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REVIEW

High burden and unmet patient needs in chronic kidney disease

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Abstract: Chronic kidney disease (CKD) is a complex debilitating condition affecting more than 70 million people worldwide. With the increased prevalence in risk factors such as diabetes, hypertension, and cardiovascular disease in an aging population, CKD prevalence is also expected to increase. Increased awareness and understanding of the overall CKD burden by health care teams (patients, clinicians, and payers) is warranted so that overall care and treatment management may improve. This review of the burden of CKD summarizes available evidence of the clinical, humanistic, and economic burden of CKD and the current unmet need for new treatments and serves as a resource on the overall burden. Across countries, CKD prevalence varies considerably and is dependent upon patient characteristics. The prevalence of risk factors including diabetes, hypertension, cardiovascular disease, and congestive heart failure is noticeably higher in patients with lower estimated glomerular filtration rates (eGFRs) and results in highly complex CKD patient populations. As CKD severity worsens, there is a subsequent decline in patient health-related quality of life and an increased use of health care resources as well as burgeoning costs. With current treatment, nearly half of patients progress to unfavorable renal and cardiovascular outcomes. Although curative treatment that will arrest kidney deterioration is desired, innovative agents under investigation for CKD to slow kidney deterioration, such as atrasentan, bardoxolone methyl, and spherical carbon adsorbent, may offer patients healthier and more productive lives.

Keywords: quality of life, economics, disease classification, treatment, eGFR

Introduction

Chronic kidney disease (CKD) is a debilitating disease affecting approximately 7% of all people aged 30 years and older, which translates to more than 70 million people in developed countries worldwide.[1] This number is likely to be much higher given the unknown prevalence in underdeveloped countries. The increased prevalence of diabetes, hypertension, and obesity and an aging population will only perpetuate the rise of CKD.[2–5] Patients have been, and continue to be, diagnosed with CKD later in the disease cycle, and therefore have to be prepared for life on dialysis or to undergo kidney transplant. However, with better screening, early management, and innovative pharmacologic therapies, the disease progression may be delayed and patients with CKD may enjoy healthier and more productive lives.

The objective of this targeted literature review is to present the clinical, humanistic, and economic burden of CKD and the current corresponding unmet treatment need. We searched the PubMed database via the National Library of Medicine Gateway and conducted supportive desktop research (eg, ClinicalTrials.gov). Search categories

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included "chronic kidney disease," "epidemiology," "disease classification," "progression," "patient-reported outcomes," "economics," and "treatment." The language and date limits applied to the search were English only and 1980 to February 2012, respectively. Original research, key reviews, current guidelines, and drug-specific reports/press releases were selected for inclusion. Findings are presented qualitatively.

The complex clinical nature of CKD is characterized and presented, including a description of the foundational interrelated factors of disease and progression that underlie the true burden and unmet medical needs of CKD. Further, current treatment options are reviewed to outline the existing unmet treatment need. Future treatments under development to address these key unmet needs are also presented.

Increasing prevalence and global burden of CKD

The trend for increased prevalence of CKD in the USA and select countries, irrespective of the calculation, implies persistent and rapid growth worldwide. Reported prevalence estimates across countries range broadly from approximately 2.0% to 44%.[1–5] The broad range in prevalence exemplifies the differences in patient populations and unmet clinical, humanistic, and economic needs across the globe. In the USA, the fastest increase in prevalence is occurring among those aged 65 years and older. Across three databases, the Kidney Early Evaluation Program, National Health and Nutrition Examination Survey, and Medicare, prevalence in the elderly population (aged $\geq$ 65 years) was approximately 44%, with the highest representation observed in those aged 80 years and older.[4] Across countries (Australia, Canada, China, Iceland, Italy, Japan, Mexico, Netherlands, Norway, Singapore, Spain, Switzerland, Thailand, and USA), estimates were similarly high in the elderly and ranged from 23.4% to 44%.[1,4]

Prevalence estimates for several modifiable risk factors affecting initiation and/or progression of disease have also increased. National Health and Nutrition Examination Survey 2001–2008 data report that diabetes, hypertension, cardiovascular disease, and congestive heart failure are more prevalent in patients with estimated glomerular filtration rates (eGFRs) $<$60 mL/min/1.73 m^2; additionally, the prevalence of hypertension is twofold and the prevalence of cardiovascular disease is fivefold greater compared with those with eGFR $>$ 60 mL/min/1.73 m^2.[5] As the prevalence of diabetes, hypertension, and other risk factors rise, so does the severity of CKD. For example, the frequency of diabetes increased more than five times by CKD stage and eGFR category. Diabetes occurred in an estimated 7% of patients in stage 1/2 (eGFR $>$ 60 mL/min/1.73 m^2), 18% of patients in early stage 3 (eGFR 45 mL/min/1.73 m^2 to $<$60 mL/min/1.73 m^2), 27% of patients in late stage 3 (eGFR 30 mL/min/1.73 m^2 to $<$45 mL/min/1.73 m^2), and 40% of patients in stages 4 and 5 (eGFR $<$ 30 mL/min/1.73 m^2).[5]

Given the increase in CKD prevalence and associated risk factors, more global epidemiological research is needed to better characterize the international burden of CKD. With improved patient-level definitions of CKD, large-scale epidemiological studies may present more adequately representative populations with CKD across countries.

