HHS Public Access

Author manuscript

Nat Rev Nephrol. Author manuscript; available in PMC 2016 February 01.

Published in final edited form as:

Nat Rev Nephrol. 2015 August ; 11(8): 491–502. doi:10.1038/nrneph.2015.85.

Early chronic kidney disease: diagnosis, management and models of care

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Abstract

Chronic kidney disease (CKD) is a prevalent condition in many countries, and it is estimated that over $1 trillion is spent globally on end-stage renal disease (ESRD) care. There is a clear clinical and economic rationale for designing timely and appropriate health system responses to limit progression from CKD to ESRD. This article reviews the gaps in our knowledge about which early CKD interventions are appropriate, the optimal time to intervene, and what model of care to adopt.

The available diagnostic tests exhibit key limitations. Clinical care may improve if early-stage (1–3) CKD with risk for progression towards ESRD is differentiated from early CKD that is unlikely to advance. It is possible that CKD should be re-conceptualized as a part of primary care. Additional research is needed to better understand the risk factors for CKD progression. Systems modelling can be used to evaluate the impact of different care models on CKD outcomes and costs. The US Indian Health Service experience has demonstrated that an integrated, system-wide approach, even in an underfunded system, can produce significant benefits.

Introduction

Chronic kidney disease (CKD) is a common condition characterized by evidence of kidney damage or dysfunction, as well as an increased risk of cardiovascular disease.[1, 2] CKD is currently classified based on a patient's estimated glomerular filtration rate (eGFR) and urinary albumin excretion rate (AER) (Table 1);[3] clinicians look for markers of renal damage (e.g., abnormalities of urinary sediment or organ structure) to diagnose CKD in people with eGFRs of ≥60 mL/min/1.73 m^2. Diabetes and hypertension cause up to two-thirds of CKD;[4] less common causes include glomerulonephritis, nephrolithiasis, and polycystic kidney disease. In a small proportion of cases, progressive kidney damage leads to end-stage renal disease (ESRD). ESRD patients require dialysis or kidney transplantation to survive. The rate of CKD progression varies between patients depending on disease etiology and pathology.[5, 6]

In the US, the prevalence rate (95% CI) of CKD among non-institutionalized adults increased from 12.0% (10.4% – 13.5%) to 14.0% (12.4% – 15.7%) between 1988–94 and 1999–2004; this rise may have flattened off, with recent data (2007–2012) suggesting that the rate is now 13.7% (12.1% – 15.2%).[7] CKD is prevalent in most high-income countries,[1, 5] although data suggest that the UK rate decreased from 6.7% to 6.0% between 2003 and 2009–2010.[8]

In many high-income countries, ESRD patients represent <0.1% of the total population, but account for between 1% and 2% of health-care spending.[9] It is estimated that over $1 trillion is spent worldwide on ESRD care.[10] There is a clear clinical and economic rationale for designing progression from CKD to ESRD.[11–14] This article outlines the gaps in our knowledge about which early CKD interventions are appropriate, the optimal time to intervene, and what model of care to adopt.

CKD diagnosis

The first step in outlining an intervention strategy is to define which patients have early CKD. The publication of the first CKD guidelines in 2002 by the National Kidney Foundation, a US voluntary health organization, was an important step to bring policy attention to CKD. These guidelines, referred to as the KDOQI guidelines, were adopted by countries and institutions worldwide and form the basis for CKD classification.

Based on current prevalence estimates,[7] 44.6 million people in the US – including 33.6% of people aged 60 years or older – have CKD. Over 95% of these individuals are classified as having stages 1–3, prompting some to call the current situation a “silent epidemic”[10] and the “tip of the iceberg.”[15] A recent study suggested that a person born in the US today has a lifetime risk of developing CKD stages 3a+, 3b+, 4+, and ESRD of 59.1%, 33.6%, 11.5%, and 3.6%, respectively.[16] The prevalence rates are based on eGFR readings – a proxy measure of renal function – usually calculated using the CKD-EPI (CKD Epidemiology Collaboration) or MDRD Study (Modification of Diet in Renal Disease) formulae. Albuminuria levels provide supplemental information.

eGFR equations and age-related decline in renal function

These high lifetime risks for CKD call into question whether there is a distinction between early CKD and normal age-related decline in renal function. Reductions in renal blood flow and mass, as well as increased glomerulosclerosis, are part of the normal ageing process, with eGFR falling by about 0.75 mL/min/1.73 m^2 per year from the age of 40.[17] This rate of progression seems non-linear, with eGFR loss in elderly patients slowing below 45 mL/min/1.73 m^2.[18] In population studies, the majority of patients assigned as having CKD are aged over 60 years, and most of these patients do not have significant albuminuria.[19, 20] It is therefore difficult to differentiate between age-related loss of kidney function and renal disease.[21] The data suggest that, for a given reduction in eGFR, elderly patients are less likely to progress to ESRD.[18, 22] The role of the ageing process has long been recognized for other organ systems. For example, the natural decline in forced expiratory volume with age forms a referent for the identification of premature or accelerated loss of respiratory function.[23]

