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REVIEW

Evolving strategies for early diagnosis, proactive prevention and treatment of CKD

Alberto Ortiz [1,2,3], Motoko Yanagita [4,5], Hideki Yokoi [6] and Roser Torra [2,7]

[1]Department of Nephrology and Hypertension, Health Research Institute-Fundación Jiménez Díaz University Hospital, Universidad Autónoma de Madrid (IIS-FJD, UAM), Madrid, Spain
[2]RICORS2040-Renal, Madrid, Spain
[3]Departamento de Medicina, Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain
[4]Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[5]Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University, Kyoto, Japan
[6]Department of Nephrology, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan
[7]Nephrology Department, Fundació Puigvert, Institut de Recerca Sant Pau (IR-Sant Pau), Departament de Medicina, Universitat Autònoma de Barcelona, RICORS2040-Renal, Madrid, Spain
Correspondence to: Alberto Ortiz; E-mail: aortiz@fjd.es

ABSTRACT

Chronic kidney disease (CKD) is among the fastest growing global causes of death, forecasted to become the third leading cause of death in Western Europe and Japan by 2050. In contrast, mortality from cardiovascular disease is decreasing. Cardiovascular medicine is focused on identifying people at high risk and intervening to prevent cardiovascular events. The focus of kidney medicine has evolved over time. Last century the focus was on treating kidney failure by kidney replacement therapy (KRT). However, KRT outcomes are suboptimal. Life expectancy is up to 44 (women on dialysis) to 22 years (women with functioning kidney grafts) shorter on KRT than in the general population. The 21st century has witnessed an explosion of highly effective kidney-protective drugs that may both prevent and slow the progression of CKD while addressing the full cardiovascular–kidney–metabolic (CKM) syndrome spectrum, i.e. also improving cardiovascular and metabolic outcomes. However, these advances have met a barrier: 20th century concepts on whom to test for CKD, which focus on assessing albuminuria just in people with diabetes mellitus. This outdated concept limits early diagnosis and treatment in up to 80% of people who eventually develop kidney failure. Clinical trials suggest that starting kidney protective therapy because CKD was diagnosed based on albuminuria, when glomerular filtration rate is normal, may delay the need for KRT for up to nearly 3 decades, meaning that many older subjects would not require KRT. To improve outcomes, the next two steps in kidney medicine should involve the widespread adoption of the ABCDE (albuminuria, blood pressure, cholesterol, diabetes and estimated glomerular filtration rate) approach for early detection and treatment of CKM risk, followed by developing the concept of pre-CKD that may guide pharmacologic interventions targeted to prevent CKD, on top of healthy lifestyle measures for the entire population, not just for those at risk.

Keywords: albuminuria, chronic kidney disease, CKD screening, pre-CKD, primary prevention

THE IRRESISTIBLE ASCENT OF CHRONIC KIDNEY DISEASE (CKD) AS A MAJOR CAUSE OF DEATH

Chronic kidney disease (CKD) has long been unjustly overshadowed by other global health priorities, despite its significant global prevalence, estimated at near 850 million, and profound impact on public health, becoming the most common risk factor for coronavirus disease 2019 death [1–4]. The estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (UACR) thresholds used to diagnose CKD (eGFR <60 ml/min/1.73 m^2 or UACR ≥30 mg/g) are associated with an increased risk of progression to kidney failure requiring kidney replacement therapy (KRT), acute kidney injury, ischaemic heart disease, cerebrovascular and peripheral vascular disease, atrial fibrillation, heart failure, all-cause death and cardiovascular death [5]. However, in contrast to other major chronic diseases, whose impact on mortality is declining, CKD is consistently climbing in the global ranking of leading causes of death [6]. Population ageing, coupled with the increasing burden of overweight/obesity and diabetes, are increasing the burden of CKD within a wider cardiovascular–kidney–metabolic (CKM) syndrome framework [7]. In Japan and Western Europe, where life expectancy is longer, CKD will become the third leading cause of death within 25 years (Fig. 1A), while in Central and Eastern Europe, age-standardized death rates from CKD will increase by 23% to 40%, while for ischaemic heart disease and stroke the rates will decrease by ≈50% in all regions (Fig. 1B) [6]. These contrasting forecasts point out the path for improving kidney health outcomes and proving wrong the dire forecasts. This is a recipe as old as medicine itself, already coded almost 5000 years ago by one of history's first medicine books, the *Inner Canon of the Yellow Emperor* (*Huangdi Neijing*): focus on prevention and early intervention (Fig. 2) [8]. This may seem counterintuitive for a specialty born in the 20th century to treat kidney failure by providing KRT. However, life expectancy on KRT is up to 2 (transplantation) to 4 decades (women on dialysis) shorter than in the general population and dialysis is unsustainable and unaffordable on a global basis [9]. In contrast, cardiovascular medicine has focused on prevention and early treatment, defining