Clinical burden

Complexity of disease

Attention to traditional measures of kidney function (eg, eGFR) is no longer adequate to optimally manage and care for patients with CKD. With the increase in CKD patients diagnosed with diabetes, hypertension, and obesity, consideration must also be given to these and other preexisting, emerging risk factors and comorbid illnesses. Patients with significantly increased risk, with or without confirmed CKD, may require more aggressive management to avoid the consequences of accelerated disease progression.

Disease classification and staging

The diagnosis, treatment, and management of CKD depend on classification and staging of the disease as set forth by international, country-specific, and other clinical guidelines.[6–13] As evidenced by a variety of definitions and staging systems in the scientific literature, identification of optimal patient care strategies and interpretation of data are complicated. To date, the most frequently cited and used CKD staging system is that developed by the National Kidney Foundation, Dialysis Outcomes Quality Initiative[12,14,15] (Table 1).

Although measurement of eGFR is considered the gold standard for diagnosing and evaluating progression of CKD, there is a movement among clinicians and researchers to improve clinical guidelines specifically related to diagnosis, classification, and staging. The following frequently reported criticisms of current guidelines have prompted the discussion for modification of current clinical guidelines.[16,17]

- A diagnosis based on current eGFR estimation formulas is imprecise.
- There is an absence of risk-stratification across patients; those at high risk for disease progression are not identified, and stage 3 is too broad (eg, stage 3 should

Table 1 Classification of chronic kidney disease

Stage	Description	By severity		By treatment
		eGFR (mL/min/1.73 m²)	Related terms	
1	Kidney damage with normal or ↑ eGFR	≥90	Albuminuria, proteinuria, hematuria	"T" for all kidney transplant recipients
2	Kidney damage with mild ↓ eGFR	60–89	Albuminuria, proteinuria, hematuria	
3	Moderate ↓ eGFR	30–59	Chronic renal insufficiency, early renal insufficiency	
4	Severe ↓ eGFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD	
5	Kidney failure	<15 (or dialysis)	Renal failure, uremia, ESRD	"D" for all dialysis-treated patients (hemodialysis, peritoneal dialysis)

Adapted by permission from Macmillan Publishers Ltd: *Kidney Int.*[100] Copyright 2005.
Note: The arrow up indicates increasing eGFR and the arrow down indicates decreasing eGFR.
Abbreviations: ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate.

be stratified into 3a [eGFR 45–59 mL/min/1.73 m^2] and 3b [eGFR 30–44 mL/min/1.73 m^2]).

- Patient variability (age, sex, race, ethnicity) is not considered in current methods of evaluation (eg, eGFR and proteinuria estimation, at risk for progression, prognosis).

In an effort to collaborate and provide a foundational set of international CKD guidelines that address these criticisms, Kidney Disease Improving Global Outcomes (KDIGO) formed a dedicated workgroup. Publication of the KDIGO "Clinical practice guideline on CKD classification and management" is anticipated in 2012. The proposed guideline structure and associated discussion points are as follows:[17]

- Guideline 1: Definition and stages of CKD. Stages modified and enriched to include different degrees of proteinuria; splitting stage 3 into 3a and 3b; define differences between kidney damage and disease.
- Guideline 2: Identification and evaluation of CKD. eGFR, high-risk population evaluation, appropriateness and frequency of testing.
- Guideline 3: Estimation of glomerular filtration rate (GFR). New equations that address "within-individual" biological variability, age, and ethnicity.
- Guideline 4: Estimation of proteinuria. Regional variability in methods; change lexicon from microalbuminuria to albuminuria mild, moderate, or severe.
- Guideline 5: Definition of progression of CKD. Definition of change in eGFR, acute versus chronic change, duration and stability of change, prognostic indicators, frequency of testing.

Because of the complex nature of CKD, emphasis on well-defined disease classification and staging is paramount for optimal patient care. The evidence presented here elucidates several clinical unmet needs: for example, well-defined guidelines for use by primary care physicians, internists, and nephrologists; early identification, prevention, and management of patients at risk for CKD (pre-CKD); "on-time" referral to a nephrologist when patients with early CKD are progressing to intermediate or advanced stages of CKD; optimal management for patients with confirmed CKD and those at risk for accelerated progression (eg, complex cases with multiple comorbidities); and educational programs and tools developed for primary care physicians, internists, and nephrologists to address a host of topics (eg, clinical guidelines, population-specific treatment, and management).