Meta-analyses of over 1.5 million patients performed by the CKD Prognosis Consortium, however, have shown almost identical risks for ESRD in patients above and below 65 years of age with an eGFR of 45–59 and an ACR of <10 mg/g.[24, 25] These data have been interpreted as evidence against the introduction of differing thresholds for defining CKD based on age, although the interaction between renal function and proteinuria does seem to differ with age, potentially due to the competing risk for death. It has also been argued that senescent changes in eGFR are due to other disease processes rather than pre-determined renal decline.[26, 27] The differing interpretations of the current data on eGFR loss in the elderly underscore the need to consider eGFR trends as part of a clinical assessment. Although it is unclear whether these eGFR changes reflect intrinsic renal disease or normal ageing, CKD and senility are associated with an increased risk for morbidity and mortality in an additive fashion.[18]

Comorbidity is common in CKD patients. In the UK, about 64% of patients aged over 65 years that are coded as having CKD have four or more additional morbidities.[28] Whilst it is acknowledged that multi-morbidity leads to greater need for healthcare, the risk factors for multi-morbidity are ill-defined.[29] Further work is required to determine whether renal impairment in elderly patients is associated with or causes other conditions.

The formulae for estimating GFRs exhibit other well-documented limitations.[30, 31] The formulae were developed to identify patients with eGFR ≤60 mL/min/1.73 m^2 at risk for renal failure, and are not sensitive for stages 1 and 2.[32] On their own, eGFR estimates are therefore of little value in early intervention efforts; some have even called for removing the first two stages from the KDOQI guidelines,[33] while others have proposed alternative classification systems.[34] The MDRD Study equation tends to underestimate true GFR in individuals with normal kidney function,[35–38] while the CKD-EPI equation tends to overestimate it in individuals with CKD or at high risk for CKD.[39] The two equations only generate eGFR figures that are within 30% of the true values. In 15.9% of CKD-EPI cases[40] and 19.4% of MDRD Study cases,[41] the estimated values are even less accurate. There are also gender and ethnic differences in GFRs that should be accounted for.[22, 33]

Epidemiologic studies have used different eGFR formulae, which limits direct comparison due to varying accuracies at higher levels of eGFR. Most national studies also rely on point estimates of eGFR, whereas a CKD diagnosis should only be made after multiple estimates over several months; results from point estimates tend to overstate prevalence rates. Moreover, not all studies consider AER when estimating prevalence rates.

Cystatin-C-derived eGFR equations

The limitations of creatinine-based GFR estimates have resulted in investigation of other molecules, including beta-trace protein[42] and cystatin C.[43] The latter molecule has been shown to provide a more accurate estimates of renal function, including for elderly patients,[44–46] especially when used in combination with measurements of serum creatinine;[47] cystatin-C-derived formulas also seem to function well at high GFRs. The use of these formulas is now recommended to confirm or exclude CKD in patients with mild reductions in eGFR (creatinine) and an albumin creatinine ratio of <3mg/mmol.[3, 48] This strategy may lead to cost savings by reducing health-care use for inappropriately-diagnosed

CKD. Although there is now an international standard for cystatin-C measurement, the assay is not yet widely available. Diagnostic accuracy may improve if uptake of the assay increases.

Albuminuria

Although AERs provide valuable diagnostic data, albuminuria tests also have limitations, such as poor test-retest reliability,[49, 50] further supporting the need to rely on more than one prognostic factor. Albuminuria readings can vary depending on the type of assay (i.e., monoclonal vs. polyclonal),[51] the sample collection method (i.e., 24-hour collection vs. first morning void vs. random spot sample),[52] and the storage procedure.[53] Moreover, although standard thresholds for pathological albumin excretion are used across gender and age, both factors may affect urinary albumin measurement.[54–56]

Key points for clinical practice

Estimates of GFR that do not incorporate cystatin-C data are imprecise. This is often not acknowledged in the literature, and even less so in clinical practice. Clinicians need to be aware of the strengths and limitations of the diagnostic tools. Primary-care physicians (PCPs) should rely on clinical judgment when evaluating individual patients based on eGFR trends and albuminuria. Although these two parameters jointly provide accurate predictive information about the risk of ESRD,[57, 58] clinicians should also consider the severity of comorbidities, family histories, and vascular risk profiles.[59, 60] More work is needed to improve the sensitivity and specificity of eGFR formulas and other risk equations for progressive CKD.

How to define and manage early CKD?

As most CKD patients do not progress to ESRD, unselected treatment is neither clinically appropriate nor, given the global scale of the disease, economically feasible. Clinical care may improve if early-stage CKD with risk for progression towards ESRD is differentiated from KDOQI stages 1–3 CKD that is unlikely to advance. Interventional studies may also benefit from a more selective definition of early CKD. For example, the benefits of dietary salt restrictions have still not been conclusively established,[61] with a post-hoc analysis of the ONTARGET and TRANSCEND studies finding no renal benefit in patients with early CKD.[62] Given the reported benefits of a low-salt diet in patients with advanced renal failure,[63] it is possible that specific phenotypes should be considered.