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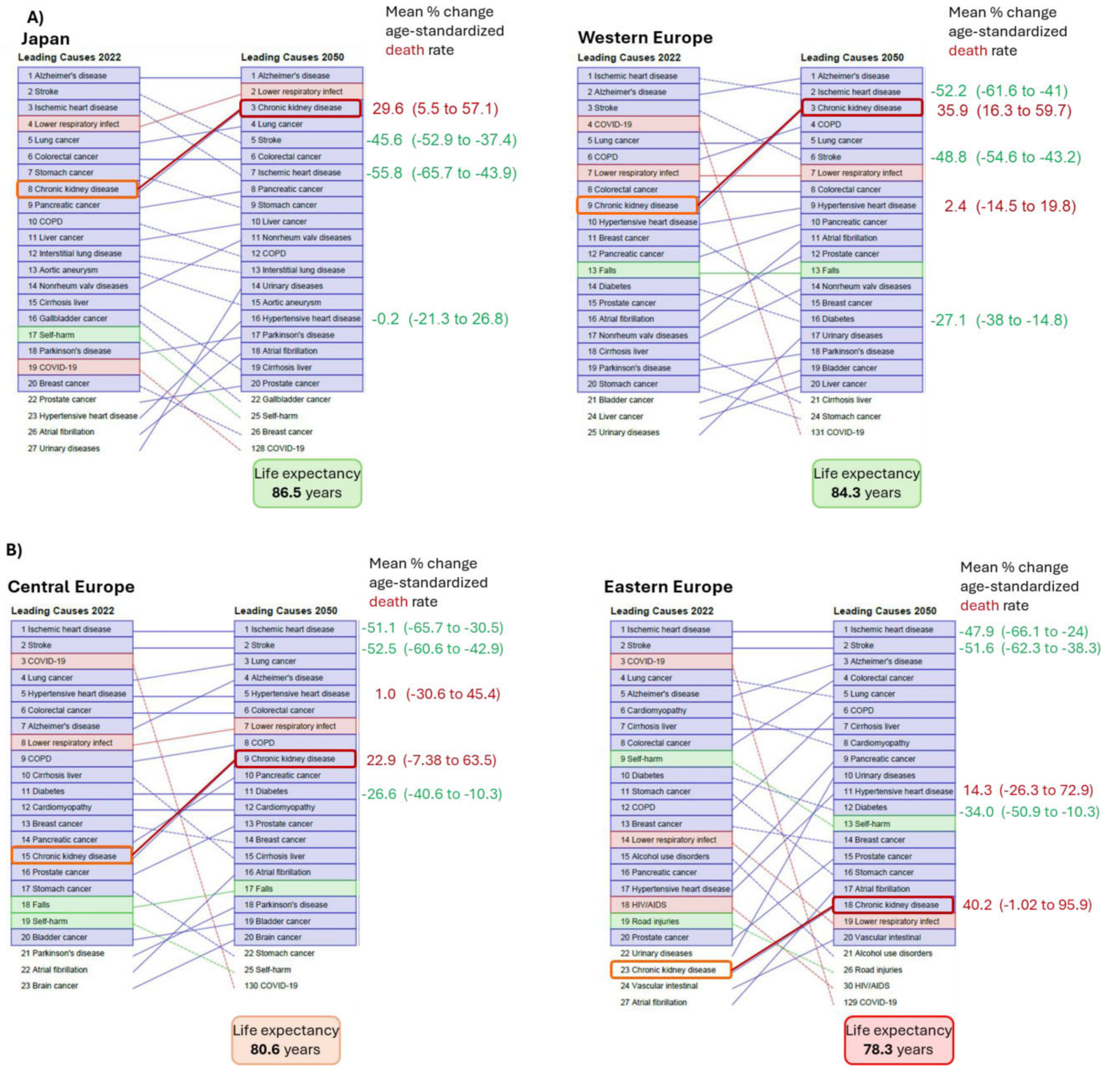


Figure 1: Global Burden of Disease (GBD) forecasts for causes of death by 2050 in Europe and Japan. Following GBD data sources, Europe was divided into Western Europe and Central and Eastern Europe due to differences in the epidemiology of multiple diseases. Numbers represent mean percent change with 95% confidence intervals from 2022 to 2050 in age-standardized death rates for CKD, diabetes and key cardiovascular causes (ischaemic heart disease, stroke and hypertensive heart disease) among the top 20 causes of death. Life expectancy is shown for 2050, calculated as the mean life expectancy for men and women. **(A)** In regions with long life expectancy, like Japan and Western Europe, CKD is forecasted to become the third leading cause of death by 2050. **(B)** In Central and Eastern Europe, forecasted 2050 life expectancy is shorter and CKD is forecasted to rank lower as a cause of death. However, deaths from CKD are forecasted to increase 23–40%, in the same range as in Japan and Western Europe. Note that in all regions shown, other components of CKM syndrome deaths are forecasted to decrease by 27–56% (diabetes, ischaemic heart disease, stroke) or remain stable (hypertensive heart disease). Data obtained from GBD 2021 Forecasting Collaborators [6].

conditions (hypercholesterolaemia, hypertension) that should be treated to prevent cardiovascular disease (CVD) before it happens (primary prevention) [10]. More recently, the range of conditions that should be identified and treated for primary prevention of CVD expanded to include diabetes and CKD, as echoed by the European Renal Association (ERA) Council [11] and National Scientific Societies [12]. This novel concept was summarized in an ERA call to action to implement the ABCDE [albuminuria, blood pressure (BP), cholesterol, diabetes and estimated glomerular filtration rate (eGFR)] approach of primary prevention of CVD and early diagnosis and treatment of CKD, prediabetes and diabetes [13] (Fig. 3).