Risk factors and comorbid illness

The intertwined nature of risk factors and comorbid illnesses complicates the characterization of CKD. These terms are often used interchangeably due to the continuous and progressive nature of this disease. Some patients may have risk factors for developing CKD, while others may have risk factors contributing to the progression of CKD. Some comorbid illnesses are risk factors for both the initiation and the progression of disease (eg, diabetes and cardiovascular disease). However, some risk factors are simply nonmodifiable patient characteristics (eg, ethnicity, sex). A host of preexisting and traditional progression factors has been reported, with emerging risk factors and biomarkers also identified.[18] Table 2 presents common risk categories and associated factors.

As noted, some conditions fit across categories (eg, preexisting and advancing cardiovascular disease) and the presence of multiple risk factors and/or comorbid illnesses

Table 2 Common chronic kidney disease (CKD) risk categories and risk factors

Risk category	Risk factors
Susceptibility	Older age, reduction in kidney mass, low birth weight, family history of CKD, US racial or minority status
Initiation	**Diabetes, hypertension,** autoimmune disease, systemic infections; urinary tract infections, stones, or obstruction; drug toxicity
Progression	**Higher proteinuria, hypertension, poor glycemic control in diabetes, smoking, obesity, dyslipidemia, cardiovascular disease, high dietary-protein intake, decreased nephron number**
End-stage decline	**Lower dialysis dose, temporary vascular access for hemodialysis, anemia,** lower serum albumin, **late referral to nephrologist,** mineral and bone disorders, metabolic acidosis

Note: Modifiable risk factors are presented in bold.
Adapted with permission from Macmillan Publishers Ltd: *Kidney Int.*[14] Copyright 2007. Other sources: Kronenberg[18]; Taal and Brenner[99]; US Renal Data System.[61]

leads to progression of CKD and increased mortality.[19] Risk factors with overwhelming impacts on patients and health care systems include diabetes,[20–25] anemia,[20,22–31] hypertension,[20–23,25,27,31] and hyperlipidemia.[4,20,32–35] Patients with multiple risk factors and/or comorbidities bear the greatest burden.[22,36,37] Importantly, several of the debilitating risk factors and comorbidities are modifiable, and disease progression may be delayed with active patient–clinician collaboration and appropriate treatment. More attention to and early active management of modifiable risk factors and comorbidities are necessary to thwart rapid disease progression.

Disease progression

Stated simply, in CKD, "disease progression" means deterioration of kidney function. However, the underlying pathophysiology of progression is intricate. It has been postulated that any loss of functional renal mass, irrespective of cause, leads to glomerular hyperfiltration with an increased single-nephron glomerular filtration rate (GFR) and, subsequently, the loss of the ability of the remaining nephrons to autoregulate.[14,38,39] Renal injury progresses, with glomerular and tubular hypertrophy, sclerosis, and interstitial fibrosis. Proteinuria, decline in GFR, hypertension, kidney failure, and death from uremia are classic clinical features of the renal injury characteristic of progressive CKD.[14]

Few studies with stage-to-stage CKD progression models have been published and each varies in terms of design and population of interest. Common prognostic variables across these models include demographic and laboratory variables such as age, sex, and eGFR, with average kidney function loss, measured by eGFR, between 2 and 8 mL/min each year.[40–45] Tangri and colleagues[44] found that the addition of fewer standard variables such as diabetes, hypertension status, blood pressure, and body weight demonstrated no improvement in model performance. However, the authors reported that these variables are clearly important for the diagnosis and management of CKD. The high prevalence of these conditions and imprecision with respect to measuring disease severity may have affected performance of these variables in this modeling study.[44] Further research is needed to accurately predict progression of CKD from those susceptible to and at risk for CKD to those actively progressing through the stages of CKD. Of note, two ongoing studies, the Chronic Renal Insufficiency Cohort study[46] and the CKD Prognosis Consortium meta-analyses,[16] are actively engaged in research to better understand kidney function and risk factors of CKD progression in diverse and complex patient populations.

Humanistic burden

Patient perspective is an important component of CKD-related care. In the case of any chronic disease without a cure, patient perspective can be the best source for understanding the illness experience, treatment expectations and experience, and unmet needs with current treatments. Given the few studies identified with measures of CKD burden from the patient's perspective, opportunities for this type of research are vast.