Screening debate

A systematic review commissioned by the US Preventive Services Task Force (USPSTF) questioned the clinical and economic value of both screening the general population and high-risk groups;[64] this stance is supported by the American College of Physicians (ACP).[65] The USPSTF review found no randomized controlled trials (RCTs) of “CKD screening in adults who were asymptomatic with or without recognized risk factors for CKD incidence, progression, or complications,” and no RCTs of “monitoring adults with CKD stages 1 to 3 for worsening kidney function or damage.”

The position of the USPSTF and the ACP is not universally supported. In the UK, the National Institute for Health and Care Excellence (NICE) advocates targeted assessment for CKD in patients prescribed high-risk medications or with diseases linked to CKD (e.g., diabetes mellitus).[48] The American Society of Nephrology (ASN) contends that universal CKD screening is appropriate given the asymptomatic nature of mild-to-moderate CKD and the ease with which investigation can be performed. Although the ASN acknowledges the lack of RCT support for this position, they propose that early and better blood-pressure control may slow progressive loss of renal function and that awareness of CKD may be relevant during hospitalization episodes. A recent systematic review concluded that proteinuria screening might be cost-effective in the diabetic and hypertensive populations. The review also found that eGFR screening may be cost-effective in diabetic patients; there were no cost-effectiveness studies of eGFR screening in hypertensive populations.[66]

Evidence gaps

The conflicting views of these stakeholders highlight the need for more RCTs of early CKD identification, screening, monitoring, and treatment. In the meantime, population health management could focus on vascular risk factor control and the CKD patients that are likely to progress to ESRD and generate higher health-care costs.[67, 68] Given the asymptomatic and insidious onset of CKD, research into new biomarkers and prognostic techniques is essential.[69–71] It is an active area of research, and new prediction models are regularly published.[72–76] More work is needed to validate and refine these models. It is important to examine the generalizability of findings across patient groups: while a model may be appropriate for one patient population in one geographic region, it may be less accurate – or even lead to erroneous conclusions – when applied for others.

Expanding the definition of early CKD must be considered in relation to the adverse outcomes associated with reduced eGFR.[77] Two recent meta-analyses by the CKD Prognosis Consortium found that diabetic and hypertensive patients with reductions in eGFR have increased risks of ESRD and death.[78, 79] In both studies, the risk for ESRD significantly rose once eGFRs dropped below 50 mL/min/1.73 m^2. The risk for death, however, increased below an eGFR of 90 mL/min/1.73 m^2. Although these data could be interpreted in support of defining mild reductions in renal function as part of a disease state, it is important to consider the difference in threshold level of risk for death and ESRD. These findings also raise the question of population versus individual risk, given that patients with a low risk for ESRD still carry a potential risk for other complications.[80] For example, most new diagnoses of diabetes come from these low-risk groups.[81] Screening patients may therefore not contribute meaningful prognostic information at an individual level regarding ESRD risk. Small reductions in eGFR have been shown to improve discrimination in models of cardiovascular risk, and the rate of change in eGFR has been considered a more potent predictor of risk than absolute values.[82, 83]

It is possible that what is currently labeled as CKD stage 1–2 should be assessed in relation to cardiovascular risk rather than renal risk. This may particularly relevant when considering the elderly population with reduced eGFR values but no significant albuminuria. In both meta-analyses,[78, 79] the risk of death and ESRD was associated with increased albuminuria

in a linear manner, emphasizing the importance of this marker in defining risk for CKD progression.

Management of early-stage CKD

There is a limited evidence base that lifestyle changes and the use of preventive medicines can reduce the risk of cardiovascular disease and possibly slow, halt, or reverse CKD progression during the early stages.[1, 84] These data are generally of low quality, but they provide some support for calorie-controlled diets,[85–88], physical exercise,[89–91] and smoking cessation[92–94]; predominantly in diabetic CKD patients. Most CKD patients have comorbidities that are amenable to a systematic approach to prevention and early management, and many patients die from cardiovascular events or other causes before they ever develop ESRD.[59, 77, 95]

The pathophysiology of increased vascular risk evolves over the natural history of CKD,[96] with traditional atherosclerotic risk factors having a proportionately greater impact in early stages. In early and pre-dialysis CKD,[97, 98] treatment with lipid-lowering agents reduces risk for cardiovascular events in spite of a lesser association between low-density lipoprotein cholesterol (LDL-C) and patient outcomes in stages 3 through 5.[99] Improved awareness of CKD as a vascular risk factor would facilitate more timely usage of these agents alongside better-known interventions such as blood-pressure control.[100] The strongest evidence of treatment benefit in patients with early CKD is from RCTs of angiotensin-converting enzyme (ACE) inhibitors[101] and angiotensin II-receptor blockers (ARBs).[102, 103] However, these studies focused on patients with proteinuric diabetic renal disease, and the data to support the use of these agents for other causes of CKD are weaker.[104]

Recent data suggest that the rate of increase in the incidence of ESRD is slowing in some countries, including Australia, Canada, northern European countries, New Zealand, and the USA, although these trends vary by sub-groups (e.g., age and race).[105] The stabilization of these incidence rates may be due to better cardiovascular risk management in the diabetic, hypertensive, and general populations, although this has yet to be shown conclusively.