We first discuss the immediate need to implement the long-neglected necessary changes that facilitate the early diagnosis and treatment of CKD. As this is achieved, work should start towards implementing primary prevention of CKD by defining a category of very high risk of CKD, potentially labelled pre-CKD [14]. The pre-CKD concept would imply the need for specific pharmaceutical treatment aimed at preventing the development of CKD, to be prescribed on top of the treatment for any other risk factors, and of lifestyle measures that should be universal, independent of CKD risk or presence. Indeed, societies should make the necessary changes to education pathways so a healthy lifestyle is adopted population-wide from childhood [15].

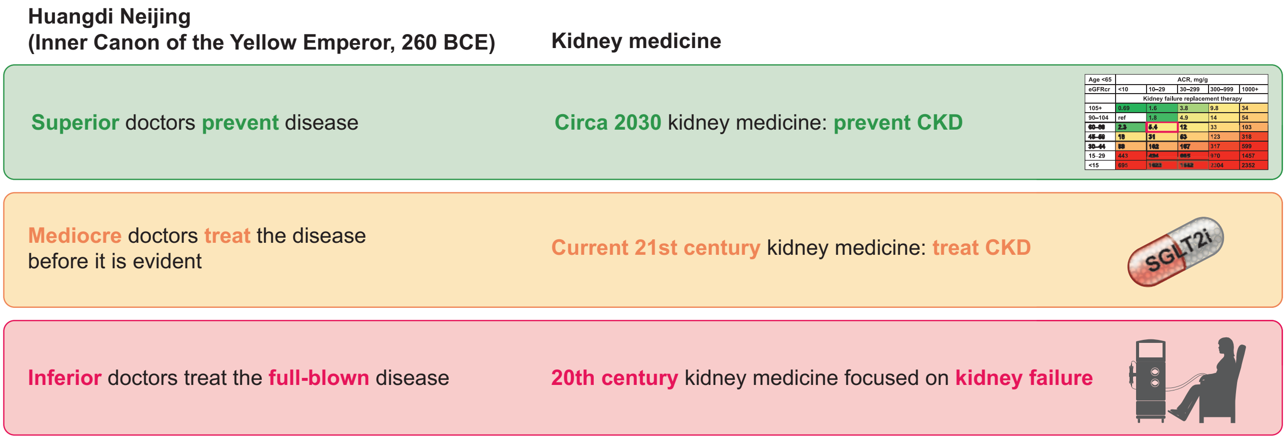


Figure 2: Forgotten lessons from older textbooks that should be applied to the kidney medicine of the 21st century. In 2025 we have the tools to diagnose (albuminuria, among others) and treat CKD (RAS blockers, SGLT2 inhibitors, non-steroidal MRAs, statins, GLP-1 receptor agonists) when diagnosed before the eGFR is <60 ml/min/1.73 m^2. However, their global uptake is suboptimal. While current guidelines on early diagnosis and treatment of CKD are implemented, work should start on defining a novel condition of very high risk for CKD that merits pharmacological treatment to prevent CKD. This novel condition may be termed pre-CKD, in an easy-to-grasp analogy to prediabetes, and should be carved out of the current KDIGO category of low risk (green cells in the KDIGO heatmap: no CKD according to eGFR and UACR values).