The most burdensome conditions commonly reported by CKD patients across identified studies were cognitive impairment, dementia, sleep disturbance, pain, and emotional and physical dysfunction. Of these, physical dysfunction was the most pervasive and debilitating.[47–54] Instruments used to measure patient perspective were the Medical Outcomes Study Short Form – 36, the Kidney Disease Quality of Life Short Form – 36 (KDQOL-36), Health Utilities Index 3, and a time trade-off approach.[47,48,50,53,54] Perception of general health as measured by the Medical Outcomes Study Short Form – 36 was low across all eGFR groups defined by Chin and colleagues.[47] With an increase in illness severity and a decrease in eGFR, mental health component scores were similarly low across groups, whereas the physical component scores were reduced significantly with reduced eGFR, particularly in those with an eGFR < 45 mL/min/1.73 m^2 (stage 3) and 30 mL/min/1.73 m^2 (stage 4).[47,53] When compared with the general population, patients with CKD scored lower on six of eight subscales – physical function, role limitation – physical, general health, vitality, role limitation – emotional, and the physical component score.[50] Mean scores on KDQOL-36 components, Health Utilities Index 3, and time trade-off suggested considerable loss of function and well-being in patients with CKD compared with the general population. Decline in eGFR was also monotonically associated with a decline in patient-reported health as measured by the Burden of Kidney Disease (BKD) and the Effects of Kidney Disease subscales (EKD) of the KDQOL-36 (CKD-specific measures; higher score indicates better health). The scores were highest (BKD: 85.9; EKD: 92.4) in patients with eGFR > 60 mL/min/1.73 m^2 (stage 1–2). With subsequent decreases in eGFR, perceived health decreased. For those with stage 3 CKD (30 mL/min/1.73 m^2 $\leq$ eGFR $<$ 60 mL/min/1.73 m^2), BKD was 85.4 and EKD was 91.6, with continued reduction to a BKD of 74.9 and EKD of 87.5 for those with stage 4 (15 mL/min/1.73 m^2 $\leq$ eGFR $<$ 30 mL/min/1.73 m^2), and BKD of 63.4 and EKD of 80.4 for those with stage 5 (eGFR $<$ 15 mL/min/1.73 m^2). The lowest perceived health (BKD: 38.6; EKD: 62.7) was observed in patients on dialysis.[48] Modifiable risk factors associated with lower quality of life were less education, less exercise, depression, history of cardiovascular disease, lower income, and unemployment.[47,48,53] Figures 1 and 2 highlight the decline in health-related quality of life with the progression of CKD.

Economic burden

CKD is associated with significant economic burden. Disease progression, increased disease severity, and deterioration of health increase resource utilization and escalate costs. Across identified studies, in the 12 to 24 months before dialysis initiation, substantial increases in costs due to hospitalization were reported.[20,21,23,25,32,36,55–58] A study in a Medicare-claims cohort of patients with CKD reported the annual mean number of days hospitalized (9.51) and mean number of physician visits (10.28).[59] The mean annual number of physician visits increased monotonically by CKD stage, with 4.43 visits in early stage CKD (stages 1 and 2 combined) and 6.53 visits in late-stage CKD (stages 3 and 4 combined).[55] Available cost data worldwide were from the USA and Germany. Irrespective of country and cost measure used (eg, total health care costs per patient, in-hospital costs, total medical payments) in each study, the identified costs were consistently high and increased with each CKD stage. Across CKD stages, total health care costs per patient ranged from US$1183 to $35,292 (per month) in the USA; annual and in-hospital costs were €3581 and €2926 to €9687,