Models of CKD care

The Wagner Chronic Care Model

There is some evidence[106, 107] to suggest that the prevailing care strategy for CKD should consist of three phases: (1) vascular risk management in primary care during early disease (e.g., exercise, dietary changes, smoking cessation, blood pressure, glycemic and lipid control, and periodic monitoring of kidney health); (2) structured care to target comorbidities that develop in progressive cases (e.g., anemia, bone disease, and secondary hyperparathyroidism); and (3) multi-professional, intensive care for patients transitioning to renal replacement therapy. For all CKD patients, PCPs should check for drug interactions that might cause acute kidney injury.

Based on the distribution of CKD cases across stages 1 through 5, almost all patients would fall into the first phase. It is possible that CKD should be re-conceptualized as a part of primary care,[108] and that an integrated care approach should be adopted to coordinate the

continuum of care for CKD patients (*Box 1*).[109] This would be aligned with the Chronic Care Model developed Dr. Edward H. Wagner, which consists of six core parts: community resources and policies, health-care organization, self-management support, delivery system design, decision support, and clinical information systems.[110–113] These changes in clinical practice are needed as the prevalence rates of diabetes and hypertension are expected to increase,[114–116] which will add to the CKD burden. A shift to a primary-care model might enable nephrologists and other specialists to focus on patients with primary kidney disease, rapidly progressing CKD, and ESRD.

PCPs should also carefully monitor the effect of certain types of drugs, contrast dyes, and environmental toxins on the kidneys; this can be done with the help of IT systems. Some prescription and over-the-counter medicines, such as non-steroidal anti-inflammatory drugs, can precipitate acute kidney injury in CKD patients. Acute kidney injury can accelerate CKD progression.[117–119]

Numerous studies have highlighted the shortcomings of primary care for CKD. Notably, there is low awareness of the KDOQI guidelines and diagnostic techniques,[120–125] suboptimal prescribing and management for diabetic and hypertensive patients,[7, 124–129] and poor recognition of known CKD risk factors.[120] One study found that only 35% of PCPs had “adequate knowledge” of CKD based on responses from 470 clinicians to a 27-question survey; for each ten-year increase in age, the odds of having adequate knowledge decreased by 26%.[130] Another study found that only 19% of family practitioners and 33% of general internists adhered to KDOQI guidelines on the laboratory and radiological evaluation of patients with CKD.[122] In a study commissioned by the US National Kidney Disease Education Program, about one-third and one-fourth of PCPs did not recognize family history and African-American race as CKD risk factors, respectively; however, there was high awareness that diabetes and hypertension are predictors of CKD.[120] These three surveys[120, 122, 130] were voluntary and had low response rates, ranging from 7.6% to 32.4%. The participants may not be representative of the general PCP population. It is likely that these findings – which already point to substantial room for improvement – overstate the quality of CKD care.

The involvement of specialists in CKD care

Although the timely involvement of specialists is needed to improve health outcomes for patients with progressive CKD, payers want to avoid unnecessary referral patterns that could deplete resources. A systematic review of the clinical and cost-effectiveness evidence on early versus late (or no) nephrologist referral found that early referral is associated with better health outcomes and might be cost-effective.[131] However, the authors did not find any randomized-controlled trials that provide data on the clinical effectiveness of early-referral strategies, and only two studies included pre-dialysis patients. The authors noted that there are insufficient data on the natural history of CKD and the costs and effects of early referral. They highlighted the need for long-term observational studies of early-CKD patients to better delineate disease progression and the incidence of cardiovascular events in patients with and without related health conditions, such as diabetes, pre-existing cardiovascular disease, albuminuria, and proteinuria. The authors also suggested that the large costs of early

referral may be unaffordable for health systems, even if early referral is cost-effective. Further research is needed to evaluate the cost-effectiveness of improved primary care for early-CKD patients.

PCPs should be involved in re-defining CKD to facilitate a paradigm shift. In the UK, early identification of CKD is financially incentivized in primary care, but some PCPs express concern over whether CKD is a genuine disease state.[132] In areas where patients are not correctly identified on CKD registers, cardiovascular management has been shown to be suboptimal, with worse blood-pressure and cholesterol control.[133] A transition to a primary-care model should be a universal decision, unlike the development of current guidelines which has been driven by secondary-care providers.[134]

Integrated care pathways for CKD

A unified patient-care strategy across health-care providers and payers might improve health-care outcomes. It is important to evaluate models of CKD care in terms of value for money and to understand what approaches achieve reliable service delivery to high-risk populations. CKD can provide a useful case study of how to implement a shift to a primary-care model that is public-health oriented, proactive, and patient-centered.

USA

Despite the fragmentation of the US health system, positive CKD trends have been observed in some public (Indian Health Service[135, 136] and Veterans Health Administration[137]) and private health-care organizations (Kaiser Permanente[138, 139]). The long-term focus of the Indian Health Service and Veterans Health Administration – patients usually remain with each agency their entire lives – encourages preventive care. In the Indian Health Service, an important intervention was the widespread use of ACE inhibitors in the early 1990s. Today, about 80% of hypertensive patients with diabetes in this population receive ACE inhibitors. The growth in CKD and ESRD rates is slowing quicker among these patients than in the general population.[135, 136] The Indian Health Service experience has demonstrated that a system-wide approach, even in an underfunded system, can produce significant benefits.

