Family Medicine and Primary Care: Open Access
Topsever P, et al. J Family Med Prim Care Open Acc 8: 247.
www.doi.org/10.29011/2688-7460.100247
www.gavinpublishers.com

Review Article

Practical Strategies for Diagnosis and Treatment of CKD

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Citation: Topsever P, Schnell O, Wanner C (2024) Practical Strategies for Diagnosis and Treatment of CKD. J Family Med Prim Care Open Acc 8: 247. DOI: 10.29011/2688-7460.100247

Received Date: 08 January, 2024; **Accepted Date:** 17 January, 2024; **Published Date:** 22 January, 2024

Abstract

The burden of Chronic Kidney Disease (CKD) will rise markedly – by 2040, it will be among the five leading causes of death worldwide. In the early stages, the disease is usually asymptomatic, which is why in many cases the diagnosis is lacking and the disease remains untreated. The uncurbed progression limits therapeutic options and increases the likelihood of End-Stage Kidney Disease (ESKD), cardiovascular events, and ultimately premature mortality. Risk factors play a central role in identifying people living with CKD who must be screened using guideline-based diagnostics. A multimorbid approach that targets kidney, but also cardiovascular risk and comprises lifestyle modifications as well as pharmacological treatment is necessary to successfully manage the disease. This review summarizes current strategies for the management of CKD with emphasis on primary care management and aims to highlight the importance of General Practitioners (GPs) in the diagnosis and care of people with CKD.

Keywords: Primary care; CKD screening; Risk factors; Multimorbidity; Comprehensive approach; Person-centred approach

Abbreviations: ARB: Angiotensin II Receptor Blockers; ACEi: Angiotensin-Converting Enzyme inhibitor; CKD: Chronic Kidney Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CVD: Cardiovascular Disease; eGFR: estimated Glomerular Filtration Rate; EKFC: European Kidney Function Consortium; ESH: European Society of Hypertension; ESKD: End-Stage Kidney Disease; GFR: Glomerular Filtration Rate; KDIGO: Kidney Disease: Improving Global Outcomes; KFRE: Kidney Failure Risk Equation; MDRD: Modification of Diet in Renal Disease; mGFR: measured GFR; NICE: National Institute for Health and Care Excellence; nsMRA: non-steroidal Mineralocorticoid Receptor Antagonist; PCE: Pooled Cohort Equation; GP: General Practitioners; POCT: Point-Of-Care Testing; RAS: Renin Angiotensin System; RRT: Renal Replacement Therapy; SCORE2: Systematic Coronary Risk Evaluation 2; SGLT2: Sodium-Glucose Cotransporter-2; T2D: Type 2 Diabetes; UACR: Urine Albumin-To-Creatinine Ratio

Background

With more than 850 million people affected worldwide, Chronic Kidney Disease (CKD) has evolved into a serious public health issue [1,2]. The global burden of CKD is expected to increase substantially from 1.2 million deaths in 2016 to as many as 4.1 million deaths in 2040, rising from 16th to 5th place among the leading causes of death worldwide [3]. This rapid trend is linked to a growing and simultaneously ageing population, which is additionally accompanied by an increase in disease-promoting risk factors such as diabetes and hypertension [3]. CKD is a progressive illness for which there is no cure, hence current treatment options aim to slow the decline in kidney function. Transition to end-stage kidney disease (ESKD) implies kidney replacement therapy, i.e., dialysis and kidney transplantation, as a life-sustaining measure [4]. To spare patients from stressful interventions, it is important to diagnose and treat CKD early. However, a major issue is that the disorder is predominantly asymptomatic in its early stages and is therefore not in the primary focus of general practitioners (GPs), resulting in a high number of undiagnosed cases [5]. Structured screening for CKD, that concentrates on identifying individuals at-risk and timely intervention can overcome this challenge. This

review emphasizes the role of GPs in the early identification of people with CKD and is intended to raise awareness of the risk factors. Diagnostic and therapeutic strategies are summarized to support optimal and earliest possible CKD management in the primary care setting.

Definition and Classification of CKD

A widely accepted definition of CKD is proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline which sets the following three criteria for the presence of the disorder: (1) a reduced kidney function manifested by a Glomerular Filtration Rate (GFR) <60 mL/min per 1.73 m^2 (2) and/or evidence of a single or more markers of kidney damage, (3) persisting for >3 months. Markers associated with kidney injury are albuminuria (urine albumin-to-creatinine ratio (UACR) ≥30 mg/g), abnormalities of either urine sediment, electrolytes, tissue or kidney structure, and a history of kidney transplantation [6].

