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Detecting and managing the patient with chronic kidney disease in primary care: A review of the latest guidelines

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Abstract

Chronic kidney disease (CKD) is a major global health problem, affecting about 9.5% of the population and 850 million people worldwide. In primary care, most CKD is caused by diabetes and/or hypertension, but a substantial proportion of cases may have alternative causes. During the early stages, CKD is asymptomatic, and many people are unaware that they are living with the disease. Despite the lack of symptoms, CKD is associated with elevated risks of cardiovascular disease, progressive kidney disease, kidney failure and premature mortality. Risk reduction strategies are effective and cost-effective but require early diagnosis through testing of the estimated glomerular filtration rate and albuminuria in high-risk populations. Once diagnosed, the treatment of CKD centres around lifestyle interventions, blood pressure and glycaemic control, and preventative treatments for cardiovascular disease and kidney disease progression. Most patients with CKD should be managed with statins, renin-angiotensin-aldosterone system inhibitors and sodium-glucose cotransporter-2 inhibitors. Additional treatment options to reduce cardiorenal risk are available in patients with diabetes, including glucagon-like peptide-1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists. The Kidney Failure Risk Equation is a new tool that can support the identification of patients at high risk of progressive kidney disease and kidney failure and can be used to guide referrals to nephrology. This review summarizes the latest guidance relevant to managing adults with, or at risk of, CKD and provides practical advice for managing patients with CKD in primary care.

KEYWORDS
cardiovascular disease, glucagon-like peptide-1, lipid-lowering therapy, primary care, sodium glucose cotransporter-2 inhibitor, diabetic nephropathy

Plain Language Summary

The kidneys contain millions of tiny filters that remove waste products from our blood, making sure we have the right amount of water and nutrients in our bodies. Chronic kidney disease (CKD) is a condition where the kidneys do not work as well as they should over a long period of time. When a person has CKD, the kidneys do not filter waste products from the blood effectively, the kidneys can leak albumin (a type of protein) into the urine, and there can be a build-up of fluid and a loss of nutrients from the body. All these features mean that our bodies cannot keep as healthy as they should.

CKD is a very common problem. It is thought that about 1 in 10 people may be living with this disease. CKD is more likely to develop as we get older, particularly in people who have diabetes and high blood pressure. However, CKD can also occur alongside other medical problems, can develop unexpectedly because of uncommon conditions, or can be inherited from family members. Most people with CKD do not have any symptoms and may not know that they have the condition.

CKD can be identified by testing for waste products in the blood (to provide an estimate of the kidneys' filtering capacity) and testing for albumin in the urine (a marker of whether the filters have become damaged). These blood and urine tests can guide how severely a person has been affected by CKD. Detecting CKD is important because, even without symptoms, CKD can increase the likelihood of a person developing other medical problems, such as heart attacks and strokes. Although it is uncommon, about 1 in 100 people with CKD may also go on to develop 'kidney failure'. Kidney failure describes a situation where external support for kidney function, such as dialysis or a kidney transplant, may be needed.

If a health care provider detects that a person has CKD, treatment aims to protect the remaining kidney function for as long as possible and to reduce the risk of heart attacks and strokes. The health care provider will recommend living a healthy lifestyle, including eating a balanced diet, keeping physically active, maintaining a healthy body weight and avoiding smoking. People with CKD should have their blood pressure checked and should receive treatment if the blood pressure is too high for them. Cholesterol-lowering tablets are recommended for most patients. For some individuals, other effective medicines may be recommended, depending on that person's level of risk of developing other medical problems. Blood tests, urine tests and blood pressure should be monitored about once per year, or sometimes more often than this if the kidneys are more severely damaged.

Most patients with CKD will be cared for by their community health care provider, but some patients may need to be seen by a specialist kidney doctor. Risk calculators can help community health care providers decide which patients most need to be seen by a specialist.

Health care providers are advised to offer treatments that they think will benefit an individual, but they should also consider the person's wishes and expectations when deciding on a course of treatment.

1 | INTRODUCTION AND SCOPE OF REVIEW

1.1 | Global burden of chronic kidney disease

Globally, chronic kidney disease (CKD) is thought to affect about 9.5% of the population, or about 850 million people in total.[1] In the context of ageing populations and the increasing prevalence of multimorbidity (including among younger people), the prevalence of CKD is set to rise further. By 2040, CKD is expected to be the fifth leading cause of death globally.

1.2 | Why target chronic kidney disease?

CKD has a huge and growing economic impact. In the UK, the annual cost of CKD to the National Health Service is about £1.45 billion, through a combination of direct (screening, monitoring and managing complications) and indirect health care costs.[2] Although kidney failure is an uncommon consequence of CKD, dialysis treatment alone uses >50% of the budget spent on CKD. In the UK, CKD is responsible for approximately 45 000 premature deaths each year, with markedly higher rates of hospitalization and longer hospital stays among people with CKD.[2,3] Disability and loss of productivity associated with the direct and indirect consequences of CKD lead to a loss of the working population and increased sick pay.

Not all cases of CKD or kidney failure are preventable; however, risk reduction strategies are effective and cost-effective if CKD is detected and managed in the early stages of the disease. Fewer than half of countries recognize CKD as a public health priority, and only a quarter have established CKD management strategies in place.[1] Appropriate and timely management is further limited by the burden of disease and widespread uncertainty about how to manage patients with CKD among non-specialists.

This article will summarize the latest guidance relevant to adults with, or at risk of, CKD. We will cover highlights of the major UK and international guidelines, with some discussion of the relevant points in the guidelines for comorbid conditions commonly seen in people with CKD (including hypertension, diabetes and heart failure). Through focused discussions with primary care health care practitioners in the UK, we have identified some of the major areas of uncertainty in managing CKD in the community. We aim to provide simple, practical and pragmatic advice to aid the non-specialist in managing patients with CKD (or at risk of CKD) in their day-to-day practice.

