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The Importance of Early Diagnosis and Intervention in Chronic Kidney Disease: Calls-to-Action from Nephrologists Based Mainly in Central/Eastern Europe

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Abstract
Background: Chronic kidney disease (CKD) has a global prevalence of 9.1–13.4%. Comorbidities are abundant and may cause and affect CKD. Cardiovascular disease strongly correlates with CKD, increasing the burden of both diseases. ***Summary:*** As a group of 15 clinical nephrologists primarily practicing in 12 Central/Eastern European countries, as well as Israel and Kazakhstan, herein we review the significant

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unmet needs for patients with CKD and recommend several key calls-to-action. Early diagnosis and treatment are imperative to ensure optimal outcomes for patients with CKD, with the potential to greatly reduce both morbidity and mortality. Lack of awareness of CKD, substandard indicators of kidney function, suboptimal screening rates, and geographical disparities in reimbursement often hamper access to effective care. ***Key Messages:*** Our key calls-to-action to address these unmet needs, thus improving the standard of care for patients with CKD, are the following: increase disease awareness, such as through education; encourage provision of financial support for patients; develop screening algorithms; revisit primary care physician referral practices; and create epidemiological databases that rectify the paucity of data on early-stage disease. By focusing attention on early detection, diagnosis, and treatment of high-risk and early-stage CKD populations, we aim to reduce the burdens, progression, and mortality of CKD.

Introduction

Chronic kidney disease (CKD) has a global prevalence of 9.1–13.4% [1–5]. In 2017, the Global Burden of Disease study found ~100 million Europeans were affected by CKD [1, 6]. CKD is the tenth most common cause of global mortality [7], projected to rise to fifth by 2040 [6, 8] and designating it a significant worldwide public health problem. The patient and societal burdens of CKD are increasing owing to ageing populations, growing medical costs, and associations between CKD and other diseases that are also increasing in prevalence [1–4, 6, 9–12].

The early stages of CKD tend to be asymptomatic, hampering timely diagnosis and treatment [13]. The management of CKD varies substantially across Europe [4, 12, 14], despite timely treatment being imperative to slow or even halt CKD progression and substantially reduce cardiovascular morbidity and mortality [1, 14]. Epidemiology also varies, with prevalence higher in Central and Eastern Europe (13.3%) than in Western Europe (10.1%) [1, 6]. Potential factors contributing to geographical variations in prevalence and management of CKD may include differences in awareness (particularly of early-stage disease, detection, screening policies, diagnosis, and early intervention); access to healthcare; use of potentially nephrotoxic drugs including non-steroidal anti-inflammatory drugs (NSAIDs); reimbursement policies for diagnosis and treatments; and patient demographics, e.g., nutrition, smoking, socioeconomics, and physical activity [4, 12, 15, 16]. These factors culminate in underuse or misuse of treatment [1]; thus, a priority action is to improve primary care management of CKD in order to reduce disease progression, morbidity, and mortality [9, 17]. Guidelines issued by organisations such as Kidney Disease: Improving Global Outcomes (KDIGO) and the American Diabetes Association (ADA) recognise the importance of early CKD diagnosis and treatment, via screening high-risk populations. Such evidence-based guidelines further bolster the need for a systematic and multidisciplinary approach across Europe to hasten and improve care for patients with CKD.

We are a group of 15 clinical nephrologists based in 14 countries: seven in Central Europe (Austria, Croatia, Czech Republic, Poland, Republic of Serbia, Slovakia, Switzerland), three in Eastern Europe (Estonia, Latvia, Lithuania), and two in Southeast Europe (Bulgaria, Romania), in addition to one each in Asia/Eastern Europe (Kazakhstan) and the Middle East (Israel). Our 14 countries encompass a wide spectrum of economic development, reimbursement legislation, and healthcare systems. Herein we initially highlight the most significant unmet needs within CKD care, highlighting disease burden and the urgent need for early diagnosis and treatment. We subsequently provide a comprehensive overview of CKD diagnosis and treatment practices/policies in our respective countries. Finally, we recommend specific calls-to-action for the medical communities in our countries, including policymakers and clinicians (primary physicians, internists, cardiologists, diabetologists, endocrinologists, paediatricians, etc.), to raise awareness of CKD's burden and to improve its management. These calls-to-action are also of relevance beyond the 14 countries included in this article.