The KDIGO guidelines recommend CKD classification (Figure 1) using the two diagnostic parameters GFR and UACR, in addition to the underlying cause. Categories for GFR range from G1 (≥90 ml/min per 1.73 m^2, normal or high) to G5 (<15 ml/min per 1.73 m^2, kidney failure). Albuminuria is grouped into three entities: A1 (ACR <3 mg/mmol ≙ <30 mg/g, normal to mildly increased) to A3 (ACR >30 mg/mmol ≙ <300 mg/g, severely increased). To exclude acute kidney injury, repeated measurements of these parameters are required before CKD can be diagnosed and categorized. Investigation into the cause of CKD includes assessment of the clinical context, social and environmental factors, personal and family history as well as medications, and is complemented by further diagnostic tests [6].

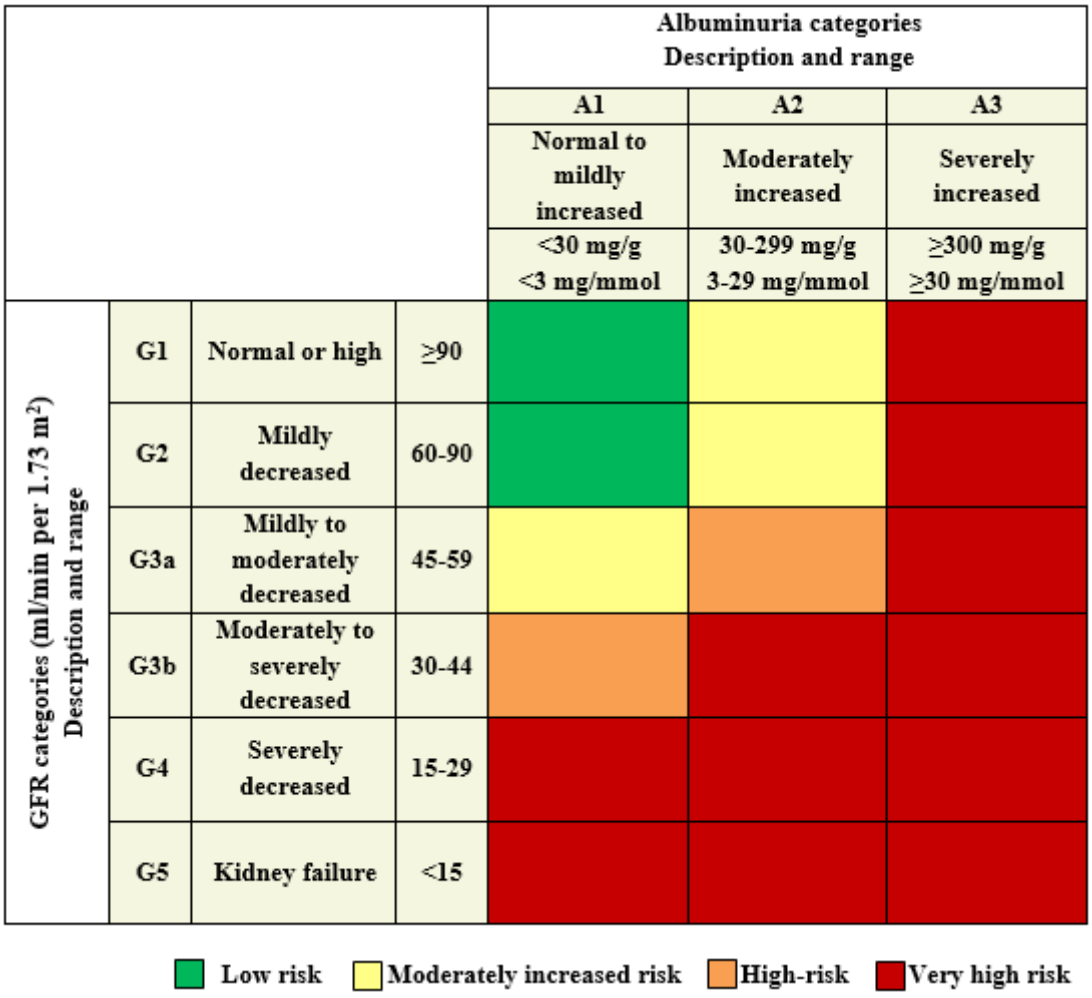

Figure 1: Chronic Kidney Disease (CKD) classification by Glomerular Filtration Rate (GFR) and albuminuria.

Risk categories are assigned to the respective disease stages. Individuals with GFR values ≥60 mL/min per 1.73 m^2 in the absence of significantly increased albumin excretion (category A1) are at low risk for adverse cardiovascular and kidney events. If there are no signs of kidney injury, there is no evidence of CKD (green). Other categories are related to CKD and are associated with moderately increased risk (yellow), high risk (orange), or very high risk (red) for adverse outcomes. Adapted from [6,7].