2 | IDENTIFICATION OF CHRONIC KIDNEY DISEASE

2.1 | Definition, classification and screening of chronic kidney disease

CKD is defined as an abnormality in kidney structure or function, that is present for a minimum of 3 months and has implications for health.[4] International guidelines recommend consideration of cause as part of the CKD definition and determination of management (see Section 3.1 below). In most cases of CKD managed in primary care, the implications for health are determined by the values of two measures: the estimated glomerular filtration rate (eGFR; as a marker of kidney filtration) and albuminuria (as a marker of glomerular damage). As eGFR declines and/or as albuminuria increases, the risk of all important adverse outcomes associated with CKD rises. This effect is multiplicative, such that people with both low eGFR and high albuminuria are at the highest level of risk. A recent meta-analysis of over 27 million individuals in 114 global cohorts confirmed risks associated with CKD (by eGFR and/or albuminuria criteria) extended to acute kidney injury (AKI), kidney failure replacement therapy, atrial fibrillation, peripheral artery disease, myocardial infarction, stroke, heart failure, cardiovascular mortality, all-cause hospitalization and all-cause mortality.[5]

A threshold of clinically significant CKD is set at eGFR <60 ml/min/1.73 m^2 and/or albuminuria >3 mg/mmol,[4,6] as these are the thresholds below and above which the risk of adverse events increases, respectively. A patient can therefore have clinically important CKD even if the eGFR is ≥60 ml/min/1.73 m^2. A reminder of the classification of CKD, including nomenclature, is shown in Figure 1.

CKD is usually asymptomatic until later stages of the disease; symptoms would not be expected unless eGFR was less than about 25 ml/min/1.73 m^2; albuminuria is usually entirely asymptomatic except in the nephrotic syndrome (see Section 2.3 below). For this reason, screening for CKD in high-risk populations is recommended: patients with type 1 or type 2 diabetes, hypertension, previous AKI, cardiovascular disease, structural urinary tract disease, gout, multisystem diseases with potential kidney involvement (e.g. systemic lupus erythematosus), family history of kidney failure or a hereditary kidney disease, or people with previous incidental findings of haematuria or proteinuria.[6] The guidelines are not specific about the frequency of screening in each of these populations, but it would be reasonable to offer screening with eGFR and albuminuria testing annually in these groups. CKD screening with eGFR and albuminuria testing has been shown to be a cost-effective strategy, at least in people with diabetes and hypertension.[7] eGFR testing should also be offered on an annual basis to adults taking treatment that could affect kidney function [calcineurin inhibitors, lithium, or non-steroidal anti-inflammatory drugs (NSAIDs)].[6]

Further discussion of eGFR and albuminuria to detect and classify CKD, including interpretation and guidance for repeat testing, is detailed in the sections below.

2.2 | Estimated glomerular filtration rate

Creatinine is a cheap and widely available filtration marker and creatinine-based eGFR (eGFRcr) is recommended for first-line testing and routine monitoring of CKD in primary care.[4,6] Over the last two decades, various groups have developed and validated several equations to calculate eGFRcr. In the UK, the equation recommended for use is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation 2009,[8] although international guidelines recommend the updated CKD-EPI equation 2021 without inclusion of a race coefficient.[9] In practice, the value reported to primary care practitioners will usually be dictated by the local laboratory conducting the test.

				Persistent albuminuria		
				A1	A2	A3
				Normal-mildly ↑	Moderately ↑	Severely ↑
				<3 mg/mmol <30 mg/g	3-30 mg/mmol 30-300 mg/g	>30 mg/mmol >300 mg/g
Glomerular filtration rate (ml/min/1.73m²)	G1	Normal or high	≥90			
	G2	Mildly ↓	60-89			
	G3a	Mildly-moderately ↓	45-59			
	G3b	Moderately-severely ↓	30-44			
	G4	Severely ↓	15-29			
	G5	Kidney failure	<15			

FIGURE 1 Classification of chronic kidney disease (CKD) according to glomerular filtration rate and albuminuria categories. This heatmap contains illustrative information about relative risks of adverse kidney, cardiovascular and mortality outcomes compared with a person without CKD. This heatmap does not provide information about the absolute risks, or competing risks, of these events: absolute and competing risks may also vary by other factors including age, sex, burden of comorbidity and/or frailty. Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

On a population level, eGFRcr estimates kidney function reasonably accurately[8–11]; however, it is worth being aware of some issues with creatinine as a marker of kidney function to guide interpretation. Creatinine is subject to significant (at least 5%) within-individual biological and analytical variability. Measurement inconsistencies of both creatinine and eGFRcr is therefore expected and should be acknowledged in the interpretation of repeat samples.[6]

There are various situations when eGFRcr is probably less accurate. In settings where creatinine is reduced (e.g. people with muscle wasting disorders, including cachexia, neurological disease and sarcopenia seen with ageing, people with limb amputations, malnourished adults), eGFRcr will be higher, suggesting better kidney function than is the case in reality. In individuals with elevated creatinine (e.g. high muscle mass in athletes or those who use protein supplements), eGFRcr will be lower, suggesting poorer kidney function than is true. Creatinine can also become elevated, with apparently reduced eGFRcr, in patients receiving drugs that block tubular creatinine secretion ('pseudo-AKI'), but in the absence of genuine kidney damage. Trimethoprim is the most common culprit in primary care, but this effect can also be seen with some treatments for the human immunodeficiency virus and tyrosine kinase inhibitors.[12]

In these scenarios, creatinine and eGFRcr results should be interpreted with caution.[6] Inaccurate eGFRcr is associated with a higher likelihood of adverse outcomes,[13] including medication-associated adverse events such as hyperkalaemia with co-trimoxazole treatment, the toxic effects of baclofen and high digoxin levels.[14]

There are no specific recommendations to use alternatives to creatinine for the estimation of kidney function in primary care in the UK. In other settings where highly accurate estimation of kidney function is required (e.g. living kidney donation, dosing of anti-cancer therapies), UK and international guidelines recommend consideration of measured GFR using an isotope clearance technique.[4,6] Internationally, cystatin C testing is additionally recommended, including in primary care, when eGFRcr may be inaccurate, and is used in a combined equation with creatinine.[4] Although cystatin C testing is available in the UK and of potential value in various clinical scenarios,[15] a lack of evidence for its accuracy and cost-effectiveness in a UK population means that cystatin C testing is not routinely recommended in current National Institute for Health and Care Excellence (NICE) guidelines.[6]

2.2.1 | What to do if the estimated glomerular filtration rate is 'abnormal'?