Disease Burden

CKD is strongly associated with a range of comorbidities [5], particularly cardiovascular disease (CVD), arterial hypertension, diabetes mellitus, and obesity [1, 2, 6, 12, 18], which are risk factors for both CKD onset and progression. CKD is a notable risk factor for CVD and CVD mortality [1]. A systematic analysis found that, in 2017 globally, 7.6% of CVD deaths resulted from impaired kidney function [1]. Patients with KDIGO CKD stage G3–4 are more likely to die from CVD than to progress to end-stage kidney disease [19]. The risk factors for CVD in CKD include hypertension, dyslipidaemia, hyperglycaemia, and vascular calcification [18]. Heart failure, especially with preserved ejection fraction, has

been recognised as a major complication of CKD; 40% of patients with chronic heart failure are estimated to have CKD [20] and CVD is the leading cause of death among CKD patients [21]. Accordingly, the 2021 European Society of Cardiology includes albuminuria as an independent risk factor for CVD [22]. The correlation between CKD and CVD ultimately increases disease burden; in 2017, 41.6% of disability-adjusted life years for patients with CVD were attributable to impaired kidney function [1].

The patient burden of CKD is higher for certain subgroups. For example, lower socioeconomic status, indicated by income and education, was significantly associated with CKD prevalence [23] and correlated with greater negative impact on patients' quality of life. The proportions of predialysis CKD patients with depression (47.1%) and anxiety (27.6%) are far greater than among the general population (where prevalence ranges from 2 to 21% [24] and 4–25%, respectively). Disease burden is also higher for older populations as ageing is associated with CKD [5]; as Central and Eastern European societies are ageing, partly due to economically motivated emigration to Western Europe, this contributes to CKD's increasing impact.

CKD and its associated comorbidities also lead to substantial healthcare resource utilisation, burdening both systems and patients. The likelihood of hospitalisation may be greater for patients with CKD than for those with non-metastatic cancer (adjusted relative rate, 1.55, 95% CI, 1.52–1.58) [25]. Another study found that hospital stays are longer, and thus more costly, for patients with non-communicable diseases when occurring in conjunction with CKD than without CKD [26].

Importance of Early Diagnosis and Treatment

Current treatment tools for CKD include renin-angiotensin-system inhibitors, statins, antiplatelet therapy, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and non-steroidal mineralocorticoid receptor antagonists [27, 28]. For patients at high risk of CKD development and progression (i.e., those with CVD, diabetes, obesity, HIV infection, multisystem disease with potential kidney involvement, family history of kidney disease, age >60 years), guidelines typically recommend regular screening to enable timely intervention, halting or delaying CKD progression [29]. Patients with estimated glomerular filtration rate (eGFR) categories G4–G5 (<30 mL/min/1.73 m^2), albuminuria (albumin-to-creatinine ratio [ACR] ≥300 mg/mmol), or substantial eGFR decline should be consulted by a nephrologist as soon as possible [30].

Arterial hypertension is a leading cause of worsening kidney function and progression to end-stage kidney disease; thus, adequate control of hypertension in patients with CKD is important, especially due to the bidirectional relationship between these two conditions. Lowering blood pressure via pharmacological and lifestyle interventions can reduce eGFR decline, disease progression, and incidence of CVD in people with CKD [19]. Hence, blood pressure regulation is a key strategy for limiting kidney damage and reducing morbidity and mortality in patients with hypertension [31]. Early treatment of CKD and comorbid cardiovascular risk factors and diseases using SGLT2 inhibitors has also been hypothesised to prevent cognitive impairment [32].

Primary care physicians have a crucial role in CKD risk stratification and accurate diagnosis (e.g., acute kidney injury vs. CKD), ideally before consulting with a nephrologist [27, 33]. The initial stages tend to be asymptomatic; fewer than 5% of patients are aware that they have early-stage CKD [27], highlighting the importance of (a) earlier screening and (b) focusing on high-risk patients in primary care to detect CKD. Furthermore, screening for early-stage CKD is pivotal to reduce morbidity and mortality [17, 27, 30], enabling the medical community to act more effectively in preventing CKD progression and its deleterious sequelae [30]. KDIGO guidelines, endorsed by the ADA, recommend that the frequency of screening/monitoring should correspond to the likelihood of disease progression (patients with the most severely decreased GFR and increased albuminuria should be monitored most regularly) [17, 34]. CKD stage G3a is considered a turning point in disease progression and emphasises the importance of early and correct staging [30].