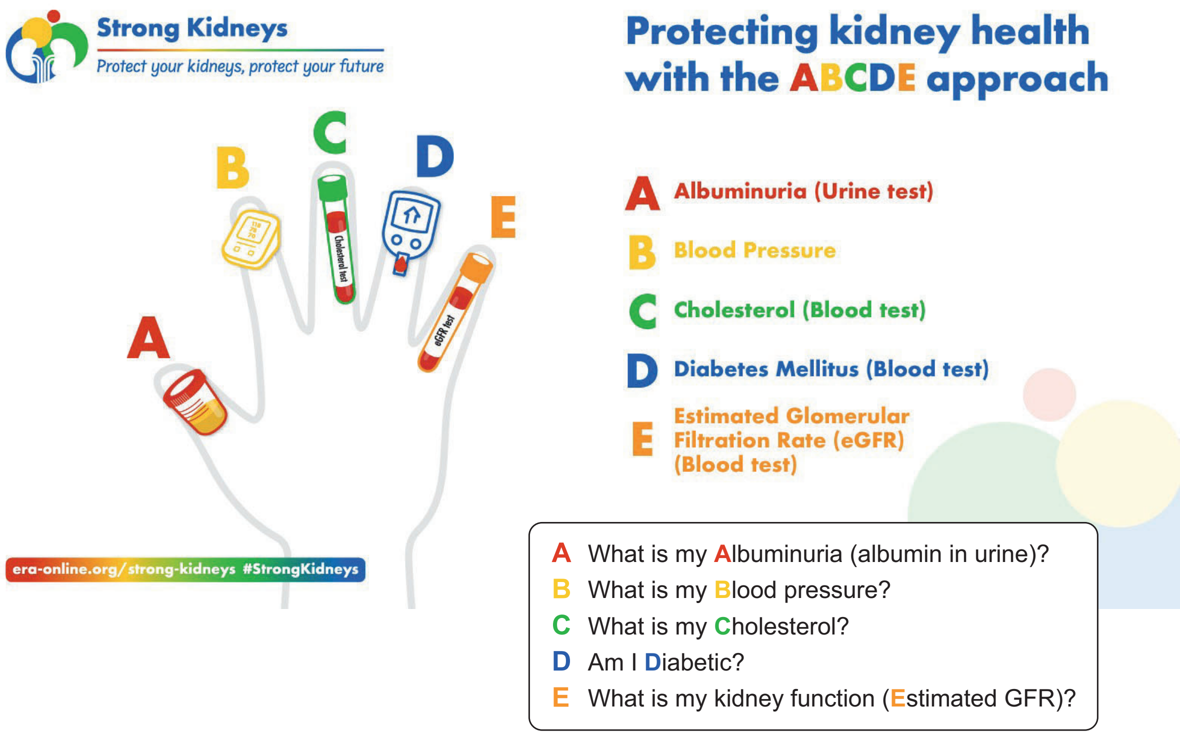


Figure 3: The ABCDE framework for assessment of CKM syndrome. This framework focuses on items that usually only the healthcare system can provide through urinalysis, physical exam and blood sampling to diagnose CKD, hypertension, hypercholesteraemia or diabetes (glycaemia). Each of these conditions requires a specific pharmacologic approach to improve cardiorenal outcomes in addition to universal lifestyle changes applicable to the entire population [13]. Other items, such as smoking history or weight to assess body mass index, are usually known by healthcare users without needing the intervention of healthcare workers.

AS EASY AS ABCDE: IMPLEMENTING A HOLISTIC APPROACH TO CKM HEALTH

The ABCDE approach [11–13] focuses on one urine test, one physical exam feature and three blood analytes that allow correctly fitting individuals into major categories in the CKM spectrum requiring specific drug interventions for the primary prevention of CVD, according to the 2021 European Society of Cardiology (ESC) guidelines [10]. There is a need for immediate action, since people dying from CKD or needing KRT by 2050 may already have diagnosable and actionable early CKD or may benefit from CKD prevention. The ABCDE approach may also increase awareness about the significance of CKD, as it is currently vastly underdiagnosed [16]. Among >50 000 primary care patients in Sweden selected

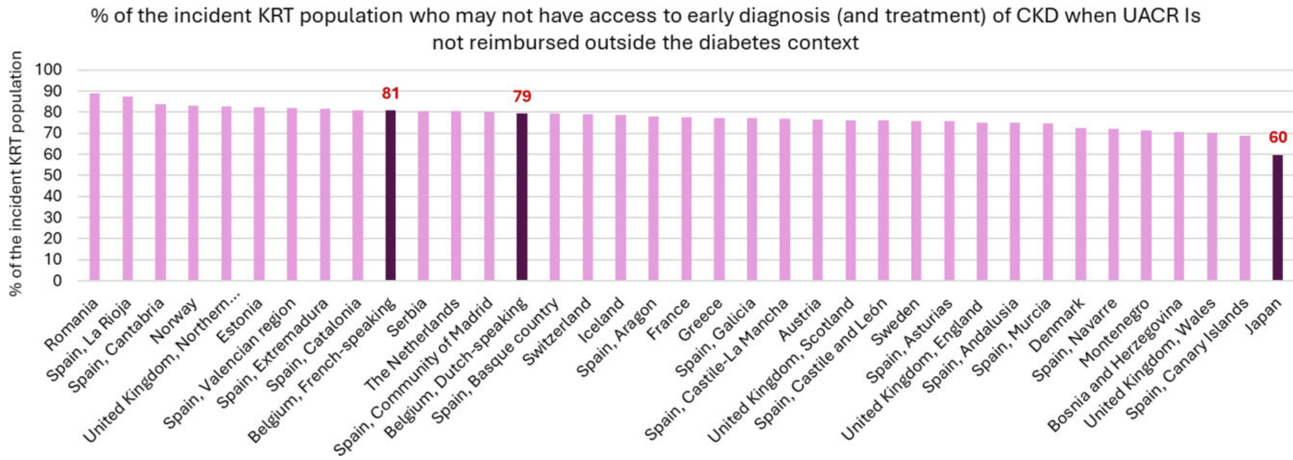


Figure 4: Incidence of non-diabetic kidney disease as a cause of kidney failure in ERA Registry countries in 2022 and in Japan in 2021. Data are expressed as a percentage of the population initiating KRT whose primary renal diagnosis was not diabetic kidney disease. This provides an estimate of individuals who may not be identified as having CKD before GFR is <60 ml/min/1.73 m^2 in the absence of albuminuria testing, unless they develop other diagnostic features of CKD, such as proteinuria or polycystic kidney disease diagnosed by imaging. Belgium and Japan are colour-coded, because in these countries albuminuria testing is not reimbursed outside the diabetes context. Data obtained from Boenink *et al.* [23] and Hanafusa *et al.* [24].

because they had CKD G3–G5, CKD was the least commonly coded major diagnosis in electronic health records and uncoded patients were more exposed to nephrotoxic drugs [17].

Of the ABCDE components, BP is part of every physical exam, while serum cholesterol, glycaemia and creatinine are frequently part of blood tests. Each of these components allows diagnosing a condition (hypertension, hypercholesterolaemia, diabetes, CKD) that has a treatment that improves health and decreases the risk of CVD and death [10, 18, 19]. They may even diagnose a condition, prediabetes, that allows intervention for the primary prevention of a more severe condition, diabetes [20]. The problem is that a CKD diagnosis based on eGFR values is a late diagnosis: the kidneys have already lost roughly half of their functional mass at this stage and the risk for CKD progression and death is thus much higher, despite current interventions, than the risk conveyed by CKD with preserved CKD [14].