Kaiser Permanente of Southern California, a vertically-integrated health maintenance organization in the US, has deviated from the KDOQI guidelines.[139] The organization instead applies a composite risk assessment to target patients whose conditions are expected to worsen, and it uses IT systems that automatically recommend treatment options based on patient information. The Hawaiian network of the organization has also started providing care to CKD patients based on risk stratification, and has found that this approach is associated with a statistically-significant reduction in disease progression.[138]

UK

In the UK, there is growing integration between primary and secondary care. A 2003 study, which preceded automated eGFR reporting, reviewed the electronic primary care records of over 130,000 patients and found high rates of undiagnosed CKD.[140] While automated eGFR reporting has improved recognition of CKD in primary care and has increased referral rates,

this study also suggests that it is possible to alert PCPs about missed opportunities for preventive prescribing.

A similar model of CKD management to the one introduced by Kaiser Permanente[138] was phased in between 2003 and 2006 in the West Midlands region of England. Early results show that patient outcomes have improved, including a reduction in the population-adjusted incidence of renal replacement therapy.[141] Another study evaluated the health outcomes of patients with CKD stages 4–5 treated in primary care with a disease management program; the program was similar to a secondary care multi-disciplinary clinic. The study found that the program improved health outcomes and reduced eGFR loss over a nine-month period.[142] Intensive, target-driven disease management programs have produced positive outcomes in diabetes care,[143] and there is the potential for such approaches to be applied to CKD care.

Other international experiences

Other countries, including Australia and Canada, are transitioning to primary-care models for CKD in the general population. Similarly to the Indian Health Service, Australia has also long relied on community-based CKD care for the population of the Tiwi Islands, an aboriginal community. The Tiwi Islands model focuses on blood-pressure and lipid control and health education to try to improve cardiovascular health and preserve renal function. The published data suggest that this strategy has markedly improved cardiovascular and renal health outcomes in this population.[144] These international experiences suggest that a holistic care model can be successfully applied across different types of health systems.

Systems modeling

As previously described, physicians should consider the limitations of population-based estimating equations and evaluate individual patient characteristics when predicting risk and developing treatment plans. Structured, early CKD intervention programs can form the basis for such personalized care. Given the heterogeneity of patients with early CKD, and the variable risks in different population segments, clarity on the appropriate scope and impact of such programs is needed. Health-care providers, payers, and the general public need to know whether it is cost-effective or not to invest in CKD intervention programs.

Systems modeling is an inexpensive method to study the effects of different interventions on chronic-disease outcomes and costs.[145–147] The software can be used to design comprehensive care models in patient populations and observe the diabetes, hypertension, CKD, and ESRD burdens over time. Systems modeling allows for sensitivity analysis to test the degree of uncertainty around the model assumptions. This can give an indication of the reliability and strength of the results, and highlight areas where more research is needed.

Alongside systems modeling, long-term prospective cohort studies are needed to understand the clinical and economic value of different intervention strategies from a payer or societal perspective. Ideally, these studies should incorporate RCTs of CKD treatments into the study designs. It is also important to conduct economic analyses alongside outcome evaluations. Notably, the Nord-TrØndelag Health Study (HUNT) in Norway,[148] the aforementioned Kaiser Permanente[139] and English West Midlands[141] studies, and most

CKD quality improvement studies do not consider costs. If health-economic evaluations were built into these population-based studies, it would generate useful evidence to guide care approaches. Relevant stakeholders should also establish registries to monitor the long-term health and cost effects of different care pathways and timing of care initiation.

Conclusion

There is insufficient evidence on the clinical and economic benefits of early CKD intervention, especially in comparison to diseases like diabetes and stroke. There are no RCTs of the clinical and cost outcomes of early intervention strategies, and comprehensive patient-level data are not readily accessible. However, it is possible that early diagnosis, treatment, and management of CKD could alter the natural history of the disease and generate substantial cost savings. A better understanding of the merits and demerits of different care approaches for CKD, and where evidence is lacking, is essential to improve health outcomes and to minimize expenditure.

CKD, like many chronic conditions, is in essence a broad indicator of overall health. Patients with mildly or moderately depressed eGFRs usually have comorbidities that are more relevant to their current and future well-being than a CKD diagnosis. These comorbidities should remain the focus of treatment and management, as few patients who are diagnosed with CKD develop ESRD.

The difficulty for physicians to identify progressive CKD patients has weakened the effectiveness of early interventions. Although new biomarkers that may improve CKD detection and prognosis are becoming increasingly available, it is unlikely that any silver bullet will fully address the disease burden of CKD. It is important to promote a unified care strategy across health-care providers and payers. This holds true for CKD, a particularly complex disease involving many providers over a patient's lifetime, but also applies to other chronic illnesses.