Diagnostic gaps

It has been demonstrated in population-based studies that CKD is significantly underdiagnosed. Without CKD screening as part of the studies, around half of those with the condition would not have been diagnosed [8,9]. The multinational, observational REVEAL-CKD study collected comprehensive data on people living with stage 3 CKD between 2015 and 2020 in developed countries. The recently published results show that the prevalence of undiagnosed stage 3 CKD ranges from 61.6-95.5% across countries, with lower rates of diagnosis in women (vs. men) and older individuals (vs. younger individuals). In a U.S. sub-database of the study, the median time for undiagnosed individuals with stage 3 CKD to get diagnosed was 4.75 (4.68-4.82) years [5,10]. This complete lack or delay of diagnosis and concomitant interventions allows unrestrained progression of CKD, which is linked to an increased risk of cardiovascular events, hospitalization, and death [11]. Particularly sobering is the low rate of UACR testing (overall prevalence of 1.8 - 5.5% across countries), even in a post-diagnosis monitoring setting (0.05 measurements per person-year) when guidelines recommend a frequency of at least once per year in high risk populations [5, 6, 12]. In people with type 2 diabetes (T2D) the detection of CKD appears to be comparatively low. Only 1.1% (stage 1), 4.9% (stage 2), 18% (stage 3), 52.9% (stage 4), and 58.8% (stage 5) of individuals with CKD were diagnosed in a U.S. study, respectively. Interestingly, the rate for UACR testing was also found to be poor (15 months prior to the study 52.9% of individuals without UACR measurement), which might explain low detection rates of early CKD stages [13].

Risk Factors for CKD and Implications for Screening

CKD becomes symptomatic mainly in late stages, while early disease can often be only detected by screening. Therefore, risk factors play an important role in identifying individuals with CKD (Figure 2).

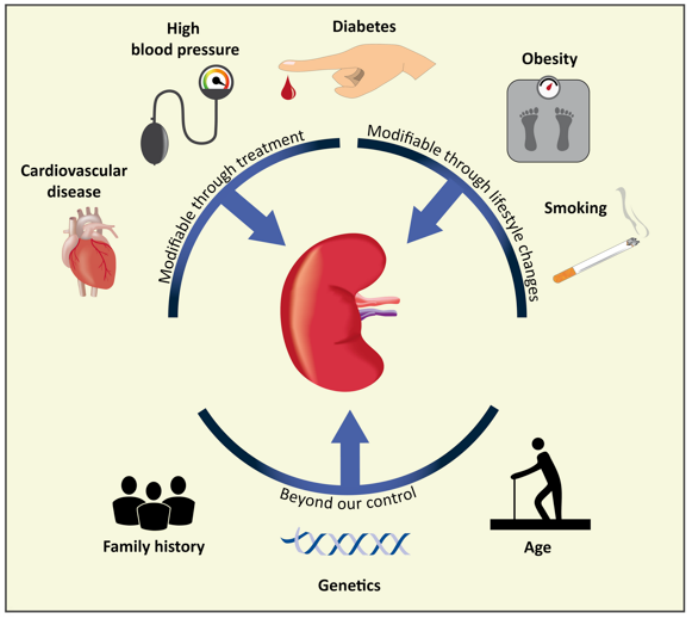

Figure 2: Risk factors for the incidence and progression of chronic kidney disease (CKD).

Among all risk factors, diabetes and hypertension are the most prominent (14). Globally, diabetes ranks first [14] with a threefold increase in the risk of CKD [15,16] and a prevalence of CKD among individuals with type 2 diabetes (T2D) ranging from 6.0-39.3 % [17]. However, in some regions, e.g., East Asia, hypertension is the number one risk [14,18]. Not surprisingly, people with both conditions are at greater risk of developing CKD than those with just one condition (18). Due to the close link between kidney and heart, cardiovascular diseases (CVDs) are inevitably another potent risk factor for CKD, as reflected by the high prevalence of CVD in CKD of up to 47.2% [19-23]. Other common factors associated with an increased risk of CKD include obesity, dyslipidemia, smoking, and a history of acute kidney injury [16, 24, 25]. However, this list can be extended with less common or socio-economic-related risk factors, e.g., multisystem diseases affecting the kidney (e.g., systemic lupus erythematosus and human immunodeficiency virus) and environmental exposure to nephrotoxins [26-28].

Non-modifiable risk factors comprise gender, age, ethnicity, and other genetic determinants. While the prevalence of CKD is higher in women, the progression of CKD appears to be faster in men and older individuals [29-31] (Figure 2). Among the risk factors, there are modifiable and non-modifiable components.