Any kidney function test result should be interpreted in the context of previous results (where available) as well as the clinical situation.

If eGFR is <60 ml/min/1.73 m^2 and no previous results are available,

1. If unwell, consider admission to hospital for further investigation and management.
2. If not unwell, re-test within 2 weeks.[6]
   a. Is this AKI? Use clinical judgement in the interpretation of a changing kidney function test over 2 weeks. Review potential causes, e.g. recent medications [trimethoprim, NSAIDs, renin-angiotensin-aldosterone system inhibitor (RAASi) or sodium glucose cotransporter-2 inhibitor (SGLT2i)]. Depending on the severity of AKI, hospital admission and/or specialist advice may be required.
3. If blood test is stable at 2 weeks, re-test in 3 months (or ideally a further two times over a minimum of 3 months to determine the rate of progression).[4,6]
   a. Is this CKD? Check for albuminuria, and use a urine dipstick for non-visible haematuria (see Section 2.3 below). If CKD is confirmed on blood and/or urine tests, ensure CKD is coded in the clinical record (see Section 2.1 above) and manage as CKD (see Section 3 below).

2.3 | Albuminuria and non-visible haematuria

Albuminuria is both a marker of glomerular damage and a driver of further glomerular damage. The presence of albuminuria at any level is abnormal. With rising albuminuria, the risk of adverse outcomes (including cardiovascular disease, cancer, AKI, kidney disease progression and kidney failure, and all-cause mortality) increases, even when eGFR is normal.[5,16,17] Small changes in albuminuria have a much more pronounced effect on these future outcomes than mild reductions in eGFR. Importantly, albuminuria is modifiable with treatment, and improvement in albuminuria over time is associated with a lower risk of a plethora of adverse outcomes.[18] Some of the beneficial effects of treatments recommended for CKD are mediated, at least in part, by improvements in albuminuria.[19,20] Improved detection, monitoring and treatment of albuminuria is therefore paramount in altering the disease course, morbidity and mortality associated with CKD.

Although albuminuria testing is clearly recommended in people with CKD and at high risk of CKD, the rate of albuminuria testing is suboptimal, and there are currently no evidence-based guidelines to recommend the frequency of albuminuria testing. Consensus reports suggest annual testing among people with diabetes,[4,21] and this is achieved in about 70-80% of individuals with diabetes.[22–24] However, guidance is less clear about the frequency of albuminuria testing required among people with hypertension without diabetes or CKD,[6,25–27] and testing of albuminuria in this group is much lower (20-30%).[22,23] As the prevalence of albuminuria in hypertension is similar to that seen in diabetes, annual albuminuria testing in people with hypertension would be a reasonable approach.

Urine albumin-creatinine ratio (UACR) is the preferred measure to detect glomerular disease. At low levels of albuminuria, the urine protein-creatinine ratio (UPCR; measuring proteinuria, including albuminuria and other urinary proteins) is insensitive. When UACR is ≥70 mg/mmol, UPCR can be used as an alternative.[6] If UACR is not available, conversion calculators can approximate UACR from UPCR

or urine dipstick protein (https://ckdpcrisk.org/pcr2acr/).[28] Urine dipstick should be performed as well as UACR to test for non-visible haematuria.[4,6]

2.3.1 | What to do if you detect albuminuria?

1. Confirm albuminuria on an early morning urine sample.
2. Consider the cause: is there pre-existing diabetes or hypertension? Does the patient have a cause for visible haematuria, such as menstruation? Could they have a urinary tract infection? Have they participated in vigorous exercise?[4]
3. Where the presence of albuminuria is confirmed (UACR ≥3 mg/mmol).
   a. Manage blood pressure to target (see Table 1), starting with renRAASi.
   b. SGLT2i after introduction of RAASi (if eGFR ≥20 ml/min/1.73 m^2)
   c. The frequency of testing should be guided by severity (see Table 2) and the potential for improvement with blood pressure control. Although not specifically advised in official guidance, it is appropriate to repeat UACR testing while uptitrating antihypertensive treatment. This will inform both the intensity of the required blood pressure control and the likelihood of a requirement for referral to a nephrologist after the blood pressure target has been achieved.
4. If UACR ≥30 mg/mmol (UPCR >50 mg/mmol) with non-visible haematuria, refer to nephrology.[4,6]
5. If UACR ≥70 mg/mmol (UPCR ≥100 mg/mmol) after blood pressure control,[4,6] including if UACR is in the nephrotic range but there is no evidence of nephrotic syndrome, refer to nephrology. One caveat is that referral may not be required if the elevated UACR is known to be caused by diabetes and the patient is already on appropriate treatment with RAASi +/− SGLT2i.[6]
6. If there is new evidence of nephrotic syndrome (spot UACR >200 mg/mmol or UPCR >300 mg/mmol, hypoalbuminaemia <30 g/L and peripheral oedema), this warrants urgent referral to nephrology. Depending on the centre, an assessment will often be offered within days for further investigation +/− renal biopsy.

2.3.2 | Non-visible haematuria without proteinuria

Where non-visible haematuria (≥1+) is identified on dipstick in the absence of proteinuria, this is 'persistent' when the dipstick is positive in two of three tests.[6] Persistent non-visible haematuria in requires urgent further investigation on suspicion of urinary tract malignancy in individuals >60 years.[32] Otherwise, persistent non-visible haematuria should be monitored annually with repeat dipstick, eGFR, albuminuria or proteinuria testing, and blood pressure monitoring, unless the non-visible haematuria resolves.[6]

TABLE 1 Blood pressure targets from major guidelines in chronic kidney disease and hypertension.