ALBUMINURIA TESTING IS REGRETTABLY UNDERUSED

In contrast to other ABCDE components, uptake of albuminuria testing is very low. Despite guidelines dating back >20 years, the UACR screening rate is ≈35% in diabetes and 4% in hypertension without diabetes [21]. The ratio of undetected (due to lack of screening) to detected CKD diagnosed based on UACR ≥30 mg/g was estimated at 1.8 in diabetes and 19.5 in hypertension [20]. Furthermore, among those with ACR <30 mg/g, the median 5-year incidence of ACR ≥30 mg/g across cohorts was 24% in diabetes and 22% in hypertension: these new-onset cases of CKD would also be missed if albuminuria is not monitored [20].

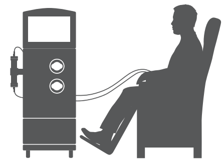
A recent audit of hospital care users disclosed that 23–43% had assessments for BP, cholesterol, glycaemia and creatinine in electronic health records, but only 1% were tested for albuminuria [22]. Moreover, albuminuria was the only cardiovascular risk factor assessed less frequently in women than in men, identifying albuminuria as a contributor to gender inequality in cardiovascular risk and CKD assessment despite the greater impact of kidney failure on life expectancy in women [9]. There are multiple actionable barriers for the low uptake of albuminuria that should be individually approached, as they may be country specific. In Japan and Belgium, albuminuria is not reimbursed outside the diabetes context, depriving 60–80% of the population ultimately needing KRT of a means for early diagnosis and treatment of CKD that may prevent or delay KRT [23, 24] (Fig. 4). When albuminuria is not reimbursed, proteinuria is used as an alternative. Issues associated with this practice include delayed diagnosis of CKD and, outside nephrology, confusion between albuminuria and proteinuria reference values and meaning. CKD is associated with a loss of urine concentrating ability. Thus urinary proteins may be diluted and protein dipstick may not be sensitive enough to detect early kidney injury. Furthermore, the bulk of urinary proteins are tubule-secreted proteins such as uromodulin and epidermal growth factor. As tubular mass decreases, urinary excretion of these proteins may decrease [25, 26], while albuminuria increases. As a result of these diverging trends, total proteinuria may remain roughly stable despite progressive kidney injury. There is additionally a lack of awareness among physicians of the fact that CKD can be diagnosed based solely on albuminuria values, of the clinical implications of high albuminuria values, their pathogenic link to accelerated biological aging and CVD and the range of therapeutic options available to decrease albuminuria and improve outcomes. Finally, neither the general public nor health authorities are usually aware of albuminuria and its low cost and significance. Universal screening for certain types of cancer that contribute less than CKD to overall mortality (Fig. 1) is offered by some healthcare systems. However, testing methods for cancer screening may be more expensive than albuminuria or require additional, invasive confirmation, while albuminuria is already a diagnostic criterion for CKD. While patients frequently ask about their BP or serum cholesterol values, they usually do not ask about nor know how to interpret albuminuria values.

ALBUMINURIA IS AN ACTIONABLE CRITERION FOR THE DIAGNOSIS OF CKD AND OF CKM RISK

CKD is defined by a decrease in eGFR to levels <60 ml/min/1.73 m^2 or by the presence of markers of kidney damage such as albuminuria, urine sediment abnormalities, electrolyte or other disorders due to tubular dysfunction and histologic and structural

A

Up to **5.4** tickets for the lottery of KRT in patients not meeting eGFR nor UACR criteria to diagnose CKD



Age <65	ACR, mg/g				
eGFRcr	<10	10–29	30–299	300–999	1000+
	Kidney failure replacement therapy				
105+	0.69	1.6	3.8	9.8	34
90–104	ref	1.8	4.9	14	54
60–89	2.3	5.4	12	33	103
45–59	18	31	53	123	318
30–44	88	102	167	317	599
15–29	443	424	605	970	1457
<15	695	1023	1582	2304	2352

Age 65+	ACR, mg/g				
eGFRcr	<10	10–29	30–299	300–999	1000+
	Kidney failure replacement therapy				
105+	6.4	13	17	61	123
90–104	ref	1.6	3.2	9.0	34
60–89	1.7	2.6	5.9	14	47
45–59	5.8	7.5	17	43	84
30–44	18	22	42	97	182
15–29	106	121	185	344	584
<15	541	607	952	1306	1569

B

Up to **103** tickets for the lottery of KRT in patients not meeting eGFR criteria to diagnose CKD

Figure 5: KDIGO heatmaps for risk of kidney failure requiring KRT. Heatmaps are shown for ages <65 years and ≥65 years. In this figure, risk has been equated to the number of tickets for the lottery of KRT. The reference would be 1 lottery ticket. Note that the number of tickets conferred by a diagnosis of CKD based on an eGFR <60 ml/min/1.73 m^2 or UACR >30 mg/g is higher for younger people. However, the reference risk is higher for older people. Thus the absolute risk of KRT is higher for older people. **(A)** When GFR is >60 ml/min/1.73 m^2 and UACR is <30 mg/g, patients are not considered to have CKD based on these parameters. However, note that the number of lottery tickets may already be as high as 5.4 for individuals with an eGFR of 89 ml/min/1.73 m^2 and a UACR of 10 mg/g. **(B)** When GFR is >60 ml/min/1.73 m^2, patients are not considered to have CKD based on eGFR. If albuminuria is not tested, we may miss, and not treat, persons with >100 tickets for the lottery of KRT unless proteinuria is assessed and correctly interpreted. Data obtained from the Writing Group for the CKD Prognosis Consortium [5].