The American Diabetes Association (ADA) and KDIGO have agreed that individuals with type 1 diabetes should be screened annually starting five years from diagnosis and people affected by T2D should be screened yearly directly after diagnosis [32]. Additionally, conclusions of a KDIGO controversies conference imply that people with hypertension and/or CVD should also be targeted in screening and that the examination of individuals with other risk factors for CKD should be based on individualized clinical assessment and shared decision-making [33].

Since individuals are often being cared for because of other diseases/risk factors that have already been identified, primary care is predestined for CKD screening and offers the opportunity to intervene early in the course of the disease.

Diagnostic tools

GFR assessment

GFR is a measure of the kidney's ability to filter blood plasma and is the sum of the filtering capacities of the single nephrons. It is mostly determined indirectly as an estimate derived from measurements of a blood sample. The determination is based on endogenous filtration markers, such as creatinine and cystatin C, which in healthy individuals show stable serum levels. Creatinine originates from a muscular degradation process and therefore levels depend on muscle mass, whereas cystatin C is a ubiquitously expressed protein, rendering it a more uniform marker across populations and a superior biomarker [34-36]. However, due to economic and availability reasons, creatinine is currently the preferred indicator for initial investigations [37]. Two methods are commonly used to measure serum creatinine: the Jaffe technique, which is a colorimetric approach, and enzymatic assays. Comparison of the two methods shows that the Jaffe technique produces greater measurement inaccuracies and therefore can lead to more misclassifications [38,39].

Generally, it can be assumed that decreasing kidney function and GFR is coupled with an increase in serum concentrations of the endogenous marker molecules, yet other determinants than glomerular filtration influence the absolute values. To account for this, estimation equations have been developed that incorporate demographic and clinical variables, enabling more precise estimates of GFR (eGFR) to be reported [40]. Established formulas are the creatinine and/or cystatin C based equations of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The European Kidney Function Consortium (EKFC) has published another creatinine-based formula for the entire age spectrum, which has been supplemented by a cystatin C formula, both of which have a high degree of accuracy [41, 42]. CKD-EPI and EKFC formulas outperform the previously developed Modification of Diet in Renal Disease (MDRD) formula in terms of accuracy and should be preferably used in routine clinical practice [41,43]. Moreover, formulas that include both biomarkers yield better estimates [44]. Measuring GFR (mGFR) via plasma or urinary clearance of exogenous filtration markers is the gold standard, but complex and time-consuming therefore only useful when it is essential to know the exact kidney function (Figure 3) [45].

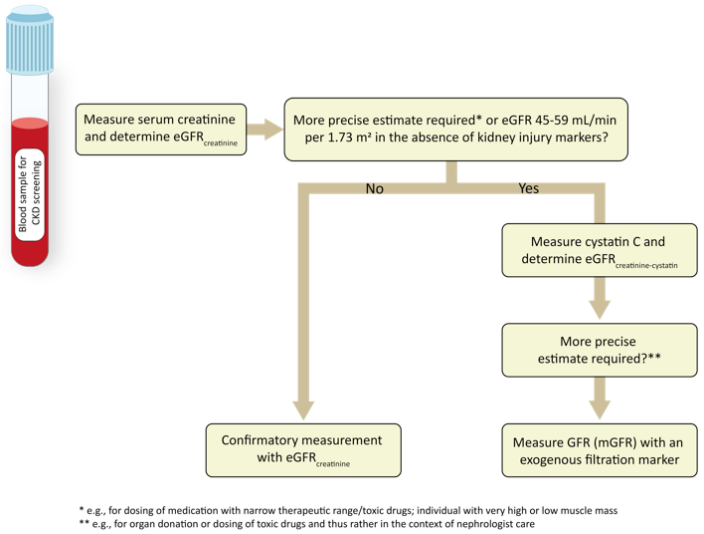

Figure 3: Suggested protocol for glomerular filtration rate (GFR) assessment according to KDIGO.

For CKD diagnosis a confirmatory measurement after three months is recommended, if an eGFR <60 mL/min/1.73 m^2 is detected to rule out transient falls in the parameter [7]. Estimated GFR (eGFR) is determined from blood samples and requires confirmatory measurements.

Albuminuria assessment

The urine of healthy people contains no or only very little amounts of albumin, thus its presence in urine is an indicator of a defective glomerular filtration barrier, with 30 mg per day representing the cut-off value for pathological urinary albumin excretion [46].