Treatment targets	KDIGO[4,29]	ACC/AHA[30]	ESC/ESH[27,31]	ISH[26]	NICE[25]
General population	NA	<130/80	<130/80	<130/80	<140/90 <130/80 if UACR ≥70 mg/mmol
CKD	<120 systolic[a]	<130/80	<130/80	<130/80	<140/90 <130/80 if UACR ≥70 mg/mmol

Note: All guidelines generally recommend considering less intensive individualized targets in patients with advanced age and/or frailty, high risk of falls and fractures, very limited life expectancy or symptomatic postural hypotension.
Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; CKD, chronic kidney disease; ESC/ESH, European Society of Cardiology/European Society of Hypertension; ISH, International Society of Hypertension; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable; NICE, National Institute for Health and Care Excellence; UACR, urine albumin-creatinine ratio.
[a]In patients with functioning kidney transplants, the target should be <130 systolic and <80 diastolic.

TABLE 2 Suggested frequency of monitoring of chronic kidney disease.

	UACR (mg/mmol)		
eGFR, ml/min/1.73 m^2	ACR category A1 <3	ACR category A2 3-30	ACR category A3 >30
eGFR category G1 ≥90	Annual	Annual	4-monthly (×3 per year)
eGFR category G2 60-89	Annual	Annual	4-monthly (×3 per year)
eGFR category G3a 45-59	Annual	6-monthly (×2 per year)	4-monthly (×3 per year)
eGFR category G3b 30-44	6-monthly (×2 per year)	4-monthly (×3 per year)	4-monthly (×3 per year)
eGFR category G4 15-29	4-monthly (×3 per year)	4-monthly (×3 per year)	At least 3-monthly (≥4× per year)
eGFR category G5 <15	At least 3-monthly (≥4× per year)	At least 3-monthly (≥4× per year)	At least 3-monthly (≥4× per year)

Abbreviations: ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio.

2.4 | Coding

Coded CKD is associated with better quality CKD and cardiovascular disease management: better blood pressure control, higher rates of UACR testing, prescribing of RAASi and statins, lower prescribing of NSAIDs and lower rates of other medication and dosing errors.[22,33,34] However, recent evidence shows that biochemical CKD is not coded in the clinical record of 35-55% of individuals[22,33] and is less probable in women compared with men, younger people, people from areas of greater socio-economic deprivation, and non-White racial/ethnic groups.[33,35] Underlying the importance of risk recognition, coding of CKD in the clinical record is recommended[4] and can be improved through quality improvement interventions.[36]

2.5 | Recall and monitoring

There is little to no evidence to support clear guidelines for the frequency of monitoring in CKD. UK guidelines recommend a minimum frequency for monitoring according to the severity of eGFR and albuminuria abnormalities (Table 2); however, more frequent monitoring may be required in those with a faster rate of deterioration in kidney function, other risk factors (such as diabetes, heart failure and hypertension), and those with recent changes to their treatment (e.g. RAASi, NSAIDs, or diuretics).[6] There is no evidence to guide the frequency of UACR testing, but this could be performed alongside eGFR monitoring or more frequently if the result may warrant titration of risk reduction strategies (see Section 3 below). Guidelines allow for some tailoring in monitoring and can consider patient preferences, including conservative management of advanced CKD.

3 | MANAGEMENT IN PRIMARY CARE

3.1 | Consider the cause

Most CKD seen in primary care in the UK is caused by diabetes and/or hypertension; however, it is important to be aware of the alternatives and avoid attributing the cause to diabetes and/or hypertension if the presentation is atypical (Figure 2). In patients with a new diagnosis of CKD, a full clinical history and examination, including social, environmental and family history, is recommended.[4] Consider an obstructive cause if the patient has urinary tract symptoms. Rare or genetic causes of CKD make up about 5-10% of CKD seen in primary care but cause 25% of cases of incident kidney failure.[37] Consider the possibility of renal involvement in patients with relevant multisystem disorders (e.g. systemic lupus erythematosus). In situations where the cause is uncertain or an uncommon cause is suspected, refer to nephrology.

3.2 | When to offer a renal ultrasound scan in primary care

1. Suspected structural abnormalities in the urinary tract, including urinary tract obstruction, should be considered when the patient has a history of urinary symptoms, including visible or persistent non-visible haematuria.[4,6]
2. Family history of polycystic kidney disease and over the age of 20 years (ultrasound is insensitive for the diagnosis of polycystic kidney disease in patients younger than this).[6]
3. Presentation with advanced CKD (stage G4-5; eGFR <30 ml/min/1.73 m^2).[6]
4. Rapid progression of CKD (see Table 3).[6]

3.3 | Communicating diagnosis

Fewer than half of patients with CKD are aware that they have a problem with their kidneys, even among those at high risk of progressing to kidney failure.[38,39] To promote better awareness and patient self-management, UK and international guidelines recommend educating patients about a diagnosis of CKD[4,6] and the implications for cardiovascular disease risk. CKD will lead to kidney failure in only a minority of patients, and specific discussion about kidney replacement therapy (dialysis and kidney transplant) should be reserved for patients with severe or progressive CKD who require specialist care. There are some excellent patient resources providing CKD education, which can be accessed through professional organizations such as Kidney Care UK in booklets, online written and short video formats.[40]

3.4 | Lifestyle

Following healthy lifestyle measures is the cornerstone of the management of all chronic diseases, including CKD. The evidence and guidance for lifestyle management in CKD have not changed substantially in recent years, and we will not perform a detailed review of these points here. In brief, major guidelines in CKD,[4,6] diabetes[21] and hypertension[25] recommend similarly that patients living with these conditions should follow healthy dietary patterns, engage in recommended levels of physical activity (including both aerobic and resistance training), avoid smoking and reduce body weight to avoid obesity.