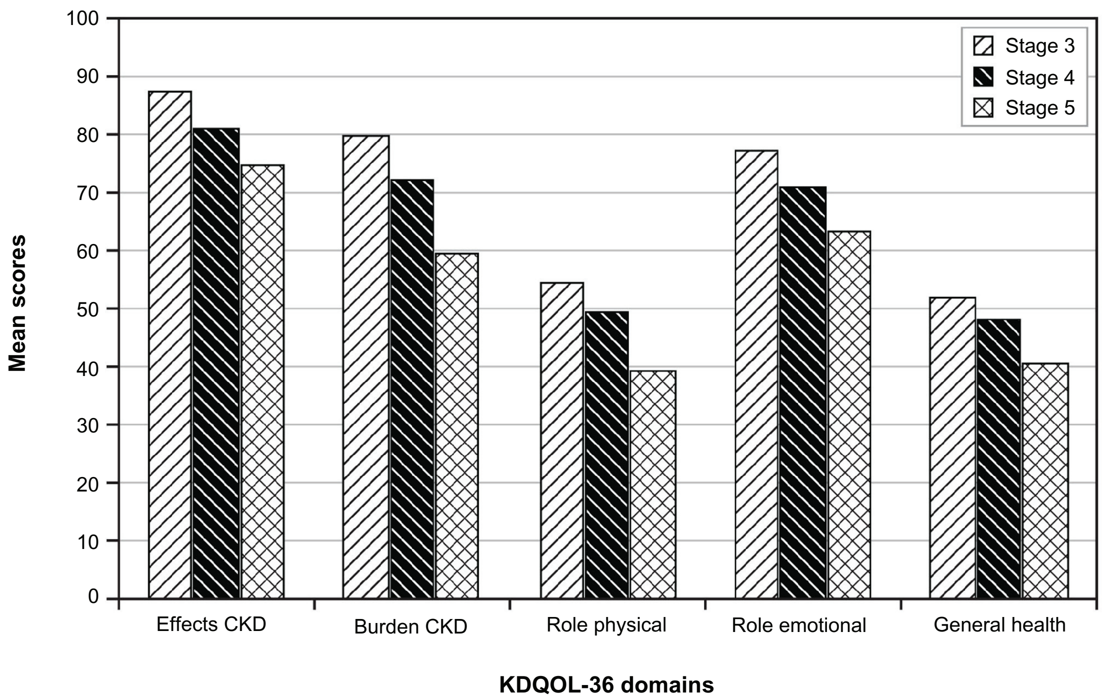

Figure 1 Health-related quality of life and progression of chronic kidney disease (CKD) by stage.
Note: Statistical significance observed for trend within each domain $P < 0.001$.
Adapted from *Clin J Am Soc Nephrol*. Mujais SK, Story K, Brouillette J, et al. Health-related quality of life in CKD patients: correlates and evolution over time. Copyright. 2009.[51]
Abbreviation: KDQOL-36, Kidney Disease Quality of Life – 36.

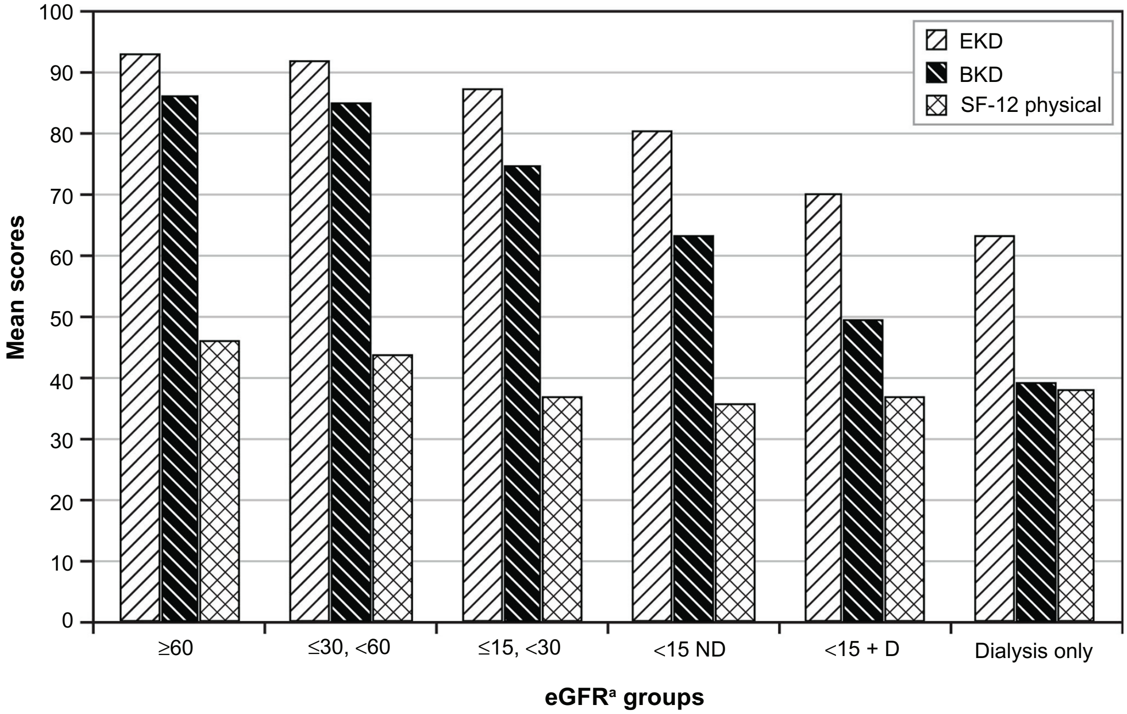

Figure 2 Health-related quality of life (HRQOL), quality of life (QOL), and progression of chronic kidney disease by glomerular filtration rate.
Notes: [a]mL/min/1.73 m^2. HRQOL measured by Kidney Disease Quality of Life (KDQOL) – 36; QOL measured by SF-12; EKD: $P < 0.0001$ for all nondialysis and dialysis only groups; BKD: $P = 0.0002$ for all nondialysis groups; $P < 0.0001$ for dialysis only group; SF-12 Physical: $P = 0.0001$ for all nondialysis groups; $P = 0.0002$ for dialysis only group. Adapted with permission from Macmillan Publishers Ltd: *Kidney Int.*[48] Copyright 2005.
Abbreviations: BKD, Burden of Kidney Disease, subscale of Kidney Disease Quality of Life; D, dialysis; CKD, chronic kidney disease; EKD, Effects of Kidney Disease; subscale of eGFR, estimated glomerular filtration; KDQOL; SF-12 Physical, Medical Outcomes Study Short Form – 12, physical component; ND, no dialysis.

respectively, in Germany.[20,25,33,60,61] By stage, cost data were available from select studies (Table 3).