Albuminuria is associated with the progression of CKD and increased risk for cardiovascular events, thus is an important prognostic marker [47,48]. According to the KDIGO classification, stage 1-2 CKD can only be diagnosed by persistent albuminuria or other markers of kidney impairment, but not by reduced eGFR alone. The simplest method of detecting albuminuria is to use urinary dipsticks, but also the most inaccurate approach as their sensitivity for moderately increased albuminuria is rather weak [49]. They are therefore more suitable for preliminary investigations and should be followed by more detailed testing. Quantitative results obtained by normalization of urinary albumin to urinary creatinine (urine albumin-to-creatinine ratio, UACR) from spot urine samples are

more meaningful. International guidelines for CKD recommend UACR for technical, standardization, and precision reasons [6, 50]. If screening for CKD reveals a UACR ≥30 mg/g, re-testing in three months is suggested to confirm persistent albuminuria for diagnosis [7]. Transient increases in urinary albumin can be caused by e.g., menstruation, febrile illness, acute hyperglycemia, uncontrolled hypertension, exercise, urinary tract infections, and heart failure [51, 52]. It should be noted that the detection of severely increased albuminuria (UACR >300 mg/g) requires prompt consultation with a nephrologist [6, 7]. The gold standard for assessing albuminuria is a 24-hour urine collection, but this is laborious, so determining ratios from a spot urine sample, preferably a morning void mid-stream sample, is a more practical option.

To support early CKD diagnosis and treatment, UACR point-of-care testing (POCT, Figure 4) has been demonstrated to be effective, particularly in secondary prevention. In individuals with T2D the screening in spot urine with UACR POCT produced a diagnostic yield of 10.6% and 13.4% for newly diagnosed and suspected CKD, respectively. A change of medication based on the UACR POCT was performed in 21.6% of individuals with T2D and mostly in those with a severely increased UACR of >30 mg/mmol. The majority of physicians involved in the study regarded UACR POCT as very important for people with diabetes (75%) and important for individuals without diabetes (75%) [53]. Thus, POCT tools should be made available in primary care to improve diagnostic rates and quality of care. The technique enables to screen fast for structural changes in the kidney to diagnose chronic kidney disease (CKD).

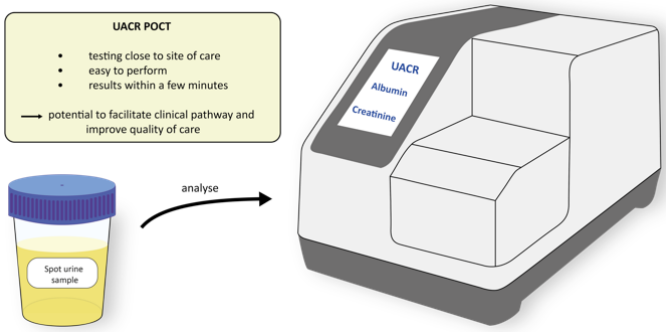

Figure 4: Urine albumin-to-creatinine ratio (UACR) point-of-care testing (POCT).

Further diagnostics

Urinalysis

Urinalysis can give insights into the presence and cause of CKD, is simple, and therefore should be performed when screening for CKD. Chemical analysis with urinary dipstick tests can provide evidence of urinary tract infections, pH, glycosuria, hematuria, and the previously described albuminuria. Signs of the latter two are hallmarks of glomerular disease [54].

Ultrasound imaging

Studies have proven that kidney size and echogenicity correlate with kidney function [55,56]. Notably, compared to the more traditional reporting of kidney length, cortical thickness and kidney volume are better surrogates for kidney function. Cortical thinning is a more suitable indicator for the early stages of CKD, whereas a reduced kidney volume becomes apparent at later stages of CKD [56].

Risk prediction tools

For people with diagnosed CKD, risk prediction tools help to identify individuals at high risk of ESKD or adverse cardiovascular outcomes. Thus, they offer guidance for preventive therapies and referral to specialist services on a personalized level. There are numerous equations developed, however, only tools with a low bias and externally validated methods that have been verified in the population for which the application is intended should be used [57]. A recommended equation for the use in practice that predicts the two- and five-year risk for kidney failure is the Kidney Failure Risk Equation (KFRE) based on either four (age, sex, eGFR, urine ACR) or eight variables (additionally serum albumin, phosphorous, bicarbonate, and corrected calcium). Since this formula was developed for individuals with CKD stage 3-5, its calculation is only accurate for this population [58]. To evaluate cardiovascular risk in people with CKD, the QRISK3 model, and the pooled cohort equation (PCE) or the Systematic COronary Risk Evaluation 2 (SCORE2) that utilize kidney-specific parameters for calculation, can be applied [59-61]. A compilation of risk calculators including most of the listed risk models is accessible under the following link: https://www.ckdpc.org/risk-models.html) [62].