While international guidelines (e.g., KDIGO) provide excellent general recommendations for screening/monitoring and treatment, local/national guidelines should also be consulted [30, 35]. Local guidelines do vary. For example, nephrologists and diabetologists in Slovakia have developed guidelines (last updated 2021) stating that a diabetic patient with eGFR <60 mL/min/1.73 m^2 and/or albuminuria >300 mg/day (or proteinuria >0.5 g/day) should be consulted by a nephrologist [36]. On the other hand, Bulgarian guidelines recommend nephrologist referral at eGFR <30 mL/min/1.73 m^2, with earlier referral in cases of suspected non-diabetic glomerular disease or rapid decline in kidney function [37].

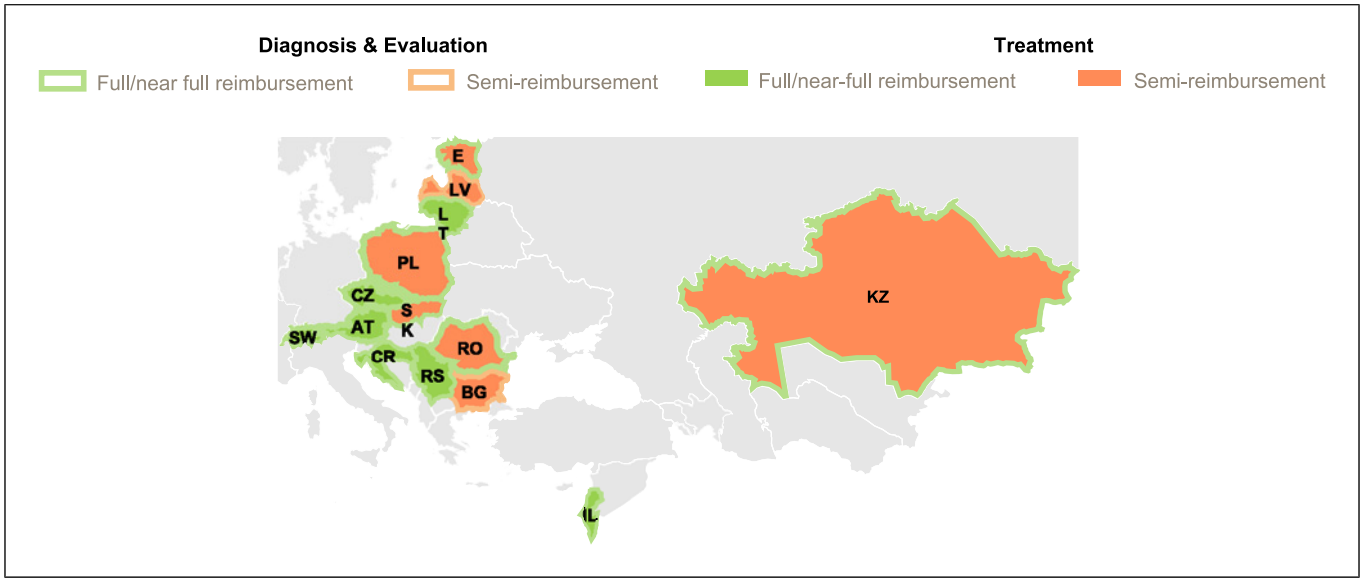

Fig. 1. Map of reimbursement policies for CKD by diagnosis/evaluation and treatment. AT, Austria; BG, Bulgaria; CR, Croatia; CZ, Czech Republic; E, Estonia; IL, Israel; KZ, Kazakhstan; LV, Latvia; LT, Lithuania; PL, Poland; RO, Romania; RS, Republic of Serbia; SK, Slovakia; SW, Switzerland.

Barriers to Diagnosis and Treatment

Patients with CKD experience significant barriers to diagnosis and treatment. Although major clinical practice guidelines identify eGFR as the preferred indicator of kidney function, serum creatinine continues to be the most widely used endogenous marker [38]. Additionally, screening via ACR measurement is widely recommended for individuals at high risk of CKD [39–41]; however, suboptimal ACR screening rates result in many undiagnosed CKD cases, particularly at early stages (G1–2) [42]. Despite recognition that screening for early CKD in high-risk groups is cost-effective, financial incentives, such as pay-for-performance programmes, are lacking [17]. Other reasons for the suboptimal screening rate include low awareness of CKD amongst healthcare professionals (HCPs), the perceived complex nature of CKD, and a lack of standardised and structured CKD care outside of that given in nephrology departments. Such barriers to early CKD diagnosis and management may impede timely and efficient treatment.