In reported studies, the impact of CKD on employers is also significant. Of the studies identified, most were conducted in an older working population with CKD. This was not unexpected given that most patients with CKD are elderly. As the general working population increasingly includes individuals older than 65 years, the working population with CKD may also increase, thereby placing a profound and growing burden on employers.

All identified studies that evaluated an employer population with CKD were conducted in the USA.[29,37,62,63] In a matched case-control study, employees with CKD were older; more likely to be male; and more likely to have hypertension, diabetes, and other chronic comorbid conditions than controls.[37] Annual costs attributable to CKD

Table 3 Increased cost by chronic kidney disease (CKD) stage

Country, cost measure (denomination)	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
USA					
Employer, unadjusted total medical payments (US$)[37]	–	–	$9727	$19,419	$30,366
Employer, per member per year costs (US$)[62]	$5000–$12,000		$15,000–$28,000		Exceeds $70,000
Managed care, annualized total medical costs (US$)[36]	–	$7050	$6026	$7623	–
Managed care, annual total health care costs of CKD in specialist clinic and other setting (US$)[58]	–	–	$10,132–$14,000	$12,386–$16,545	$18,522–$23,445
Germany					
Hospital data, in-hospital costs (€)[33]	€2926	€3466	€4208	€9687	

ranged from US$1187 for stage 3 to US$21,826 for stage 5.[37] Upon evaluation of an employer-sponsor population health improvement program, workdays missed exceeded 10 hours per week for employees with CKD.[64] Unadjusted costs are presented in Table 3.

Anemia-related morbidity is of significant concern in the workplace. Overall burden and/or costs for patients with CKD and anemia are significantly higher than for those with CKD and no anemia.[24,26] Treatment for predialysis employees with anemia resulted in improved work productivity by 91.5%, reduced absenteeism by 52.3 days per year, and reduced health care costs by approximately US$4417 per patient per year.[63] A similar study reported incremental direct and indirect cost savings with anemia treatment in employees with CKD and anemia compared with those whose anemia was untreated.[29]

Current treatment options

Over the past few decades, few new treatment options have been made available for CKD patients. Without curative treatment, the primary aims remain to slow the progression of CKD and subsequent loss of kidney function and cardiovascular disease. Current objectives to address these outcomes include control of hypertension, dyslipidemia, proteinuria, hyperglycemia, anemia, and bone mineral disorders.[12] Given the complex nature of CKD and the interrelated risk factors, comorbidities, and complications represented in these patients, a comprehensive and collaborative treatment strategy of nonpharmacological (lifestyle management) and pharmacological management is recommended.

Lifestyle management

Key components of lifestyle management are those supporting the primary treatment aims of CKD. Obesity, smoking, sedentary lifestyle, high cholesterol, and hypertension increase the risk for adverse outcomes in patients with CKD.[12,42,65–70] Other important components of lifestyle management are mental health and social support. Although understudied, an important pilot study in late CKD was identified. Cabness et al[71] proposed evaluation of psychological measures linked to biophysiological measures in patients with CKD. As has been found with other chronic and debilitating diseases, mental health and social support may be of significant value to patients with CKD.[72]

Current renoprotective drug therapy

Current renoprotective drug therapy includes treatment with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), statins, insulins, and insulin sensitizers, depending on patient need. All of these therapies reduce proteinuria. In addition to their primary use, antihypertensive agents and those for hyperglycemia also demonstrate a slowed decline in or improvement of GFR. Supporting studies for each class are summarized in current Kidney Disease Outcomes Quality Initiative guidelines.[73]

Hypertension

Optimum control of hypertension is paramount in the management of CKD. In multiple clinical trials, ACEIs or ARBs slowed progression of diabetic and nondiabetic kidney disease between 16% and 56%.[74–79] The landmark trial by the Collaborative Study Group demonstrated the effectiveness of ACEIs in slowing progression of diabetes and CKD in patients with type 1 diabetes and macroalbuminuria, regardless of presence or absence of hypertension.[77] In patients with type 2 diabetes and overt nephropathy, ARBs were more effective than conventional therapy in the progression of nephropathy, despite similar blood pressure control.[74,77,80] In patients with nondiabetic CKD, ACEIs slowed disease progression, and the benefits were greater in patients with higher levels of proteinuria.[75,78,79,81] As evidenced by the African American Study of Kidney Disease trial, setting blood pressure targets reduced proteinuria and slowed progression in African Americans with hypertensive CKD.[82] Special attention and further research are needed to optimally manage hypertension in other at-risk and high-risk populations.