Acknowledgments

No sources of funding were used to prepare this manuscript. The authors have no conflicts of interest that are relevant to the content of this article. We would like to thank Dr. Shari Ling and Dr. Kimberly Smith (Food and Drug Administration, Washington DC, USA) for their useful comments on earlier versions of this article.

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Box 1. Prevention strategies for early-stage CKD

Primary and secondary

- Clarification of CKD staging and prognostication to improve PCP engagement
- Patient and clinician education to link public health programs to kidney health

Target population

- Development of high-quality evidence to guide screening programs for CKD and RCTs
- Patients at risk of AKI or with previous AKI
- Continued assessment of high-risk populations

Impact assessment

- Assessment of patient awareness of disease and personal clinical data
- Proportion of patients experiencing cardiovascular events, a preventable loss of renal function, or requiring referral to secondary care

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; PCP, primary care physician; RCT, randomized controlled trial.

Box 2. Service delivery for CKD

Primary care

- Patient assessment by eGFR trend and/or trajectory reporting
- Classification of CKD based on risk for progression
- Identification of CKD as an indicator for elevated cardiovascular risk, with early modification of traditional risk factors
- Patient advocacy and self-management during early-stage CKD
- Referral to secondary care for specialist treatment of CKD complications

Secondary care

- Multidisciplinary management of disease complications
- Ongoing support for patient self-management programs
- Integration with other secondary care services to manage the burden of comorbidities
- Personalized treatment goals with consideration of quality of life
- Integration into primary care to support periodic monitoring of stable patients by PCPs
- Structured follow-up for patients having experienced AKI, with data collection to describe long-term effects on GFR trajectory

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PCP, primary care physician.

Box 3. Workforce, ICT, and other strategies to improve care for early-stage CKD

Workforce

Essentials and supportive

- Motivated and educated workforce and patient population
- Easy access to laboratory monitoring
- Specialist nursing staff to support patient understanding of the disease
- Financially viable secondary care renal services for a potentially smaller but very ill patient population

PCP-specialist interface

- Multi-specialty clinics in primary care to support PCP education and patient care
- Defined referral and discharge criteria for secondary care

Role of ICT and decision-support systems

- Integration of primary and secondary care records
- Accessible results reported to patients in any location
- Automated analysis of eGFR and/or trends in proteinuria
- Incorporation of validated predictive models for ESRD into laboratory reports
- Electronic prescribing linked to biochemical results

Health-economic impact and health-system financing

- Economic analyses built into all studies of CKD screening and treatment
- Financial incentives balanced towards prevention of progression to ESRD
- The establishment of CKD registries to permit health-economic analyses

Leadership, governance, and role of national and international organizations

- International, evidence-based accordance between national and international bodies regarding CKD screening and treatment
- Increased data sharing between health systems of epidemiologic trends in CKD
- Strong patient representation in all organizations

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ICT, information and communications technology; PCP, primary care physician.

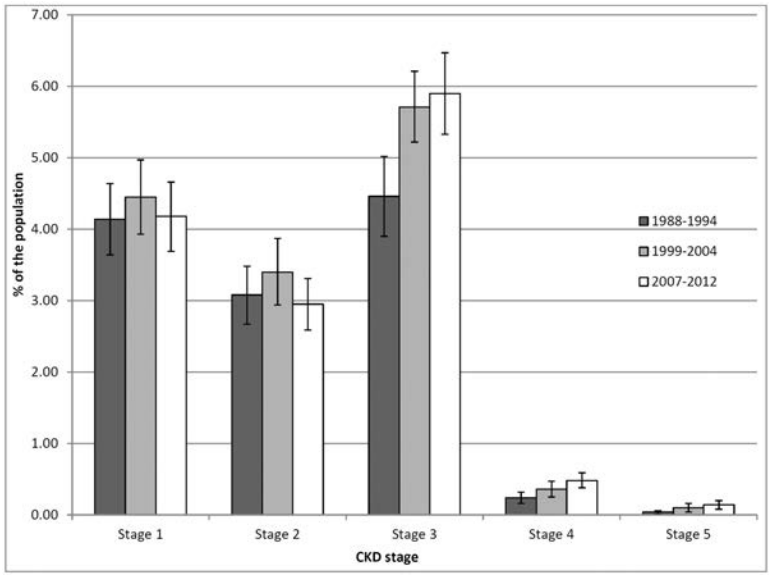

Figure 1.

The prevalence of CKD by stage in the USA, 1988–2012. The prevalence estimates are based on samples of non-institutionalized adults (aged 20 years or older) who participated in the National Health and Nutrition Examination Survey (NHANES) during the study years. The sample sizes varied across 1988–1994 (n=15,488), 1999–2004 (n=13,233), and 2007–2012 (n=15,502). The proteinuria measures were based on albumin-creatinine ratios from spot morning urine samples. The estimated glomerular filtration rates were calculated using the CKD-EPI creatinine formula. Stage 3 corresponds to a glomerular filtration rate of 30-59 mL/min/1.73 m^2. The error bars show the 95% confidence intervals. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government.