Restrictive reimbursement policies are a significant financial barrier to CKD treatment. Only a small proportion of countries worldwide provide free or subsidised treatment for CKD patients. According to the Global Kidney Health Atlas, only 28% (45/159) of countries provide free treatment and only 20% (32/159) offer subsidies [4].

Figures 1 and 2 and online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000538765) summarise the reimbursement policies for CKD diagnosis/evaluation and treatment in the 14 countries in which we practice as clinical nephrologists: seven in Central Europe (Austria, Croatia, Czech Republic, Poland, Republic of Serbia, Slovakia, Switzerland), three in Eastern Europe (Estonia, Latvia, Lithuania), and two in Southeast Europe (Bulgaria, Romania), in addition to one each in Asia/Eastern Europe (Kazakhstan) and the Middle East (Israel). Reimbursement for diagnosis and evaluation of CKD varies by country across our 14 nations and, as shown on the map of Europe (Fig. 1), is generally less comprehensive in the east. As shown in detail in online supplementary Table 1, country-specific limitations may be placed upon screening reimbursement, such as to particular patients and healthcare settings in Bulgaria and Romania. In Bulgaria, albuminuria testing is only reimbursed for people with diabetes or if ordered by a nephrologist, the latter being notable because patients with undiagnosed early-stage CKD may present first to primary care practitioners, thus delaying treatment. In Romania, ACR reimbursement may also be limited to secondary and tertiary healthcare services. Other country-specific issues regarding diagnosis/evaluation and treatment of CKD are covered in detail in online supplementary Table 1.