abnormalities persisting for >3 months [27]. Additionally, eGFR categories (G1–G5) and albuminuria categories (A1–A3) allow risk stratification and tailoring of management strategies. Progressing CKD categories correlate with increasing risks of disease progression, along with premature all-cause and cardiovascular death. However, there is less awareness that CKD associated with high cardiovascular risk can be present even in persons exhibiting normal GFR (≥90 ml/min/1.73 m^2) if they have a UACR >30 mg/g (A3). Albuminuria is associated with an increased risk of death in a linear manner from UACR 2 mg/g and the greatest increase in absolute risk is observed in those >75 years of age [28]. Note that 2 mg/g is well below the threshold of 30 mg/g used to diagnose CKD. In this regard, the diverse risks associated with a diagnosis of CKD increase when eGFR becomes lower but also when UACR increases, even if eGFR remains stable. This is illustrated in Fig. 5. The risk of kidney failure is represented as lottery tickets for this adverse outcome, as a means of increasing awareness. Note that GFR and albuminuria values that are not diagnostic of CKD are already associated with an increased risk of KRT (Fig. 5A), as discussed below for CKD prevention. Additionally, GFR values that are not diagnostic of CKD may be associated with up to ≥100 tickets for the lottery of needing KRT during a lifetime when albuminuria is high (Fig. 5B). If albuminuria is not assessed, these patients will lose the opportunity for early intervention aimed at reversing albuminuria and associated cardiovascular risks and stabilizing GFR at non-CKD levels [5]. To improve outcomes, the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on CKD recommend considering up to four drugs for the treatment of high-albuminuria patients: renin–angiotensin system (RAS) blockers, sodium–glucose co-transporter 2 (SGLT2) inhibitors, statins and, for people with type 2 diabetes, non-steroidal mineralocorticoid antagonists [27]. Based on the results of recent clinical trials, glucagon-like peptide-1 (GLP-1) receptor agonists will soon be added to this list [29]. Thus albuminuria, by itself, even if all other ABCDE components are normal, allows the diagnosis of a condition (CKD) that requires treatment to delay the need for KRT and improve survival. This concept does not differ from the concept that high glycaemia values, by themselves, even if all other ABCDE components are normal, is diagnostic of a condition, diabetes mellitus, that requires treatment to delay the

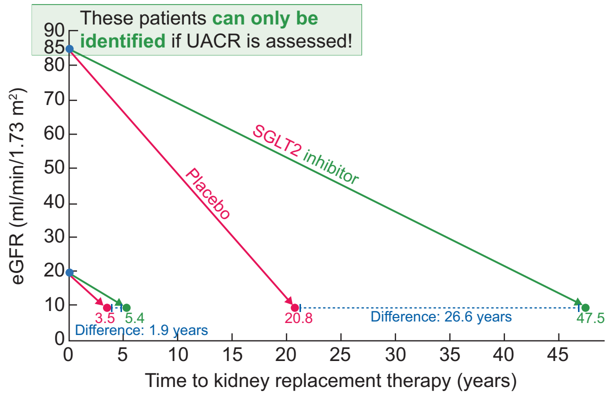


Figure 6: Hypothetical transformation of chronic eGFR slopes into time to kidney failure in the EMPA-KIDNEY trial. Hypothetical lines have been traced starting from baseline eGFR values within the inclusion criteria range to eGFR 10 ml/min/1.73 m^2, a point where KRT may be needed, corresponding to chronic eGFR slopes of participants on placebo and on empagliflozin obtained from the EMPA-KIDNEY Collaborative Group [30]. In the clinical trial, the two CKD inclusion criteria were low eGFR or high albuminuria values. Thus patients with an eGFR of 85 ml/min/1.73 m^2 were only enrolled if they had high albuminuria values. The model assumes that patients will live up to the point where they need KRT and that the chronic eGFR slopes observed during the trial will remain stable over time. Figure adapted from Fernández-Fernandez *et al.* [31].

need for KRT and improve survival. We thus do not understand why albuminuria is not tested in as many people as glycaemia. Indeed, only albuminuria testing allows identifying individuals with CKD and an eGFR of 85 ml/min/1.73 m^2, such as those participating in randomized clinical trials, whose eGFR slope under SGLT2 inhibitors suggests that the need for KRT may be delayed by nearly 3 decades as compared with patients on placebo (Fig. 6). In contrast, a later start of therapy, when eGFR has already decreased to advanced CKD, may delay KRT by <2 years (Fig. 6) [30, 31].

A further question is what links albuminuria to CKD progression or CVD. For many years it was thought that albuminuria was a consequence of CVD. Thus neither assessment of albuminuria nor treatment of albuminuria were deemed necessary because preventing and treating CVD should be the approach. Recent clinical trials have made it clear that RAS blockers, mineralocorticoid receptor antagonists (MRAs), SGLT2 inhibitors or GLP-1 receptor agonists share an anti-albuminuric effect in addition to providing cardiovascular and kidney protection [27, 29, 33, 34]. In mediation analysis, albuminuria reduction induced by a non-steroidal MRA mediated 84% and 37% of the treatment effect on the kidney and cardiovascular outcomes, respectively [34]. This clinical observation is well aligned with recent pathophysiology advances.