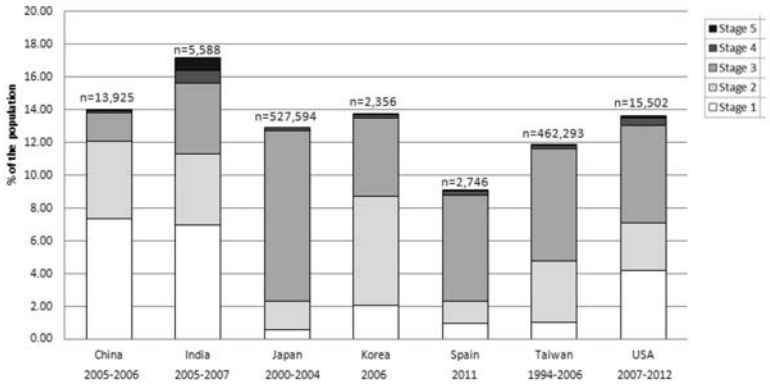

Figure 2.

The breakdown of CKD by stage (1–5) in selected countries with data available from the 2000's. Stage 3 corresponds to a glomerular filtration rate of 30-59 mL/min/1.73 m^2. The Chinese study used a sample of individuals from Beijing, the Indian study used a sample from thirteen academic and private medical centres located throughout the country, and the Korean study used a sample from seven urban cities. The other studies used nationally-representative samples. For Japan, the prevalence estimate for stage 4 includes both stages 4 and 5. All studies either sampled adults aged ≥18 years or ≥20 years, except for the Korean study which included adults aged ≥35 years. All studies used a version of the four-variable MDRD study equation to determine eGFR, except for the USA study data which used the CKD-EPI creatinine formula. The Chinese, Korean, Spanish, and USA studies measured proteinuria by using the spot morning urinary albumin-creatinine ratio. The remaining studies used a urine dipstick analysis for proteinuria. The Chinese study also measured haematuria by dipstick test.

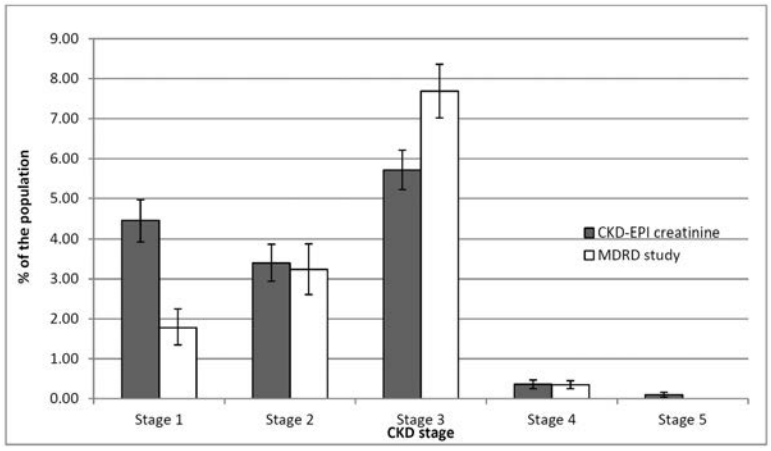

Figure 3.

Comparison of CKD prevalence by eGFR formula (CKD-EPI creatinine vs. four-variable MDRD study) in the USA, 1999–2004. The prevalence estimates are based on samples of non-institutionalized adults (aged 20 years or older) who participated in the National Health and Nutrition Examination Survey (NHANES) during these years (n=13,233). The CKD-EPI data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government. The four-variable MDRD study data were reported by Coresh et al (2007). Both studies used measures of albumin-creatinine ratios from spot morning urine samples. Stage 3 corresponds to a glomerular filtration rate of 30–59 mL/min/1.73 m^2. The error bars show the 95% confidence intervals. Coresh et al (2007) did not estimate the prevalence of stage 5 with the MDRD study equation as they deemed that “estimates of this stage are likely to be unreliable due to the small number of individuals and the likelihood that many of these individuals are ill or receiving dialysis and would have a low response rate.”

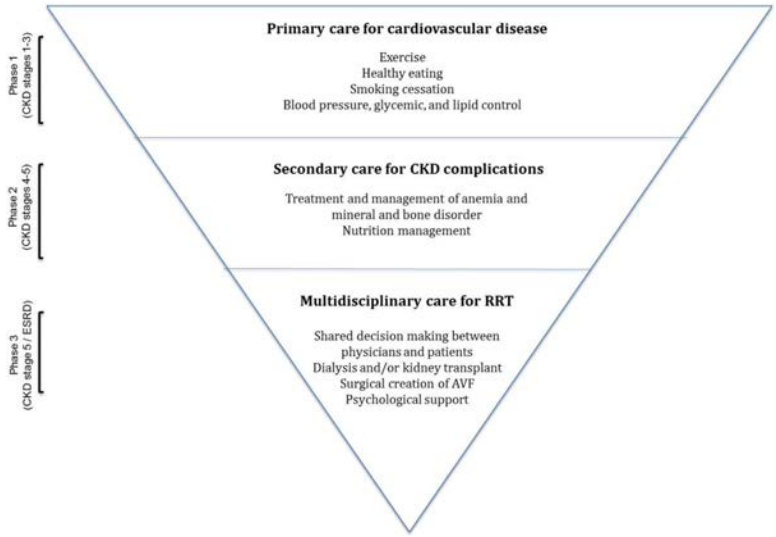

Figure 4.