Treatment of CKD

Pre-treatment stratification

Depending on the CKD stage and the respective risk category that can be assigned after screening, further measures are taken (Figure 5). Upon diagnosis of CKD, treatment needs to be initiated immediately. Furthermore, routine monitoring to enable appropriate therapy and timely referral to specialist services are important aspects in the prevention of CKD progression. The delayed consultation with a nephrologist in people with CKD has been shown to worsen clinical outcomes [63]. Several guidelines recommend referral from stage 4 (GFR <30 ml/min per 1.73 m^2) or earlier and mention numerous other criteria for referral, e.g., haematuria, abrupt or large sustained falls in GFR, severe albuminuria, resistant hypertension, or persistent hyperkalaemia [6,32,50]. For people with progressive CKD, validated prediction tools such as the KFRE can guide timely referral for planning Renal Replacement Therapy (RRT).

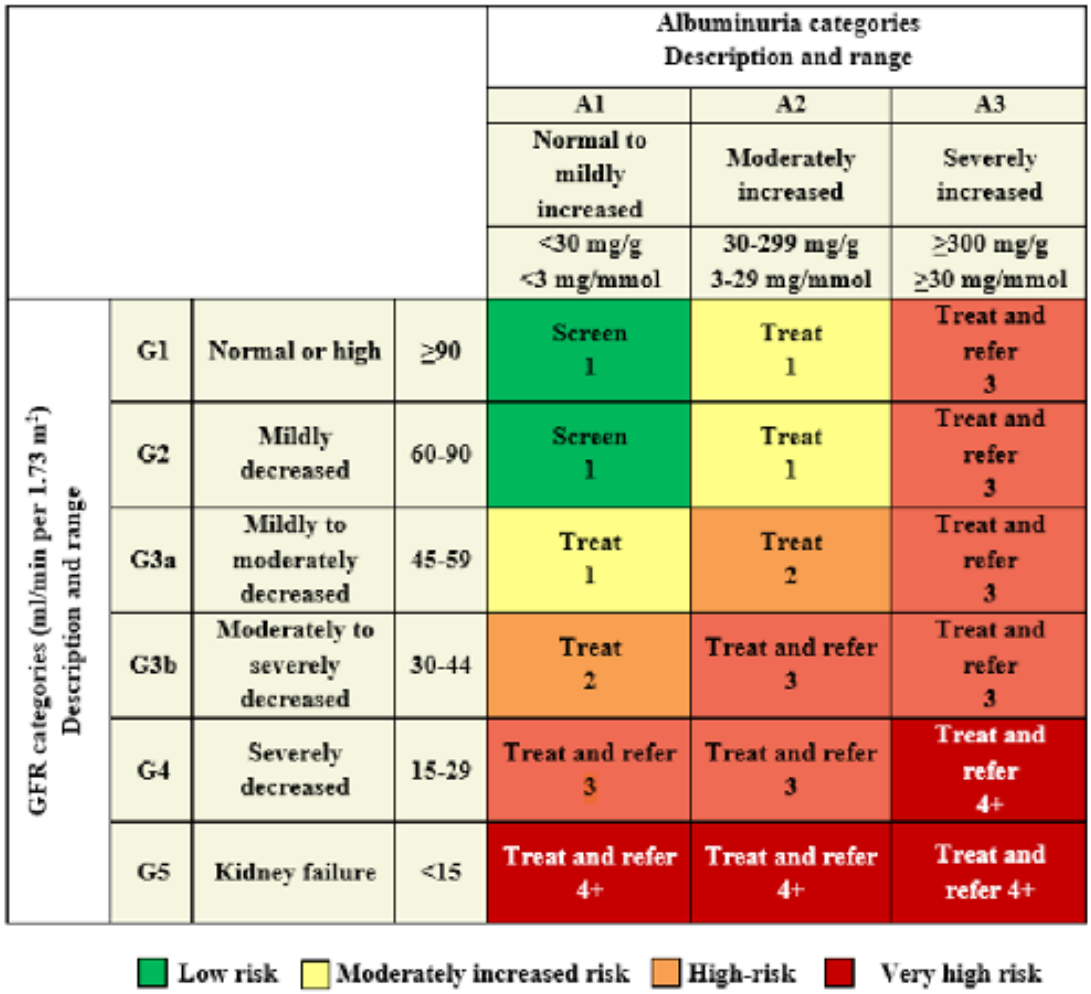

Figure 5: Chronic Kidney Disease (CKD) classification by glomerular filtration rate (GFR) and albuminuria, including further guidance.

The numbers in the coloured boxes, which represent risk categories for adverse cardiovascular or kidney outcomes, indicate the suggested screening/monitoring frequency per year. In the absence of markers of kidney injury and normal GFR, the presence of CKD is not evident (green, low risk), with screening recommended once per year. After diagnosis, CKD is treated and monitored once per year (yellow, moderately increased risk) to four times or more per year, i.e., every 1-3 months. Further risk categories are associated with high risk (orange) or very high risk (light and dark red) for adverse outcomes. Individuals with a very high risk require referral to a nephrologist. Adapted from [6, 7, 32].