Dyslipidemia

Dyslipidemia is a cardiovascular risk factor for CKD. It is associated with decreased renal function in the general population and in patients with CKD. Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) are recommended for treatment of dyslipidemia in patients with CKD.[73] Results from the landmark Study of the Heart and Renal Protection (SHARP) trial support statin therapy to reduce cardiovascular events in a varied group of patients with advancing CKD. Although improvement in renal outcomes was not found, a 17% risk reduction in major atherosclerotic events was observed in CKD patients treated with ezetimibe and simvastatin compared with placebo, despite lower compliance (ezetimibe/simvastatin: 71%; placebo: 9%).[83] With improved compliance, statin therapy may result in significantly greater cardiovascular benefits than observed in Study of Heart and Renal Protection (SHARP).[83]

Hyperglycemic control for diabetic nephropathy

Hyperglycemia, the defining feature of diabetes, is a fundamental cause of kidney damage. In patients with diabetes, the target HbA_{1c} (glycated hemoglobin) is less than 7%. Intensive glycemic control prevents the development and progression of albuminuria.[84–87] The Diabetes Control and Complications Trial (DCCT) demonstrated a 54% reduction in risk of albuminuria in patients with type 1 diabetes with intensive antihyperglycemic therapy.[84] The follow-up study to DCCT, Epidemiology of Diabetes Interventions and Complications (EDIC), demonstrated persistent beneficial effects on albumin excretion and reduced incidence of hypertension up to 8 years after the DCCT study was completed. Long-term benefits of intensive treatment were clearly demonstrated in the EDIC study.[85] No data evaluating the renoprotective effects of tight glycemic control in patients with established nephropathy were identified.

Although current renoprotective pharmacotherapies are the mainstay of CKD treatment, they are only partially effective; 20% to 40% of patients progress to unfavorable renal outcomes in spite of therapy.[88] None of the current agents target all pathological mechanisms in CKD. Nor do they adequately reduce eGFR decline or significantly delay or stop progression to ultimately reverse disease or thwart adverse renal endpoints. Therefore, continued research to find new agents with new mechanisms of action may lead to more effective therapy for patients with CKD (Table 4).

Emerging renoprotective drug therapy

A variety of new renoprotective agents targeting primary destructive pathological mechanisms of CKD are in development.[89] Those identified via ClinicalTrials.gov include AST-120 (spherical carbon adsorbent), atrasentan, bardoxolone methyl, CTP-499, pentoxifylline, and VTP-27999. To date, AST-120 and bardoxolone methyl have advanced to Phase III clinical trials.[90–92] Brief descriptions of agents with ongoing Phase II and Phase III trials follow.

Atrasentan (ABT-627)

Atrasentan is a highly selective endothelin-A receptor antagonist that blocks the effect of endothelin-1, a protein that constricts blood vessels, raises blood pressure, and affects kidney function. Phase II data with atrasentan showed reduction in albuminuria.[90] A Phase IIb study is recruiting patients with type 2 diabetes and nephropathy currently treated with the maximum tolerated dose of a renin–angiotensin system inhibitor. Atrasentan (dose not reported) is an oral agent with once-daily administration.[93] Data availability was not reported.

Bardoxolone methyl (RTA-402)

Bardoxolone methyl is an antioxidant inflammation modulator – a potent inducer of the transcription factor NrF2, an important biological target that controls the production of many of the body's detoxification enzymes. This agent activates the NrF2 pathway aiming to decrease oxidative stress and inflammation, which contributes to kidney decline. Phase IIb data suggest the potential to prevent patients from progressing to later-stage disease and dialysis; reversal of disease is also suggested. A Phase III clinical trial, Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes is currently recruiting patients with CKD in type 2 diabetes. Bardoxolone methyl 20 mg is an oral agent with once-daily administration. Trial results are expected in June 2013.[90,91]

Table 4 Current renoprotective drug therapy

Risk factor or comorbid condition and current therapy	Renoprotective effects
Hypertension	
Angiotensin-converting enzyme inhibitors	Lower blood pressure
Angiotensin-receptor blockers	Reduce proteinuria
	Slow decline or improved GFR
Dyslipidemia	
Statins	Lower cholesterol
	Reduce proteinuria
Hyperglycemia	
Insulin	Reduce proteinuria
Insulin sensitizers	Slow decline or improve GFR

Note: Hirsch[88] and National Kidney Foundation.[12]
Abbreviation: GFR, glomerular filtration rate.

