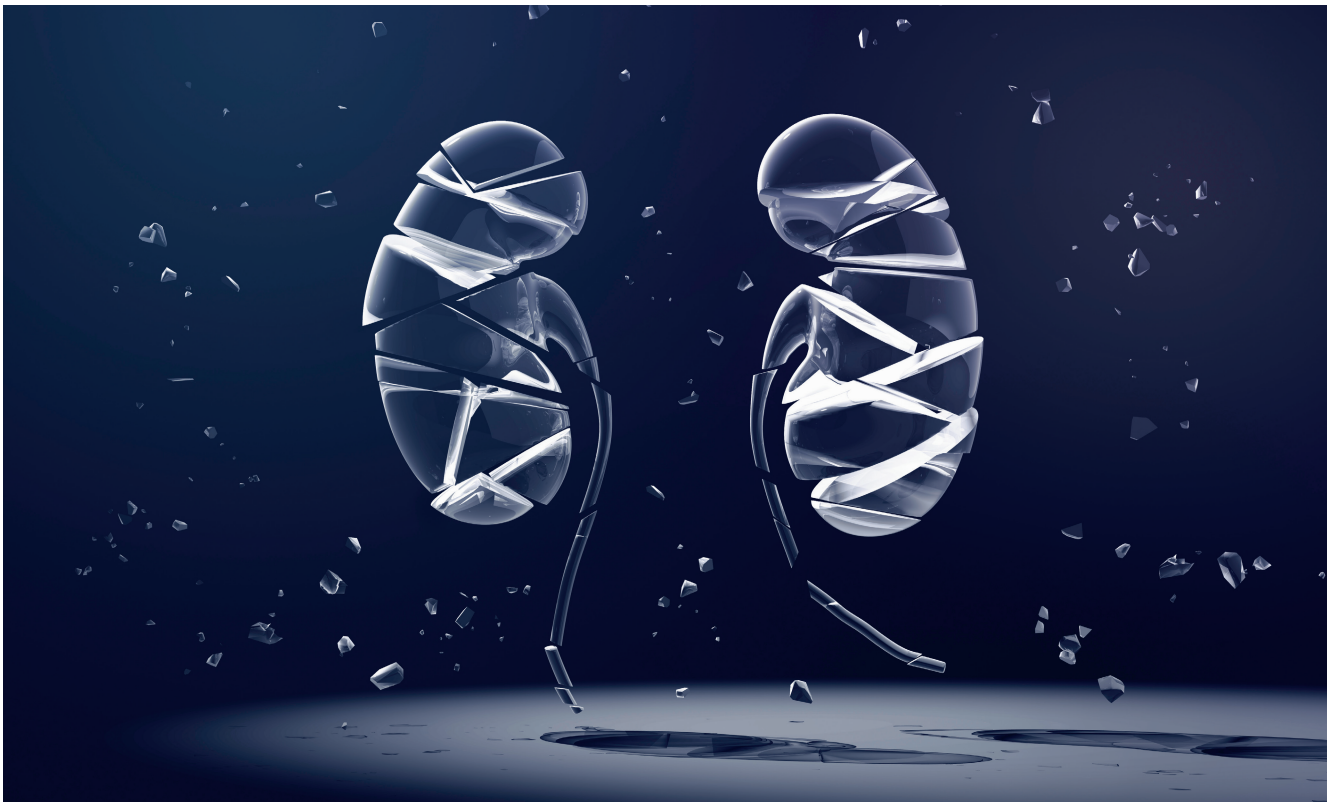
# CKD IS A HIDDEN THREAT

Early screening and cardio-renal drug combinations are key to **PREVENTING MORE DEATHS** from chronic kidney disease.



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▲ Chronic kidney disease often goes undiagnosed, magnifying cardiovascular risk in people with type 2 diabetes.

**The International Diabetes Federation estimates that around 537 million adults have diabetes.** It's well known that people with diabetes and CKD are at high risk for kidney failure, atherosclerosis, heart failure and premature death[1]. "What is often not recognized is that CKD itself is a hidden threat that magnifies cardiovascular risks in people with type 2 diabetes," says nephrologist Rajiv Agarwal of Indiana University School of Medicine.

The microvascular and macrovascular damage wrought by diabetes has similar effects in multiple organs. Glucose sits on structures in the kidneys and across the vasculature, damaging the endothelial lining. But even in the absence of diabetes, endothelial dysfunction in the kidney increases the risk of atherosclerotic lesions in the coronary arteries and stroke[2]. Patients with kidney disease are also likely to develop high blood pressure and stickier platelets that aggregate more aggressively, raising the risk of heart attack.

Left undetected or poorly controlled, CKD will ultimately progress to kidney failure, requiring dialysis or transplantation, but only if patients haven't first succumbed to cardiovascular disease.

"One problem is that kidney disease often goes undiagnosed," says Meike Brinker, global clinical leader at Bayer. Patients newly diagnosed with diabetes may already have early stages of kidney injury, even if they lack symptoms. "If you don't test for albuminuria [the presence of albumin in urine], you won't know if there's already damage. By the time symptoms start, it's almost too late."