Lifestyle modifications

Lifestyle modifications are feasible worldwide, impact CKD and multi-morbidity, and directly involve the patient in disease management, which is why counselling about it should be part of good practice [64]. Guidelines recommend dietary modification for people with CKD on protein, salt, potassium, phosphate, calcium, acid load, and lipids [64-66]. Specifically, for protein intake a reduction to 0.8 g protein/kg/day for individuals with diabetes and a limited sodium intake of <2-2.3 g/day are proposed [65, 66]. Smoking cessation eliminates a risk factor for CKD and CVD, which frequently co-exist and mutually worsen outcomes, and is therefore recommended. Additionally, exercise and weight loss are adaptions with a positive impact on CKD [6,50].

Equally important is the way in which lifestyle modifications are communicated to the individual being cared for. Motivational interviewing which is characterized by an empathic dialogue to establish rapport and elicit patient values, has been shown to improve outcomes in primary care. Other recommended evidence-based counselling techniques are e.g., the five A´s approach, and the transtheoretical model [67].

Renin-angiotensin system (RAS) inhibitors

The RAS inhibitors used for CKD treatment are angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEi). KDIGO recommends their use in people with albuminuria at the highest licensed and tolerated dose, though people without hypertension should have severely increased albuminuria (>300 mg/g). If hypertension is present, the KDIGO and the European Society of Hypertension (ESH) suggest the administration of RAS inhibitors starting at moderate albuminuria (UACR >30 mg/g), excluding individuals with kidney failure [1, 49]. Additionally, the ESH mentions that monotherapy with a RAS inhibitor may not be sufficient to achieve adequate blood pressure control, defined by the ESH as target values of >70 to <90 mmHg for diastolic blood pressure and >120 to <140 mmHg for systolic blood pressure in individuals with CKD, and that a combination therapy of blood pressure-lowering medication may be needed for this [68]. However, combination of ARBs and ACEis is discouraged because the risk of adverse events outweighs the benefit [6]. Monitoring serum potassium one to two weeks after starting RAS inhibitor therapy or its dose escalation is crucial due to the increasing risk of hyperkalaemia [69].

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

SGLT2 inhibitors have proven cardio- and nephroprotective properties [70], leading to a powerful synergistic effect in the treatment of people with CKD. Their benefit for individuals with CKD independent of diabetes was proven in the two landmark trials DAPA-CKD (dapagliflozin) and EMPA-KIDNEY (empagliflozin). Investigation of dapagliflozin has shown a 50% risk reduction for the primary outcome (composite of a sustained decline in eGFR ≥50%, ESKD, or death from renal or cardiovascular causes) in participants without T2D [71]. The EMPA-KIDNEY trial´s study population comprised 54% individuals with CKD who had no diabetes and has shown a 28% risk reduction for the primary outcome (composite of progression of CKD defined as ESKD, a sustained decrease in eGFR to <10 ml/min per 1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes or death from cardiovascular causes) with empagliflozin [72]. The National Institute for Health and Care Excellence (NICE) guideline recommends the SGLT2 inhibitor dapagliflozin for treating CKD independent of diabetes as an add-on to RAS inhibitors, unless contraindicated, when eGFR is above 25 ml/min per 1.73 m^2 at treatment initiation and albuminuria (≥200 mg/g, ≥22.6 mg/mmol) is present [50]. Interestingly, results from the EMPA-KIDNEY trial indicated that people without albuminuria may also benefit from SGLT2 inhibitors [72]. Currently, dapagliflozin and empagliflozin are the only SGTL2 inhibitors approved by the European Medicines Agency and Food and Drug Administration for the treatment of CKD with or without diabetes.

Non-steroidal Mineralocorticoid Receptor Antagonists (nsMRA)

In individuals with CKD and diabetes, the nsMRA finerenone presents a novel option to improve kidney and cardiovascular outcomes, which can complement the previously described interventions (Figure 6) [73]. Convincing results from studies led to its approval as a first-in-class agent for the treatment of CKD (with albuminuria) associated with T2D, and to its integration into guidelines suggesting its use in corresponding individuals with an eGFR of ≥25 mL/min per 1.73 m^2 and serum potassium ≤4.8 mmol/L in addition to maximum-tolerated RAS therapy and with appropriate potassium monitoring [32, 74]. Combination with a SGLT2 inhibitor as an add-on to a RAS inhibitor for nephro- and cardioprotection is supported by the European Renal Association [75]. Pharmacological and non-pharmacological interventions are used to improve kidney and cardiovascular outcomes in individuals with CKD.