3.5 | Cardiorenal risk reduction

CKD management has progressed enormously in recent years, with a selection of new therapeutics available to reduce the risk of CKD progression and prevent major adverse cardiovascular and renal events and reduce premature mortality. Irrespective of the underlying cause,

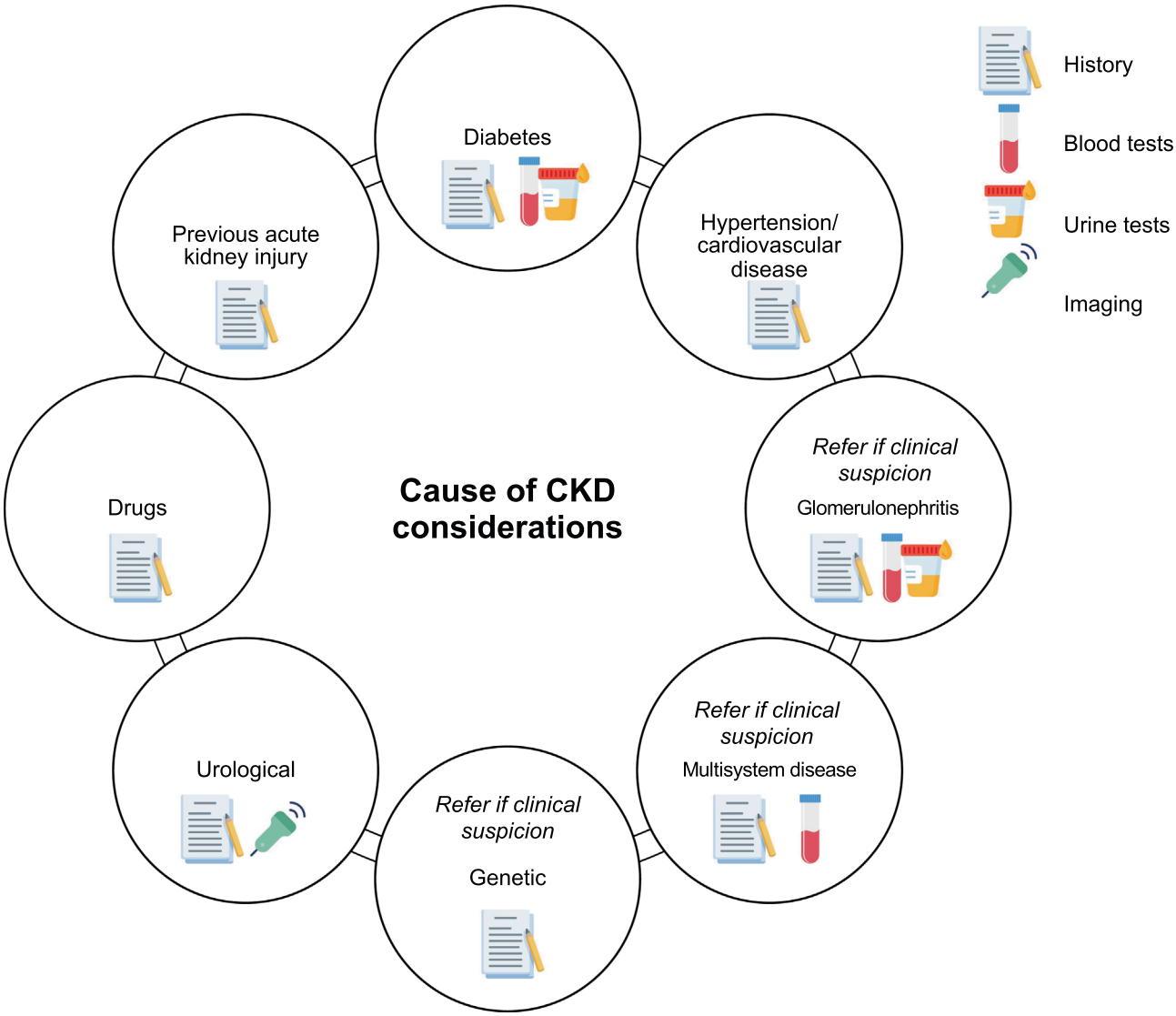

FIGURE 2 Classification of chronic kidney disease (CKD) according to cause.

TABLE 3 Definition of rapid progression of chronic kidney disease.

Starting eGFR, ml/min/1.73 m^2	Sustained[a] change in eGFR (ml/min/1.73 m^2) within 12 months reflecting rapid progression[b]
90	75
80	65
70	55
60	45
50	38
40	30
30	23
20	15

Abbreviation: eGFR, estimated glomerular filtration rate.
[a]Persistent over at least 3 months, i.e. not reflecting acute kidney injury.
[b]Higher value of: 15 ml/min/1.73 m^2 decline; 25% decline in eGFR and change in eGFR category.

blood pressure control with RAASi [angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), but not both], treatment with high-intensity statins and SGLT2i are indicated in almost all patients with non-dialysis CKD, with some additional treatment options in patients with type 2 diabetes, heart failure and/or in other special circumstances. We have included a simple illustration of treatments to consider among patients with CKD (Figure 3), with a more detailed discussion of the guidance in the subsections below.

3.5.1 | Blood pressure

Depending on the stage and cause of CKD, hypertension in CKD is observed in 60-90% of individuals. As in the general population, hypertension in CKD should be diagnosed using standardized techniques, preferably using home or ambulatory readings.[25] Among people with CKD, blood pressure should be checked at least annually,