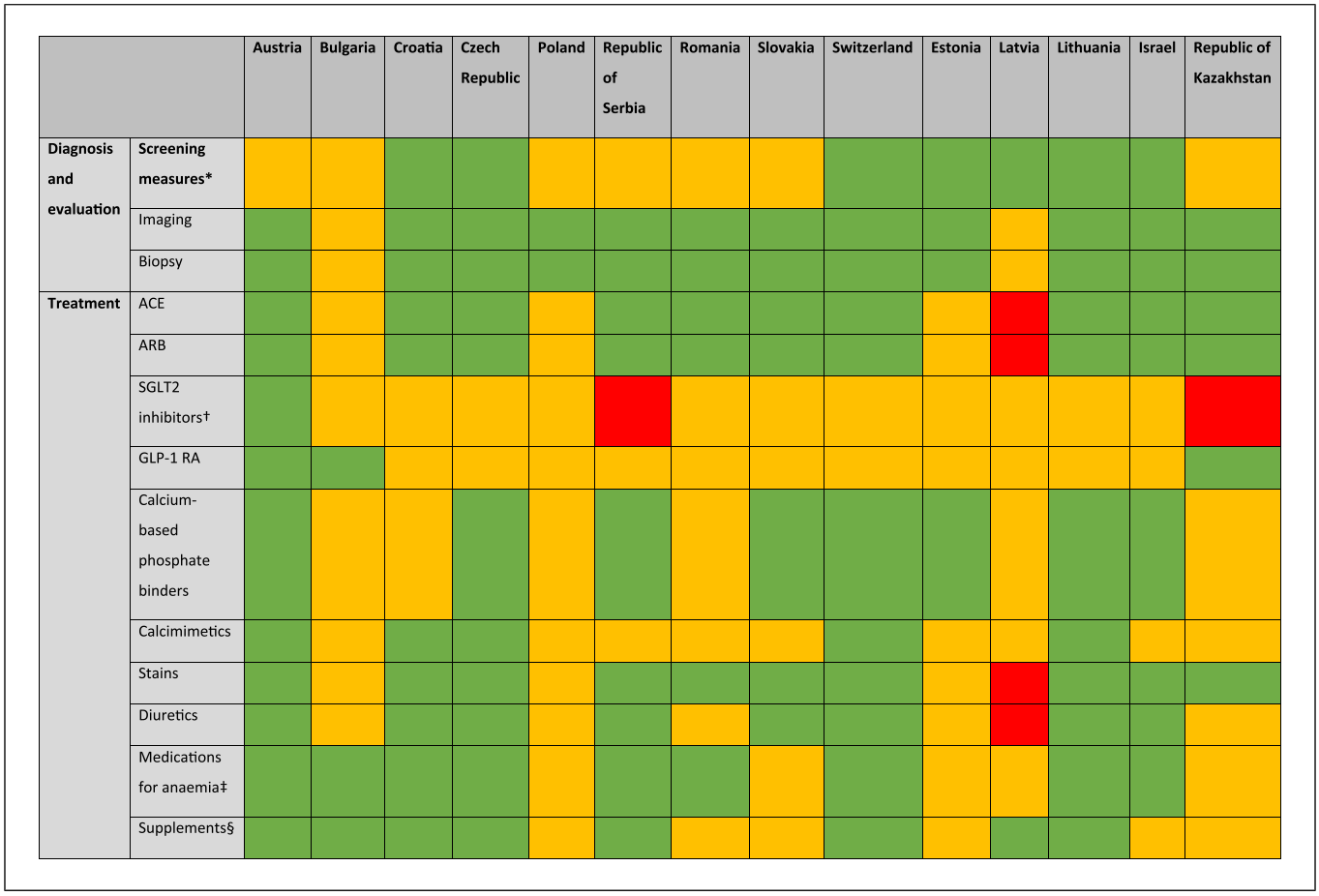

Fig. 2. Country-specific reimbursement policies for CKD by diagnosis and evaluation method and treatment. *Screening measures include ACR, eGFR, serum creatinine, blood chemistry. †SGLT2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin. ‡Medications for anaemia include ESA and iron preparations. §Vitamin D analogues include calcitriol and paricalcitriol. Figure is based on authors' perspectives. Colour coding is as follows: green represents good levels of reimbursement, e.g., full reimbursement or numerous screening/treatment options. Orange represents partial reimbursement policies, or full reimbursement with criteria and restrictions, e.g., full reimbursement dependent on the speciality of the prescribing HCP. Red represents no reimbursement. ACE, angiotensin-converting enzyme; ACR, albumin-to-creatinine ratio; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2, sodium-glucose co-transporter-2.

As expected, there is a complex picture of therapeutic reimbursement policies across our 14 nations (Fig. 1, 2; online suppl. Table 1). Across most of the 12 Central/Eastern European countries, SGLT2 inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and calcimimetics are only partially reimbursed and limitations are placed based on the speciality of the prescribing HCP. For instance, in Bulgaria, full SGLT2 inhibitor reimbursement is only applicable if prescribed by endocrinologists, with partial reimbursement when prescribed by other specialists, and in the Czech Republic SGLT2 inhibitors are fully financed when prescribed by a nephrologist. Other examples of reimbursement restrictions include that SGLT2 inhibitors may only be reimbursed for patients with type 2 diabetes, such as in the Republic of Serbia, Latvia, Lithuania, and Kazakhstan. Some nations offer only partial reimbursement for treatments, as in Estonia, where the costs for angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), SGLT2 inhibitors, and GLP-1 RAs are 75% reimbursed for most patients. ACE inhibitors and ARBs are fully reimbursed across most of the countries. Furthermore, calcium-based phosphate binders, statins, diuretics, medications for anaemia (erythropoiesis-stimulating agents and iron preparations), and supplements (vitamin D analogues, including calcitriol and