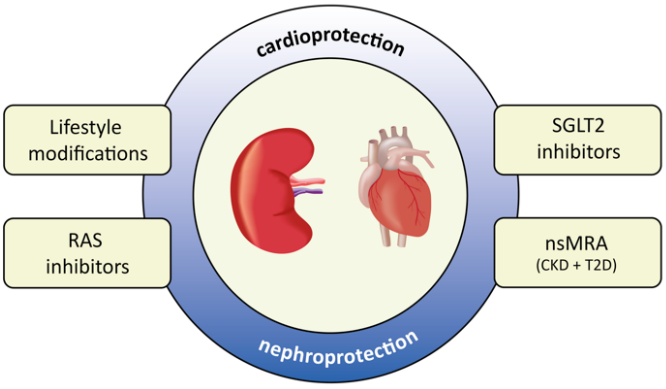

Figure 6: Treatment of CKD.

Further strategies for cardiovascular risk reduction

Considering that more people with CKD die from CVD than from ESKD and that atherosclerotic events play a major role in this, intervention in individuals at risk is essential [76, 77].

Antiplatelet therapy should be offered to patients in whom the cardiovascular benefit exceeds the increased risk of bleeding [50]. Lipid-lowering therapy can also be considered after the full lipid profile has been determined at least one time following CKD diagnosis. Individuals with CKD not on RRT who are aged ≥50 years can be treated with statins at any stage of the disease. If eGFR is <60 ml/min per 1.73 m^2 a combination with ezetimibe is also appropriate. In adults aged <50 years with CKD not on RRT statin treatment is recommended if there is evidence of coronary disease, diabetes mellitus, prior ischemic stroke, or an estimated 10-year incidence of cardiovascular events is >10% [78]. The KDIGO guidelines advocate a fire-and-forget strategy instead of a treat-to-target strategy which does not require repeated lipid measurement [78].

Call for action

The need for effective CKD screening is an urgent and global issue. When CKD cases are diagnosed late, or even missed, the number of people living with ESKD increases, to the detriment of all diseased individuals and health care resources. Evidence-

based guidelines are available, but these also need to be transferred into practice. Individuals with risk factors, e.g., heart failure, hypertension, other CVD, and diabetes should be in focus and must be routinely screened for CKD. Albuminuria is as important a disease criterion as GFR and is particularly relevant in the diagnosis of early stages of CKD, which is why its assessment in screening and monitoring is crucial. The use of SGLT2 inhibitors and nsMRA, which have cardiovascular- and nephroprotective properties, is specifically advisable and should not be withheld from eligible patients. Lastly, it is important to remember the red flags to consult a nephrologist in case of complications, a significant worsening of the disease, or other unclear findings.

Conclusions

CKD is underdiagnosed and, moreover, its prevalence is expected to increase substantially in the following years. To address this burden, it is essential that preventive strategies, including the early detection by screening of people at risk for CKD, are embedded in the daily practice of GPs and that guideline-based management is adopted to gain widespread implementation. Understanding risk factors for individual risk stratification and diagnostic tools for early diagnosis is the basis for this, consolidated by knowledge of pharmacological and non-pharmacological intervention options to delay or prevent morbidity and mortality due to CKD. Managing CKD requires a person-centred, comprehensive [79], and multimorbid approach that does justice to individual risk, and the interconnectedness of the kidney and the cardiometabolic organ systems and involves a multidisciplinary healthcare team. However, the initial steps, from diagnosis to initiation of treatment, are the responsibility of primary care. Therefore, primary care should be empowered and equipped with the necessary infrastructure like POCT tools, and reimbursement of GP-prescribed drugs for the management of CKD.

Declarations

Competing Interests

PT received honoraria/consultation fees from Eli Lilly, LifeScan, AstraZeneca and participated in company sponsored speaker´s bureaus for AstraZeneca, Eli Lilly, Boehringer Ingelheim and Novo Nordisk.

OS is founder and CEO of Sciarc GmbH. OS served on speaker panels and/or on advisory panels for Abbott, Bayer, Boehringer Ingelheim, Eli Lilly, Glooko, LifeScan, Lilly, Mannkind, Sanofi, and Woerwag

CW received honoraria for steering committee membership, AdBoard participation and lecturing from Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, CSL-Vifor, FMC, GSK, Lilly, MSD, Novartis, NovoNordisk and Sanofi

Funding

The publication has been funded by an unrestricted educational grant from AstraZeneca.

Authors' Contributions

PT contributed to drafting and substantively revising the manuscript, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

OS contributed to drafting and substantively revising the manuscript, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

CW contributed to drafting and substantively revising the manuscript, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Acknowledgments

The authors would like to thank René Rötzer, PhD from Sciarc GmbH for medical writing and editorial assistance.

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