An integrated care continuum for CKD that is consistent with the chronic care model. Abbreviations: AVF, arteriovenous fistula; CKD, chronic kidney disease; ESRD, end-stage renal disease; RRT, renal replacement therapy.

Table 1

Definition and classification of CKD

Table 2

Selected observational studies of the quality of primary care for CKD patients

Study	Design	Population	Period	Key results
Allen *et al* 2011[124]	Retrospective cohort	166 PCPs in 15 health centers in eastern Massachusetts, USA, caring for 11,774 CKD patients (eGFR between 15 and 60 mL/min/1.73 m^2)	2004–2008	Many of the patients were not tested yearly for urine protein (70%), had BP ≥130/80 mmHg (46%), and were not receiving appropriate treatment with ACE inhibitors or ARBs (25%). More than a quarter of patients (26%) were receiving potentially-harmful medicines.
Boulware *et al* 2006[121]	Cross-sectional (questionnaire)	National, random, stratified sample of 400 nephrologists and 800 PCPs (400 family practitioners and 400 general internists) in the USA; 959 eligible respondents. Responses obtained from 126 nephrologists and 178 PCPs (89 family practitioners and 89 general internists) (31.7%, 304/959)	2004–2005	Family practitioners (56.2%) and general internists (70.7%) were less likely to recognize CKD than nephrologists (96.0%) (P < 0.01).
Charles *et al* 2009[122]	Cross-sectional (questionnaire)	Same population as in the study by Boulware et al (2006)	2004–2005	Only 48% of nephrologists, 19% of family practitioners, and 33% of general internists followed the KDOQI guidelines on the laboratory and radiological evaluation of patients with CKD (P < 0.001).
Fox *et al* 2006[123]	Qualitative interviews	Ten PCPs from ten health care facilities affiliated with the Upstate New York Practice-based Research Network	Not stated	There was low awareness of KDOQI guidelines, and PCPs often favoured less-accurate diagnostic tests for CKD (that is, serum creatinine); there was uncertainty about the appropriate timing of referral to nephrologists.
Israni *et al* 2009[130]	Cross-sectional (questionnaire)	Random sample of 1,550 US PCPs; 1,453 eligible respondents. Responses obtained from 470 PCPs (32.4%, 470/1,453)	2007	Only 35% of PCPs had “adequate knowledge” of CKD based on responses to 27 questions; for each 10-year increase in age of the PCP, the odds of having adequate knowledge decreased by 26%.
Lea *et al* 2006[120]	Cross-sectional (survey)	PCPs in six predominantly African-American communities in the USA (number of contacted physicians not stated). Responses obtained from 464 PCPs (7.6%)	2003	About 34% and 22% of PCPs did not identify family history and African-American ethnicity as risk factors for CKD, respectively; there was high awareness that hypertension and T2DM are predictors of CKD.
Minutolo *et al* 2005[127]	Cross-sectional	Nephrologists (tertiary care) and 39 PCPs caring for hypertensive patients with CKD (eGFR between 15 and 60 mL/min/1.73 m^2) in Naples, Italy	2003	CKD patients cared for by PCPs had higher BP levels ([143±15] / [82±7] mmHg) than CKD patients cared for by nephrologists ([136±18] / [78±11] mmHg) (P < 0.0001). The risk of not attaining BP target values was 2.6 times greater in primary care than in tertiary care (nephrologists), controlling for age, sex, diabetes mellitus, and eGFR.
Ravera *et al* 2009[129]	Cross-sectional	PCPs caring for 7,582 hypertensive patients with type 2 diabetes in Italy	2005	Only 10.4% of patients with diabetes mellitus in this population achieved BP <130/80 mmHg. Of patients with eGFR <60 mL/min/1.73 m^2, only 17% had been coded as having CKD.
Ravera *et al* 2011[128]	Cross-sectional	PCPs caring for 39,525 hypertensive patients in Italy (nationally-representative sample of patients)	2005	Only 13.8% of patients with eGFR <60 mL/min/1.73 m^2 and 72.6% of patients with eGFR <30 mL/min/1.73 m^2 were coded as having CKD. Of patients with eGFR <60 mL/min/1.73 m^2, only 45.4% and 13.2% achieved BP <140/90 mmHg and <130/80 mmHg, respectively.
Razavian *et al* 2012[125]	Cross-sectional (survey)	Nationally-representative, cluster-stratified sample of 534 PCPs in Australia; responses obtained from 322 GPs (60.3%, 322/534) caring for 4,966 patients (age ≥55 years) with available data on kidney function	2008	Fewer than 18% of CKD patients (235/1,312) were correctly diagnosed with CKD. The decisions by PCPs not to prescribe BP- or lipid-lowering agents for CKD patients only adhered to guideline recommendations in 51% and 46% of cases, respectively.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II-receptor blocker; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDOQI, Kidney Disease Outcomes Quality Initiative; OR, odds ratio; PCP, primary care physician; T2DM, type 2 diabetes mellitus