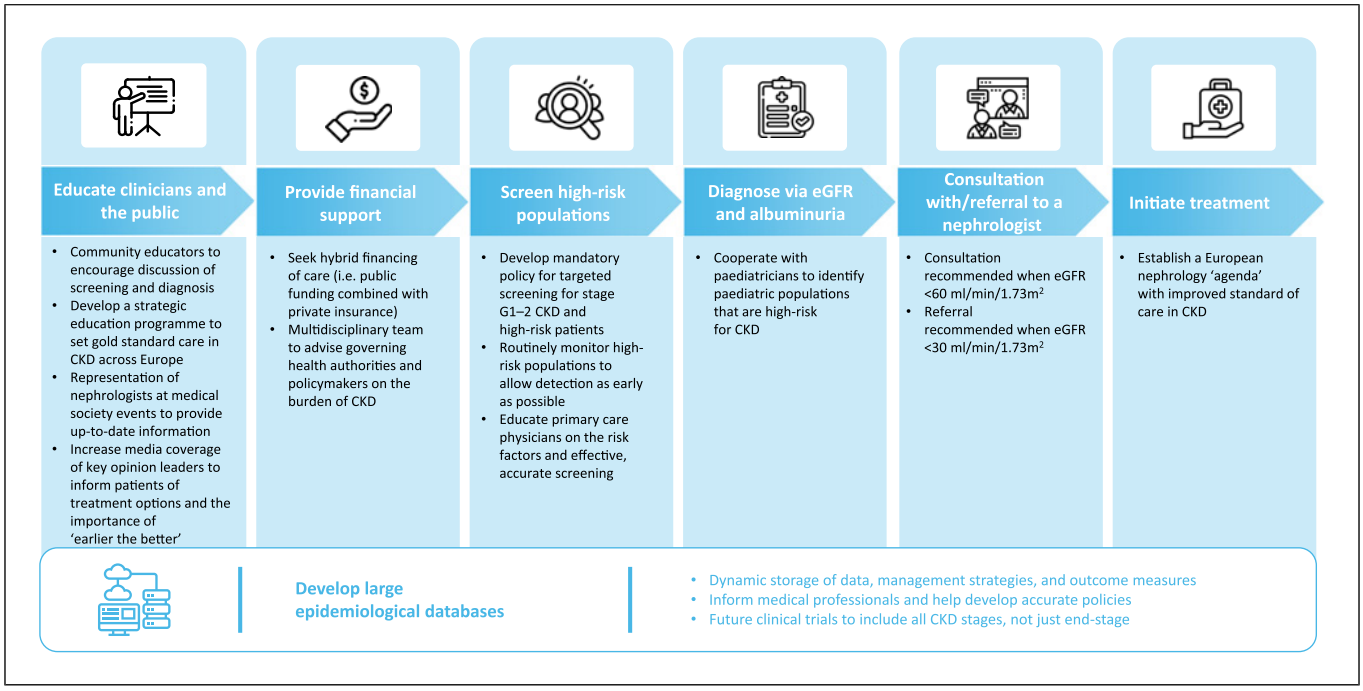

Fig. 3. Calls-to-action for improving the management of CKD from expert perspectives. CKD, chronic kidney disease; eGFR, glomerular filtration rate.

paricalcitol) are typically fully reimbursed. It is noteworthy that Latvia reports particularly restrictive reimbursement policies, with ACE inhibitors, ARBs, and statins not eligible for any reimbursement. Thus, this review highlights that geographical disparities in the availability of financially accessible care are likely to hamper timely CKD diagnosis and treatment.

Demographic factors, such as race and age, can also lead to barriers to effective CKD diagnosis and treatment [43]. Black patients may be disproportionately underdiagnosed and undertreated because current equations, which incorporate race, might overestimate eGFR values [43, 44]. Renal function decreases with age, even in healthy individuals, not uncommonly to the level of the CKD definition, which means that the use of a fixed eGFR threshold to diagnose CKD in older patients could lead to overdiagnosis [44]. Therefore, if a specific threshold is to be used for detecting actual CKD in elderly people, it could be more accurate to have it specified as 45 mL/min/1.73 m^2, not as 60 mL/min/1.73 m^2 [45]. In the absence of additional symptoms, it has been recommended to primary care physicians not to refer elderly patients based on a reduction in eGFR alone, if simply exhibiting normal age-related kidney decline. We do, however, acknowledge the importance of considering referral in the instance of lower GFR to ensure that a renal pathology is not overlooked.

Calls-to-Action: Based on Expert Opinion

The overriding goals of CKD management are to prevent/delay renal disease progression and complications (especially CVD), thus potentially increasing lifespan and quality of life. Here, we outline some calls-to-action to achieve these goals (Fig. 3).