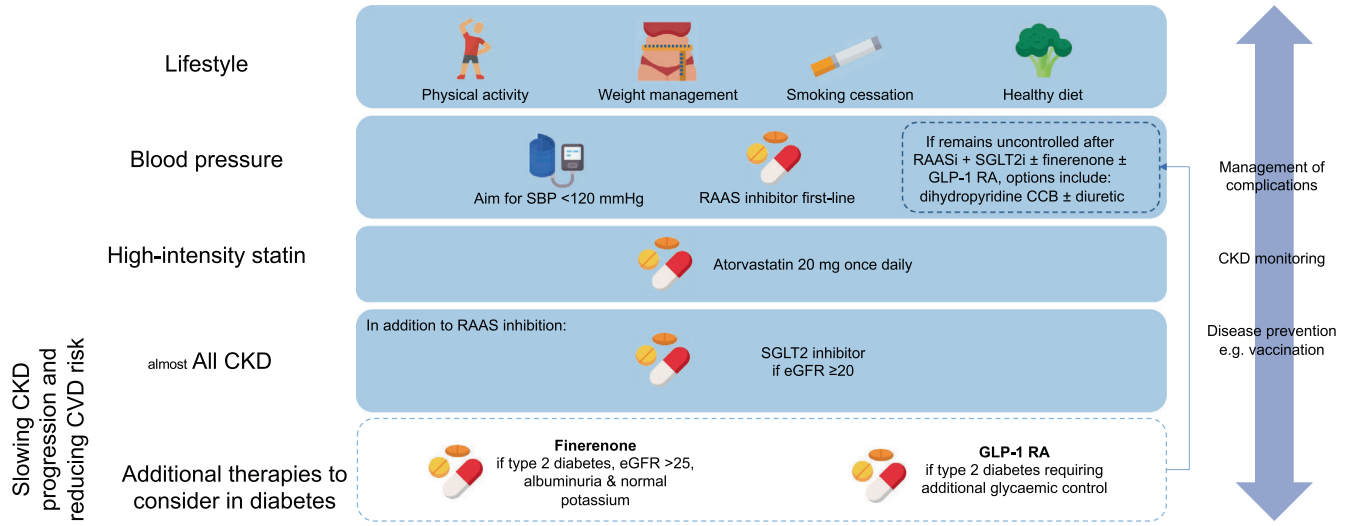

FIGURE 3 Management of CKD in primary care. CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR: estimated glomerular filtration rate in ml/min/1.73 m^2; GLP-1RA, glucagon-like peptide-1 receptor agonist; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; SGLT2i, sodium glucose cotransporter-2 inhibitor.

even if within the target range.[4,6] The frequency of blood pressure monitoring should be greater where blood pressure is suboptimally controlled and where albuminuria is elevated, as these are modifiable risk factors for progressive kidney disease and other adverse outcomes.

RAASi remain the preferred choice, where tolerated, for management of hypertension in CKD, but particularly among those with detectable albuminuria, type 2 diabetes and/or heart failure. Blood pressure management for patients with CKD should otherwise follow standard guidance for the management of hypertension.[25–27] For patients who have persistent uncontrolled or resistant hypertension (blood pressure above target on ≥4 agents, with or without CKD), a specialist referral is recommended for further assessment.[6]

Blood pressure targets have been subject to some controversy, and the recommended target varies across guidelines (Table 1). On average, the guidelines support a blood pressure target of <130/80 among people with CKD, with or without diabetes. Lower targets than this are generally not recommended in clinical practice because of an increased risk of adverse events. All guidelines recommend considering less intensive, individualized targets in patients with advanced age and/or frailty, a high risk of falls and fractures, a very limited life expectancy or symptomatic postural hypotension.

3.5.2 | Statins

Currently, cardiovascular risk scores do not adequately consider CKD as a risk factor for cardiovascular disease; cardiovascular risk scores therefore do not change risk-reduction guidance in CKD.[6,41,42] Current guidelines pragmatically suggest that people with CKD (eGFR <60 ml/min/1.73 m^2 and/or albuminuria) are considered high risk for cardiovascular disease. UK guidelines recommend atorvastatin 20 mg once daily for primary prevention of cardiovascular disease among all people with CKD.[41] In Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, recommendations vary somewhat by age and CKD status: in people age ≥50 years, statin-based regiments are recommended for those with eGFR <60 and/or albuminuria: specifically, atorvastatin 20 mg, rosuvastatin 10 mg or simvastatin 20 mg/ezetimibe 10 mg combination. In a meta-analysis of 28 trials of statin-based therapy, statin-based treatments showed no evidence of reducing major vascular events among patients treated with dialysis.[43] Statin-based therapies are not recommended for the primary prevention of cardiovascular disease in those treated with chronic dialysis[4] but can still be prescribed safely for secondary prevention in those who have had a previous cardiovascular or cerebrovascular event.

3.5.3 | Renin-angiotensin-aldosterone system inhibitors

ACEi and ARB have beneficial effects in reducing proteinuria and are recommended in patients with moderate or severe albuminuria, including in the absence of diabetes or hypertension.[4,6] In a meta-analysis of 119 trials (64 768 participants) in patients with CKD, ACEi and ARB reduced the odds of kidney failure, cardiovascular events and all-cause mortality.[44] ACEi were possibly superior to ARBs for these outcomes, although guidelines do not recommend one drug class over the other.[4,6]

Optimization of RAASi in patients with CKD is often limited by two concerns, i.e. (a) decline in kidney function, and (b) hyperkalaemia. Kidney function should be checked within about 2 weeks of starting or dose-escalating RAASi,[4,6] accepting a rise in serum creatinine of up to 30% or a decrease in eGFR of up to 25%, to maintain the prescribed dose of RAASi.[6]

UK guidelines recommend avoiding RAASi initiation if serum potassium is >5 mmol/L; however, international guidelines do not set a threshold.[4] Dietary and pharmacological measures (including cation exchange compounds such as sodium zirconium cyclosilicate and patiromer) are recommended to reduce serum potassium to facilitate initiation and avoid dose reduction because of hyperkalaemia in patients who qualify for RAASi treatment.[4,6] Because of the higher rates of adverse events, including AKI, hypotension and hyperkalaemia, RAASi (ACEi, ARB and direct renin inhibitors) should not be prescribed in combination with each other.[6]

3.5.4 | Sodium-glucose cotransporter-2 inhibitors

SGLT2is have been shown in populations of patients with CKD with and without diabetes to reduce kidney disease progression, AKI, cardiovascular risk, hospitalization with heart failure and all-cause mortality, irrespective of the primary kidney disease.[42,45–51] In the UK (broadly matching international guidelines[4]), SGLT2i are now recommended for use in people with CKD (eGFR ≥20 ml/min/1.73 m^2, excluding polycystic kidney disease, type 1 diabetes or patients with kidney transplants) in any of the following commonly overlapping clinical scenarios:[46] (a) type 2 diabetes; (b) symptomatic heart failure; (c) established coronary disease; (d) albuminuria (UACR ≥25 mg/mmol or UPCR ≥35 mg/mmol); and (e) eGFR 20-45 ml/min/1.73 m^2 in the absence of type 2 diabetes, heart failure or albuminuria.