A pathophysiological connection between albuminuria and CKD progression may depend on proteotoxicity for proximal tubular cells. The fact that there is albuminuria means that the capacity of proximal tubular cells to reabsorb albumin has been exceeded, i.e. that massive albumin reabsorption has reached toxic levels for tubular cells. This triggers a stress response characterized by release of pro-inflammatory mediators that suppress production of the anti-ageing protein Klotho downstream from the nephron, as well as in the loss of their own capacity to produce Klotho, a tubular function [35, 36]. Klotho is a key component of the gerosuppressor function of the kidneys. Klotho deficiency causes premature aging in mice, characterized by bone disease, cardiovascular calcification, left ventricular hypertrophy and cardiac fibrosis [37]. Thus the albuminuria-induced loss of a single kidney function (Klotho production), a function that we do not measure in the clinic and that predates the loss of GFR and accumulation of uraemic toxins [35], already reproduces the cardiovascular phenotype of CKD. This preclinical observation is consistent with the results of clinical trials of kidney protective anti-albuminuric medications. Interestingly, anti-albuminuric kidney-protective drugs such as SGLT2 inhibitors and MRA restore Klotho production [38, 39] and Klotho deficiency promotes hyperaldosteronism [40]. When eGFR decreases, accumulation of uraemic toxins and secondary events such as post-translational protein modifications may further increase the severity of CVD and accelerate aging [41].

PRACTICAL APPROACHES TO INCREASE ALBUMINURIA TESTING UPTAKE

Looking backwards, >20 years of guidelines recommending albuminuria testing in people with diabetes mellitus or hypertension and 13 years of albuminuria thresholds being part of the CKD definition [42] have had a suboptimal impact on albuminuria testing uptake. The list of >20 risk conditions that merit albuminuria testing according to the 2024 KDIGO CKD guidelines is not helpful [27], as it is too complex for primary care physicians to incorporate into routine clinical practice. Novel approaches are needed. The Spanish Society of Nephrology incorporated age >60 years (surprisingly, not listed by the KDIGO despite being the main risk factor for CKD and kidney failure) as a trigger for CKD screening (which includes albuminuria testing) [43]. This captures a key segment of the primary care population in an easy-to-remember manner that is larger than those encompassed by the 20 risk factors listed by the KDIGO. In some primary care environments, 80% of the population has a reason to test for albuminuria when age is included. This may facilitate a shift from a by-default 'not testing for albuminuria' approach to a by-default 'testing for albuminuria', except if people are <60 years of age, not diabetic, not hypertensive or other. A by-default 'testing for albuminuria' framework may facilitate the implementation of albuminuria testing. Alternatively, prompts generated by electronic health records may increase the uptake of albuminuria testing, the so-called active laboratory approach [44]. Incorporating semiquantitative UACR into an automated urinary dipstick is a low-cost alternative that can help to increase albuminuria testing rates and decrease costs, as quantitative UACR is only performed above certain semiquantitative UACR thresholds [45]. Finally, age-associated universal testing for albuminuria, an approach that has been found to be cost-effective [46, 47], could imitate cancer screening drives or be linked to colon cancer screening (PREVE-COLON), an approach, termed PREVE-KIDNEY, that is being pilot tested in a Madrid healthcare catchment area. In addition to identifying patients who may benefit from early treatment, these initiatives will increase awareness about CKD in the general population [48]. Japan has adopted a comprehensive, life stage–based approach to kidney disease screening through school urinary testing in students [49], workplace health checkups in the working-age population and government-mandated Specific Health Checkups (SHC) for adults ages 40–74 years. This nationwide strategy has been associated with a reduced incidence of kidney failure, with recent evidence associating higher SHC participation with significantly lower kidney failure rates [50]. Overall, a combination of the Japanese SHC and European ABCDE approaches may be optimal, implementing a Healthy Adult ABCDE periodic checkup modelled along the lines of Healthy Child checkups and aimed at preventing cardiac, renal and metabolic conditions.

PREVENTION IS THE KEY

While early diagnosis is key to preventing progression of CKD and related complications, a better approach would be to prevent CKD, as emphasized by the KDIGO Controversies Conference on Maintaining Kidney Health and Preventing CKD [14]. CKD is unique among diseases in the CKM spectrum in that current guidelines do not address prevention [27]. Cardiovascular medicine has full guidelines devoted to pharmacological primary prevention [10]. Diabetes guidelines contain the prediabetes concept and provide guidance on pharmacological prescriptions to prevent its progression to diabetes [20]. Overweight may be treated pharmacologically to prevent obesity and improve cardiovascular outcomes [51]. It is key to increase awareness that strict BP control decreases the incidence of stroke but not of kidney failure [52] and that not all antidiabetic drugs equally maintain kidney health [54, 55]. Randomized controlled trials and real-world evidence indicate that SGLT2 inhibitors and GLP-1 receptor agonists may prevent CKD in people with type 2 diabetes mellitus and, for GLP-1 receptor agonists, in people with overweight/obesity [32, 53–56]. Since not all antidiabetic drugs offer the same degree of kidney protection and intensive BP control does not protect the kidneys and may even be detrimental, it is not enough to treat risk factors such as hypertension or diabetes.