Increase Awareness: Educate Clinicians and the Public

Nephrologists in Balkan countries recently warned of low societal awareness of CKD, which hinders early diagnosis and treatment [46]. In Central and Eastern Europe, the main route of disseminating information to the public is the coordinated campaign on World Kidney Day by representatives from medical societies. To promote knowledge of CKD among the public and clinicians, we recommend the following four approaches to be considered:

1. Community educators should lead discussions around CKD screening and appropriate diagnostic tests, to break down barriers such as taboo topics like urogenital symptoms and to support better physician-patient communication. To ensure a broad and comprehensive education programme, different renal topics should be raised at different times annually. Pharmacists should be included in future communication strategies,

particularly to aid patient awareness of renal risks associated with NSAIDs as part of a wider strategy to curb NSAID use.
2. Greater media presence of key opinion leaders and medical representatives would inform patients of their treatment options and, crucially, the importance of early intervention.
3. Development of strategic education programmes (setting out the gold standard of care) would increase knowledge sharing and communication among HCPs. Such programmes should be endorsed by as many medical societies as possible, such as those encompassing primary care, CKD, and medical practice more widely. Education opportunities, such as the annual European Kidney Forum hosted by the European Kidney Health Alliance and Members of the European Parliament (MEP) Group for Kidney Health, enable upskilling and networking with other HCPs and MEPs. However, this is aimed at nephrology practitioners and patient representatives, rather than across a broader range of specialities. Clinical comprehension of CKD and its risk factors is important among the whole medical community because a variety of specialities (including primary care clinicians, internists, cardiologists, and endocrinologists) often assess the patient and prescribe treatment before consultation with a nephrologist. This is particularly the case for specialists treating patients with common comorbidities (e.g., cardiologists). It is paramount that these specialists receive education on screening guidelines and predictors of patient survival (such as eGFR), in order to initiate nephroprotective measures as early as possible.
4. Establishment of a coordinated CKD management programme outside of the nephrology department would provide clearer guidance for the wider medical community, especially cardiologists and diabetologists, and may encourage HCPs to discuss issues regarding diagnostic and treatment strategies, disease awareness, and reimbursement.

Provide Financial Support: Public and/or Private Options

Despite its global burden, CKD is rarely included in major chronic disease control strategies, impeding governments from properly addressing CKD in national policy. While full financial support from public healthcare services may be unattainable, hybrid options could be actively sought, i.e., combining public funding and private insurance. The contribution of private insurance companies is hugely impactful [12], although the medical history exclusion criteria of many policies could lead to a predominant use by healthier people. We therefore recommend a multidisciplinary panel of primary care physicians, internists, and nephrologists to advise governing health authorities and policymakers on how to improve CKD awareness, diagnose early, and inform management policies.

Screen High-Risk Patient Populations

Whilst early detection can avert CKD progression and complications, in some Central/Eastern European countries screening rates continue to be suboptimal. The Swiss Society of Nephrology has created a booklet for primary care physicians listing conditions with increased CKD risk that should warrant CKD screening, but strategies must be employed to ensure guidance translates to practice change both nationally and internationally. We recommend the following:

1. mandatory targeted screening in high-risk populations for stage G1 and G2 CKD by primary healthcare providers;
2. provision of up-to-date information on risk factors and effective screening procedures, developed by a multidisciplinary panel, promoted via educational materials and events (congresses, webinars, etc.);
3. implementation of a common EU policy for mandatory CKD screening to ensure that effective screening practices are upheld.

Timely Consultation: Including by Nephrologists

In Europe, consultation with primary healthcare services can be delayed, often leading to patients presenting to nephrologists with burdensome later-stage CKD. We recommend that national healthcare services take steps to ensure primary care providers are aware of when a referral to nephrology is appropriate and to encourage consultation or referral as soon as clinical thresholds are met, as well as for individuals with functional renal abnormalities (e.g., a rapid fall in GFR and/or a large increase in ACR). We recognise that consultation by a nephrologist for all patients with CKD stage G3a may overburden already stretched health services; thus, we recommend consultation with a nephrologist for those with eGFR <60 mL/min/1.73 m^2 and nephrology referral for eGFR <30 mL/min/1.73 m^2. Nephrology referral does not necessarily mean total takeover from primary care services, although patients with considerable GFR reductions may require specialist kidney care services.

Better practice may boost the attractiveness of the nephrology speciality, increase the availability of treatment, and may culminate in the development of a European nephrology "agenda." We recommend this "agenda" as a platform to call for initiatives such as telemetric CKD data, expert centres, prevention of

unnecessary patient travel between hospitals and to generally raise awareness of CKD among medical specialists and the public. Cooperation between nephrologists and paediatricians is required to identify high-risk paediatric populations, such as young patients with diabetes or genetic forms of CKD, who are at increased risk of developing or progressing to advanced CKD as adults. For example, in Bulgaria, paediatric nephrologists participate in scientific activities in the nephrology community to provide expert knowledge on these high-risk groups.