Prescribing considerations

The guidelines are agnostic to the choice of SGLT2i. Treatment can be continued as eGFR declines until there is a requirement for dialysis or a kidney transplant.[46] The glycaemia-lowering effect of SGLT2i diminishes with declining eGFR; eGFR is approximately <30 ml/min/1.73 m^2, SGLT2is have no noticeable effect on HBA1c.[52] Additional glucose-lowering therapy may be required in people with type 2 diabetes and CKD. In patients with eGFR >45 ml/min/1.73 m^2 and HbA1c <58 mmol/L, 50% dose reductions in sulphonylureas or meglitinides, and 20% reductions in insulin treatment, are recommended to avoid precipitating hypoglycaemia.[46] No dose adjustments are required when starting SGLT2i treatment in patients taking only metformin, pioglitazone, DPP-4/gliptins, or glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy.[46] In patients without diabetes, it is not necessary to check or monitor HbA1c in response to treatment with SGLT2i.

Blood test monitoring is not required

Initiation of SGLT2i commonly causes a small initial reversible reduction in eGFR ('eGFR dip'), followed by stabilization of eGFR and improved kidney outcomes. Blood test monitoring is neither required nor recommended after initiation of SGLT2i, and treatment should not be discontinued if the eGFR dip has occurred after initiation of SGLT2i in the absence of other adverse features.

Sick day rules

Following sick day guidance may substantially reduce the potential risk of ketoacidosis.[46] Patients should be advised to withhold SGLT2i if they are unwell (vomiting, diarrhoea, fever, sweats, shaking or not eating/drinking normally) or have planned restrictions on food intake (e.g. prolonged periods of fasting); however, they should be advised to restart treatment after the illness has subsided.

3.6 | Additional recommendations for patients with type 2 diabetes

3.6.1 | Non-steroidal mineralocorticoid receptor antagonists

The non-steroidal mineralocorticoid receptor antagonist (nsMRA) finerenone has been shown in two major trials in diabetic kidney disease to reduce the risk of major adverse kidney events (including kidney failure, a 40% reduction in eGFR and death from renal events) and cardiovascular events (including myocardial infarction, stroke, hospitalization from heart failure, and death from cardiovascular causes).[53,54] Finerenone is newly recommended for use as an add-on to optimized standard care (including RAASi and SGLT2i) in patients with type 2 diabetes, eGFR >25 ml/min/1.73 m^2, albuminuria >3 mg/mmol and normal serum potassium.[4,55,56]

Prescribing considerations for nsMRA

In the UK, it is expected that finerenone treatment will be initiated in secondary care to begin with but will eventually be prescribed in primary care.[56] nsMRA are associated with lower rates of hyperkalaemia than older steroidal MRA (e.g. spironolactone and eplerenone), but potassium monitoring is recommended within 1 month of initiation and then every 4 months for the duration of treatment.[4] If potassium rises to above 5.5 mmol/L, treatment should be suspended until potassium-lowering measures are implemented (e.g. dietary changes or potassium cation-exchange resins). Re-initiation of treatment can be considered when potassium is ≤5 mmol/L. nsMRA can be continued at eGFR <25 ml/min/1.73 m^2, but with ongoing potassium monitoring and consideration of dose reduction if required. nsMRA should be stopped if eGFR falls below 15 ml/min/1.73 m^2 or if the patient requires dialysis or a kidney transplant.[56]

3.6.2 | Glucagon-like peptide-1 receptor agonists

GLP-1RAs have proven to reduce major adverse cardiovascular events (including myocardial infarction, stroke and cardiovascular death), and there is some evidence of benefit to kidney outcomes (including kidney disease progression, kidney failure and death from kidney disease) among patients with type 2 diabetes and CKD.[55] GLP-1RAs are recommended for the treatment of patients with type 2 diabetes and CKD who are not meeting individualized HbA1c targets, and who are either already treated with or unable to tolerate metformin and SGLT2i.[55]

Prescribing considerations for GLP-1RA

Gastrointestinal side effects, particularly nausea and diarrhoea, are very common. Guidelines recommend starting with a low dose of

GLP-1RA and titrating slowly ('start low, go slow') to reduce the likelihood of experiencing side effects.[55] Because of their popular, supporting role in aiding weight loss in patients living with overweight and obesity, GLP-1RAs are currently in very short supply.[57]

3.6.3 | Dosing and prescribing

Dosing

People with CKD may be at greater risk of the nephrotoxic effects of certain medications, and dose adjustment or drug avoidance may be necessary. The Renal Drug Database (https://www.renaldrugdatabase.com/s/) is a UK-based digital tool to aid prescribers in understanding prescribing and dosing considerations for patients with CKD and/or kidney failure. The resource was written by clinical renal pharmacists, supported by the UK Renal Pharmacy Group, and provides detailed advice and monographs for drug prescribing and de-prescribing in CKD.

Non-steroidal anti-inflammatory drugs

Clinical guidelines recommend the avoidance of prolonged use of NSAIDs among people with CKD stage G3 (eGFR ≥30 ml/min/1.73 m^2) and total avoidance in people with CKD stages G4-5 (eGFR <30 ml/min/1.73 m^2). However, data confirming the nephrotoxicity of NSAIDs are limited, and alternative analgesic use (e.g. opioids) in people with CKD have their own risks. Judicious use of NSAIDs can be considered even in people with CKD stages G3-4, on a case-by-case basis and after careful consideration of the individual risk/benefit profile.[58] In CKD stage G5, NSAIDs should be avoided completely, except when providing palliative care.[58]

Sick day rules

Sick day rules for SGLT2i are covered in the relevant section above. Despite a paucity of data for effectiveness in preventing AKI or other relevant outcomes, sick day rules are often recommended for sulphonylureas, RAASis, diuretics, metformin and NSAIDs. Sick day advice is often poorly understood, associated with medication errors, and particularly with failure to restart the medications. Patients should be clearly advised of the plan to recommence medication after the illness has subsided.[4] Medication review after illness is recommended to avoid accidental discontinuation of treatments with important clinical benefits[4]; practically speaking, this may be best accomplished opportunistically while undertaking medical reviews for other reasons.