New treatments that protect both heart and kidneys could change these outcomes, if used early enough, says Brinker. But despite progress in developing innovative treatments and revisions to international treatment guidelines[1] for CKD in diabetes, patients have often not received the recommended standard of care[3].

"Many people with early stages of kidney disease will die from cardiovascular disease," says Peter Rossing, a diabetologist and research leader at Steno Diabetes Center Copenhagen. "We need to focus on trying to prevent kidney disease or, if patients already have kidney disease, stopping its progression while managing excess cardiovascular risk."

This means more screening of people with diabetes for signs of early kidney injury, and a preventive approach combining cardio- and renal-protective drugs. It's a strategy that improves clinicians' chances of delaying the silent progression towards dialysis, kidney transplantation or cardiovascular death.

## THE IMPORTANCE OF KIDNEY SCREENING

A challenge in detecting and treating early kidney disease is its lack of specific symptoms. In later stages, patients may present with fatigue, oedema, profound proteinuria (protein in the urine), anaemia or cardiovascular symptoms such as hypertension. But these symptoms are common to other long-term conditions, so referral to a nephrologist often comes too late.

The urinary albumin-to-creatinine ratio (UACR) is the standard test for albuminuria, which suggests the kidneys aren't properly filtering the blood. It is a widely available and straightforward test, yet many health-care professionals use estimated glomerular filtration rate (eGFR) to measure kidney function rather than injury. Kidneys can appear to function within normal parameters even while ailing, so underlying kidney disease may be progressing before it's diagnosed.

What's more, until very recently, physicians had few effective and tolerable options to prevent kidney injury progressing, even if it was detected at an early stage.

"For 30 to 40 years, guidelines advocated measuring albuminuria in patients with diabetes to determine their risk of kidney disease, but back then we didn't have treatments to help them," recalls Agarwal. "You'd say to the patient, 'I'm sorry, you've got kidney disease and we can't do anything about it.' The field was stuck."

In recent years, however, the field has made significant progress to unstick itself.

## THE EVOLVING CKD TREATMENT LANDSCAPE

The conventional foundation of CKD treatment in diabetes was defined by glycaemic, lipid and blood pressure control. But in the twenty-first century, drugs emerged with novel mechanisms of action, providing clinicians with an updated cardio-renal toolbox.

In 2013, a new class of drugs called sodium-glucose cotransporter 2 (SGLT2) inhibitors saw its first approval from the US Food and Drug Administration (FDA) for the treatment of diabetes. These agents block reabsorption of glucose in the kidneys, leading to its excretion in urine, but an unexpected side benefit emerged in early trials. "The trials had positive outcomes for slowing CKD progression," says George Bakris, director of the University of Chicago Medicine's Comprehensive Hypertension Center. "They also slowed heart failure progression and reduced heart failure hospitalizations, too."

The past five years have seen further developments in the CKD treatment landscape. The mineralocorticoid receptor, which regulates electrolyte and water homoeostasis and plays a crucial role in the pathogenesis of cardiovascular and kidney disease[4], emerged as a pivotal target. Steroid-based mineralocorticoid receptor antagonists (MRAs) could successfully treat cardiovascular disease, but had side effects such as hyperkalaemia that limited their use[4,5]. In July 2021, the first non-steroidal MRA, finerenone — developed by Bayer — was approved by the FDA. Non-steroidal MRAs have kidney and cardiovascular protective benefits with fewer side effects than their steroid-based counterparts.

▲ Innovative treatments such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and mineralocorticoid receptor antagonists (MRAs) have protective benefits for both the kidneys and the cardiovascular system.

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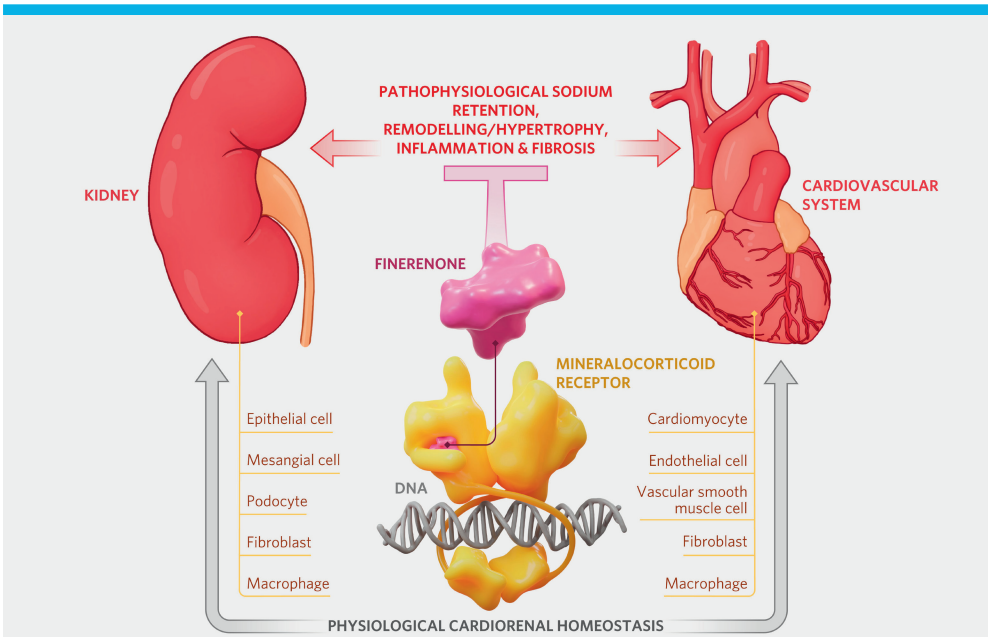
> "BACK THEN, WE DIDN'T HAVE TREATMENTS TO HELP CKD PATIENTS. THE FIELD WAS STUCK."