Create Epidemiological Databases

Epidemiological databases are lacking in Europe, especially on the prevalence and incidence of early-stage CKD. We recommend the development of agreed measurements and standardised techniques to formulate a large, dynamic database including albuminuria and kidney function values, management strategies, and outcome measures. The first step could be implementation within a single city, unifying a database among hospital laboratories, with expansion nationwide and eventually internationally. In addition, we recommend that future registry designs and clinical studies should include all CKD stages, not just late stage, to generate the data necessary to establish a more comprehensive understanding of CKD. Retrospective data are imperative to improve prevention and treatment strategies, inform healthcare policies, and advise the geographical placement of nephrologists. In particular, real-world data may provide an accurate representation of the burden across a region and guide the medical community on where to focus disease management strategies [12]. In the future, combined use of computerised medical files and artificial intelligence may expedite the database process and how it informs the medical community.

Conclusions

CKD is a major public health issue, associated with a wide range of comorbidities and complex management requirements. Focusing professional and societal attention on timely detection and therapeutic intervention in high-risk, early-stage CKD populations is, in our view, the most efficient method to reduce disease burden and ultimately save lives. Here, we have outlined some important calls-to-action for the wider medical community, namely, primary care physicians, internists, cardiologists, diabetologists, and paediatricians, along with nephrologists. Recommendations include increasing disease awareness publicly and among clinicians, such as through guidance to professional societies; developing epidemiological databases to advise health authorities and insurance policymakers; and implementing robust detection and consultation schemes centered on primary care physicians and their key role in timely CKD management.

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Conflict of Interest Statement

Adrian Covic received consultancy fees from Boehringer Ingelheim and FMC; received honoraria for lectures, presentations, bureaus, manuscripts, or events from Astra Zeneca and Boehringer Ingelheim; participated on advisory boards for Astra Zeneca, Boehringer Ingelheim, and Strada; and has a leadership role within the Romanian Society Nephrology and the European Dialysis Working Group (part of the European Renal Association). Jean Filipov received honoraria for lectures, presentations, bureaus, manuscripts, or events from Berlin Chemie, Boehringer Ingelheim, and Swixx Biopharma and participated on advisory boards for Boehringer Ingelheim. Ryszard Gellert received honoraria for lectures, presentations, bureaus, manuscripts, or events from Astra Zeneca, Astellas, Bayer, Boehringer Ingelheim, Fresenius Kabi, Fresenius Medical Care and had a leadership role in the Ministry of Health as National Consultant of Nephrology. Niels Gobin received honoraria for lectures, presentations, bureaus, manuscripts, or events from Astra Zeneca, Boehringer Ingelheim, and Pierre Fabre and participated on advisory boards for Astra Zeneca and Boehringer Ingelheim. Bojan Jelaković received consulting fees and personal fees from Berlin Chemie, Boehringer Ingelheim, and Servier; received honoraria for lectures, presentations, bureaus, manuscripts, or events from Astra Zeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Krka, Norvasc, Servier, and Viatris; and has other financial or non-financial interests within AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Medtronic, Novartis, Novo Nordisk, Servier, and Viatris. Kairat Kabulbayev received support for attending meetings and/or travel from Boehringer Ingelheim. Merike Luman received consulting fees from Astellas Pharma and Bayer; received honoraria for lectures, presentations, bureaus, manuscripts, or events from Astra Zeneca, Bayer, Boehringer Ingelheim; participated in advisory boards with Astra Zeneca and Boehringer Ingelheim; and member of the board for the Estonian Society of Nephrology. Marius Miglinas received honoraria for lectures, presentations, or events from Astellas Pharma, Astra Zeneca, Baxter, Bayer, Berlin Chemie, Boehringer Ingelheim, KRKA, Servier, Medtronic, Norameda, Novo Nordisk, Swixx Biopharma, and Viatris; participated in advisory boards with Astellas, Astra Zeneca, and Boehringer Ingelheim; and is President of Lithuanian Hypertension Society and Chairman of

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Author Contributions

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Data Availability Statement

No new data were generated or analysed in support of this manuscript.

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