Developing the concept of pre-CKD would be a great leap forward. This would apply to people with preserved GFR and UACR below the CKD diagnostic thresholds but with a high risk of kidney failure (Fig. 5B), corresponding to the concept of the blind spot of CKD [57]. These people are already down the path to develop CKD but do not yet meet CKD diagnostic criteria and, according to current CKD guidelines, are not offered kidney or cardiovascular protection despite evidence from >20 000 participants in cardiovascular safety clinical trials in type 2 diabetes mellitus that SGLT2 inhibitors halve the risk of incident CKD [53–55]. Developing the concept of pre-CKD will spur the design of clinical trials aimed at testing CKD prevention approaches that extend beyond the diabetes context, in addition to facilitating a chapter on pharmacological prevention of CKD in guidelines on diabetes mellitus and CKD. For example, people <65 years of age with an eGFR of 60–89 ml/min/1.73 m^2 and a UACR of 10–29 mg/g have a 5.4-fold higher risk of developing kidney failure than people with an eGFR >90 ml/min/1.73 m^2 and a UACR <10 mg/g. They may represent the starting point to define pre-CKD. The CKD Prognosis Consortium has developed prediction models of CKD progression that incorporate albuminuria and other clinical features and identify individuals with a high risk of future development of CKD [58]. Risk above a certain threshold may also be considered to develop the concept of pre-CKD. Using this prediction model, 1.0 million American adults without CKD had a high risk of developing CKD. Additionally, 1.5 million more people with a high risk of progression had CKD diagnosed based on a high UACR with a normal eGFR would not have been candidates for albuminuria testing if this was limited to people with diabetes [59].

COST-EFFICACY CONSIDERATIONS

Medical costs are variable from country to country and are better understood by focusing on a single country. In Spain, the cost of opportunistic albuminuria testing (e.g. adding albuminuria to other laboratory prescriptions in the primary care setting) is €0.5, meaning an investment of €0.001/day if performed annually. If positive, the follow-up test would be repeat albuminuria testing after 3 months, i.e. an overall investment of €1 can diagnose a treatable condition, CKD. For perspective, the cost of bilateral mammography, offered every 2 years to all women ages 50–69 years [60], is €45 (an investment of €0.06/day, 60-fold higher than the cost of annual albuminuria testing). A positive mammogram may require repeat imaging and an invasive breast biopsy (cost €230) to confirm the diagnosis. However, systematic screening, such as cancer screening programs, incurs additional diagnostic and treatment costs on top of the cost of the individual tests themselves. In this regard, the probability of systematic, home-based albuminuria screening being cost-effective for the Dutch willingness-to-pay threshold for preventive population screening was 95.0%, as the incremental cost-effectiveness ratio (ICER) per quality-adjusted life years (QALYs) was €9225 [46]. In contrast, a contemporary assessment of the Dutch breast screening program concluded that the cost of €20 056 (versus €15 401 for not screening) added no QALYs and thus no ICER could be calculated [61]. Despite this, the authors supported continuing the program because it reduced disease-related mortality, incidence and severity, i.e. the known benefits of early diagnosis and treatment of CKD.

CONCLUSION

The growing global burden of CKD demands immediate attention and strategies for proactive prevention and early intervention following medical knowledge dating back nearly 5000 years and successfully applied to decrease mortality from CVD. Among the components of the ABCDE framework aimed at identifying and treating cardiovascular risk factors, albuminuria is clearly underused, despite being an actionable component of the CKD diagnosis. Albuminuria values may diagnose CKD and lead to the prescription of up to five drugs with demonstrated kidney and cardiovascular protection in a similar manner that glycaemia may diagnose diabetes mellitus and lead to prescription of antidiabetic drugs. In this regard, current KDIGO screening guidelines are insufficient and should integrate early albuminuria testing in all populations at risk for CKD, including those >50–60 years of age. Since the population at risk is large, a default attitude should be considered in which albuminuria is tested annually except if individuals have no risk factors for CKD. Alternatives include adding UACR to automated urine dipstick testing and age-based universal screening linked to colorectal cancer screening programs. Since not all antidiabetic drugs offer the same kidney protection and intensive BP control does not protect against kidney failure and may even be detrimental, it is not enough to treat risk factors such as hypertension and diabetes to prevent CKD. A state of very high risk of CKD should be defined, potentially termed pre-CKD, that is treatable with current antidiabetic drugs that prevent CKD. Clinical trials are needed, testing these drugs in people with pre-CKD not having diabetes. Only prevention and early treatment will turn the tide on the growing burden of CKD, since the current trend will lead to an unaffordable and unsustainable need for KRT. Such an approach was recently emphasized by the World Health Organization resolution on kidney health [62], which recognized kidney disease as one of the six major non-communicable chronic diseases and urged countries to facilitate prevention, early diagnosis and access to treatment. Finally, a diagnosis of CKD should trigger the identification of the cause, as individual causes may have specific therapies that differ from non-specific kidney protection. Tools such as imaging, kidney biopsy and genetic testing should be considered for this purpose if the cause is not apparent from history, examination and lab results.

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AUTHORS' CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

All data are available in the article and its references.

CONFLICT OF INTEREST STATEMENT

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