Table 5 Key emergent renoprotective drug therapy

Drug/Phase	Mechanism of action	Sponsor
Bardoxolone methyl (RTA-402) Phase III[90,91]	Activation and modulation of Nrf2 (anti-inflammatory effect)	Reata pharmaceuticals
Spherical carbon adsorbent (AST-120) Phase III[92,95]	Spherical carbon adsorbent of uremic toxins	Mitsubishi Tanabe Pharma and Kureha
Atrasentan (ABT-627) Phase IIb[93]	Blocks effect of endothelin-1	Abbott
CTP-499 Phase I[96]	Anti-inflammatory, antioxidant, antifibrotic	Concert pharmaceuticals
VTP-27999 Phase I[97]	Selective renin inhibitor	Vitae pharmaceuticals

Spherical carbon adsorbent (AST-120)

AST-120 is a spherical carbon adsorbent that acts locally to remove uremic toxins and precursors in the gastrointestinal tract, thereby preventing saturation in the blood stream and nephrotoxicity. It has been approved and marketed in Japan, South Korea, and the Philippines for prolonging time to initiation of dialysis therapy and improving uremic symptoms in patients with chronic renal failure.[94] Two Phase III outcome clinical trials have been completed and data are forthcoming:[92,95] Evaluating Prevention of Progression in Chronic Kidney Disease and Evaluating Prevention of Progression in Chronic Kidney Disease Including Assessment of Quality of Life. The trials evaluated AST-120 added to standard-of-care therapy for prevention of progression in moderate to severe CKD. The dosage studied in clinical trials was 9 g/day, divided into three doses per day. Clinical endpoints studied include initiation of dialysis, kidney transplant, or doubling of serum creatinine.

Other agents

Other promising agents planned for entry into Phase II trials include CTP-499, a first-in-class candidate from the deuterium platform, with anti-inflammatory, anti-fibrotic, and antioxidant properties,[96] and VTP-27999, a potent selective renin inhibitor;[97] Phase II studies are not yet recruiting. Aliskiren was a promising agent for high-risk patients with diabetes and renal impairment until an interim review by the data-monitoring committee concluded that patients were unlikely to benefit from treatment added on top of standard antihypertensives. In addition, treatment with aliskiren was associated with more adverse events than other treatments. Upon recommendation by the data-monitoring committee, the trial was terminated in December 2011.[98]

Emergent drug therapies with anticipated renoprotective effects are presented in Table 5. These agents provide new therapeutic options for patients with CKD. Several agents have new or unique mechanisms of action and better outcomes may be expected. For agents that have advanced to Phase III trials, positive efficacy and safety outcomes are anticipated.

Conclusion

The overarching, primary unmet need for new treatment for CKD is evident. Curative treatment or the ability to arrest deterioration of the kidney in CKD is not currently possible. However, several related unmet needs provide opportunity for action. This review has summarized the considerable clinical, humanistic, and economic CKD burden; resulting unmet need; and promising new pharmacological agents that target multiple pathological mechanisms or mechanisms marginally affected by traditional therapies.

Because CKD is prevalent and growing globally, the paucity of studies across disciplines on this topic is a cause for concern. In currently available research, broad study populations characteristic of patients with CKD are not adequately represented, nor are countries. Prospective epidemiological studies are needed to adequately characterize patient populations, particularly in countries with the most rapid increase in CKD rates. This research would support disease classification and staging efforts.

Patients are key decision makers in the health care process. Qualitative research with a focus on the patient perspective has been scant. Patients can be the best source for researchers and clinicians to understand the patient's illness experience, level of health literacy, treatment expectations and experience, and unmet needs with current treatments. Placing more emphasis on the patient perspective could improve and benefit overall care.

Although the majority of papers identified were in the field of health economics, more research is needed to better understand costs (direct and indirect) in different patient populations (eg, different ethnic groups, patients of working age, and patients with multiple comorbidities), in different settings (eg, employer, managed care, Medicare, Medicaid, and national plans) across countries.

As reported, several sponsor agencies worldwide have developed guidelines for the treatment of CKD. In 2012, KDIGO is expected to publish new international guidelines on this topic. Anticipated improved classification and staging may support earlier recognition of kidney dysfunction in the primary care setting, better referral to nephrologists, and targeted treatment plans by stage of CKD.

Continued basic and clinical trial research is needed to improve the understanding of pathological mechanisms associated with CKD initiation and progression, as well as the effects of treatment in various patient populations worldwide. Better understanding of the mechanisms may lead to the development of drugs that will stop the deterioration of the kidneys, reverse disease, or effect a cure.

CKD is a prevalent, complex, and growing condition worldwide. With the aging of the population and the increase of risk factors associated with initiation and progression of disease in many nations, a significant burden is placed on patients, families, employers, health care systems, and society as a whole. With action, the unmet needs identified in this review can be addressed. The ultimate goal is to discover a curative treatment or one that will arrest deterioration of the kidney. This will offer patients healthier and more productive lives and, eventually, decrease overall system costs so that scarce resources can be allocated elsewhere.

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Authors' contributions

LB and SH performed the review and wrote the first draft. VS and BL reviewed all drafts. CCM and LB wrote the final draft. All authors contributed to the conception and design, and read and approved the final manuscript.

Disclosure

Mitsubishi Tanabe Pharma Corporation provided financial support for this research. VS and BL are employees of Mitsubishi Tanabe Pharma America. LB, SH, and CCM have acted as research consultants to Mitsubishi Tanabe Pharma America. The authors declare no other competing interests with respect to this article.

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