"We started to investigate finerenone in heart failure, but what we saw in addition was a profound proteinuria reduction that seemed to be related to benefits in clinical outcomes," says Brinker. "This prompted us to look into the CKD space as well as the heart."

Another approach in development is the use of glucagon-like peptide receptor 1 (GLP-1) agonists, which are indicated for type 2 diabetes. These work by activating pancreatic GLP-1 receptors to enhance insulin release, reduce glucagon, and lower blood glucose. GLP-1 agonists have reduced cardiovascular events in people with type 2 diabetes[6] and are being explored for their cardio-renal properties.

"Nephrologists now need to adopt the mindset of the cardiology community, using pillars of therapy," says Bakris, referring to the standardized pharmacological approach in patients with heart failure — in the case of CKD, the three treatment pillars are inhibitors of the renin–angiotensin system (RAS), SGLT2 inhibitors and non-steroidal MRAs. "The problem is nephrologists like me have never been taught to think like this."




Bayer: Adapted from Kolkhof, P., Joseph, A. & Kintscher, U. *Pharmacol Res.* https://doi.org/10.1016/j.phrs.2021.105859 (2021).

▲ Finerenone's mode of action counteracts mineralocorticoid receptor overactivation in the heart, vasculature and kidneys, thereby reducing cardiovascular and renal risk.

But Bakris believes with the advent of SGLT2 inhibitors, non-steroidal MRAs, and potentially GLP-1 agonists, clinicians can start to mix and match these agents to meet individual patient needs.

"We don't know what the single unifying mechanism is for this cardio-renal protection; there are at least 12 different mechanisms that these agents work by," Bakris explains. "But my hope is that we can use these drugs, subtract some other drugs used for hypertension, for example — as these agents do slightly lower blood pressure — and take advantage of the additional mechanisms they're offering to protect both the heart and the kidney."

## EXPLORING CARDIO-RENAL COMBINATIONS

At Bayer, the clinical development team behind finerenone is now exploring its use in combination with other agents. "We are exploring the simultaneous initiation of SGLT2 inhibitors and finerenone from a safety and efficacy perspective," says Brinker. "In cardiology, treatments are often initiated together or shortly after each other, and this is starting to happen in nephrology now, so it's important to generate data to support this."

Bayer's previous trials addressed two unmet patient populations with CKD and type 2 diabetes: those who had just been diagnosed with an early stage of kidney disease and already had increased cardiovascular risk, and a second, more advanced disease population, where the goal was to prevent both cardiovascular events and the decline in kidney function and need for dialysis. The team is now looking to build on this with studies in patients with CKD who do not have diabetes.

"Patients with diabetes have increased cardiovascular risk and therefore their kidney function is regularly checked," says Brinker. "But many more people, those with hypertension or other cardiovascular risk factors, likely already have kidney damage to some extent, the progression of which amplifies their excess risk of heart attack, stroke or heart failure."

## IMPLEMENTING THE STANDARD OF CARE

To achieve similar benefits to those seen in clinical studies, wider adoption of clinical guidelines is needed. While SGLT2 inhibitors have been included in international treatment guidelines for people with diabetes and CKD since 2018, only around 7% of these patients in the US are receiving these medicines, according to preliminary data[7] presented in a poster at the American Diabetes Association's annual conference in June 2022.

In fact, many people with diabetes and CKD are not even getting the first treatment pillar, RAS blockers. "There's a perceived risk that RAS inhibitors may cause kidney decline and they are associated with hyperkalaemia, but we know that even in people with late-stage kidney disease, if you stop these drugs it does more harm than good," says Agarwal. "The second issue is that even in the best centres, only about half of patients are having their UACR measured."

Other barriers to better treatment vary by country. In some regions, reimbursement is an issue, in others it's the cost of newer agents compared with older diabetes drugs, and/or the cost or availability of screening. Some public health agencies are pushing further in their quest for improved CKD outcomes. Rossing notes that in Denmark, the health system is establishing a nationwide network for monitoring screening and treatment of kidney disease.

Brinker believes the growing cardio-renal toolbox — and attentiveness to identifying patients in the earliest stages of kidney injury — could transform the treatment of this life-threatening disease. "Our hope is that the new medications will bring more awareness that patients can be treated earlier, and they are less likely to suffer from cardiovascular diseases and dialysis," says Brinker. "It's been frustrating from both a physician and patient perspective, but now there are more options to improve treatment of the disease." ■

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