3.6.4 | Vaccinations

Patients with CKD, including patients on haemodialysis should be offered vaccination against influenza (CKD stages G3-5) and pneumococcus (CKD stages G4-5) every year.[59] Patients with CKD stages G4-5 should additionally be offered the hepatitis B vaccination.[59] In practice, this is usually reserved for patients who would probably proceed with kidney replacement therapy (dialysis or a kidney transplant) and will often be guided by nephrology services.

The COVID-19 pandemic confirmed patients with kidney failure (requiring dialysis or a kidney transplant) to be vulnerable to severe disease, high mortality rates and an impaired response to vaccination compared with the general population.[60,61] Patients with non-dialysis CKD also experienced higher rates of adverse outcomes, including severe AKI requiring dialysis treatment.[62] Patients with CKD should be encouraged to receive additional COVID-19 vaccinations if/when they become available. Patients with CKD stage G4-5 are eligible for consideration of treatment for COVID-19 if confirmed positive.

3.7 | REFERRAL TO NEPHROLOGY

The referral criteria capture patients who require, or are suspected to require, specialist investigation, management or counselling relating to kidney disease. In the UK, these are as follows.[6]

- 5-year risk of needing kidney replacement therapy of >5%, estimated using the four-variable Kidney Failure Risk Equation (KFRE).
- UACR of ≥70 mg/mmol, unless known to be caused by diabetes and already appropriately treated.
- UACR of >30 mg/mmol, together with haematuria.
- Rapid progression of CKD (see Table 3):
  - a sustained decrease in eGFR of ≥25% and a change in the eGFR category within 12 months
  - a sustained decrease in eGFR of ≥15 ml/min/1.73 m^2 per year
- hypertension that remains above the person's individual target despite the use of at least four antihypertensive medicines at therapeutic doses
- known or suspected rare or genetic causes of CKD
- suspected renal artery stenosis.

The main recent changes in the guidelines have been (a) the removal of the criterion to refer patients with eGFR <30 ml/min/1.73 m^2, and (b) the addition of KFRE as a marker of the likelihood of kidney disease progression and kidney failure in people with CKD.[4,6] The KFRE is validated for use in people with eGFR <60 ml/min/1.73 m^2, using age, sex, eGFR and UACR to estimate the 2- and 5-year risk of kidney failure (International calculator: https://kidneyfailurerisk.com; UK calculator: https://kidneyfailurerisk.co.uk).[63–65] In the UK, KFRE >5% risk at 5 years should be used to guide patients who should be referred to nephrology.[6,22]

The limitations of KFRE are that: (a) it provides a point estimate and does not account for variation in eGFR or UACR over time; (b) it does not account for the cause of kidney disease; and (c) it does not account for the fact that some patients may have a high KFRE estimate, but the competing event of death would probably occur before kidney failure. It is therefore appropriate to consider the KFRE result in the context of the individual patient: referral to nephrology is not mandated and may be inappropriate in patients with shorter life expectancy or in those who would not want or benefit from kidney replacement therapy.

Recent work in the UK suggests that these criteria changes should not dramatically increase or decrease the number of referrals sent to nephrology from primary care.[22] However, current low rates of albuminuria testing preclude the calculation of KFRE in about one-third of the CKD population; the desired improvements in albuminuria testing will probably identify greater numbers of patients meeting criteria for referral to nephrology.[22]

3.8 | MANAGING CHRONIC KIDNEY DISEASE IN THE OLDER PATIENT

Kidney function decline is observed with increasing age, even among apparently healthy individuals; CKD, by eGFR criteria, is therefore likely to be observed in a substantial proportion of older individuals.[66,67] Most recommendations for the investigation, diagnosis and management of CKD were based on general adult populations and may not be directly transferable to older adults, particularly those living with complex, multimorbid disease and/or frailty.

Patients living with CKD who are younger will have a higher lifetime risk of major adverse cardiovascular and renal events because of a longer expected life span to accrue the risks. Even among older, apparently healthy individuals, mild CKD remains associated with adverse outcomes and warrants consideration of treatment.[5,68]

It is reasonable and appropriate to adjust the investigation, referral and treatment intensity according to the expected gain for an individual patient. Patients with the highest absolute level of risk, including older patients, those with multimorbidity and frailty, may expect to derive a higher absolute benefit from risk reduction strategies (as has been seen for blood pressure control and SGLT2i).[69–72] However, there is also a higher rate of treatment-associated adverse events in these groups, and there is only sparse evidence to guide the risk/benefit balance.[69–72] Minimizing medicalization and polypharmacy may be appropriate for those with a shorter life expectancy or to align with individuals' perspectives and treatment goals. The guidelines cannot cover all eventualities but allow the health care practitioner to exercise their clinical judgement in advising on management for an individual patient.

3.9 | CONCLUSION

CKD represents an increasingly common disease with major health and economic implications, but detection and awareness among health care providers and patients remain suboptimal. Early diagnosis of CKD, testing simple blood and urine markers in high-risk populations, is key to mitigating the risks associated with CKD. Timely risk-reduction strategies have overlapping indications to reduce kidney disease progression, cardiovascular disease and premature death. The pillars of CKD management in the community include lifestyle management, blood pressure and glycaemic control, statins and targeted interventions to reduce cardiorenal risk: RAASi, SGLT2i, GLP-1RA and nsMRA. New tools provide individualized risk assessment to guide the need for specialist care among patients at the highest level of risk. Although CKD is associated with higher risks of adverse outcomes even among older individuals, it is appropriate to individualize the approach for older individuals and among those who may not benefit from intensive investigation and treatment.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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