Chronic kidney disease

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Chronic kidney disease is a general term for heterogeneous disorders affecting kidney structure and function. The 2002 guidelines for definition and classification of this disease represented an important shift towards its recognition as a worldwide public health problem that should be managed in its early stages by general internists. Disease and management are classified according to stages of disease severity, which are assessed from glomerular filtration rate (GFR) and albuminuria, and clinical diagnosis (cause and pathology). Chronic kidney disease can be detected with routine laboratory tests, and some treatments can prevent development and slow disease progression, reduce complications of decreased GFR and risk of cardiovascular disease, and improve survival and quality of life. In this Seminar we discuss disease burden, recommendations for assessment and management, and future challenges. We emphasise clinical practice guidelines, clinical trials, and areas of uncertainty.

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Introduction

Chronic kidney disease is a general term for heterogeneous disorders affecting the structure and function of the kidney. The variation in disease expression is related partly to cause and pathology, severity, and rate of progression. Since the introduction of the conceptual model, definition, and staging of chronic kidney disease 10 years ago,[1–4] guidelines have recommended a shift from kidney disease being recognised as a life-threatening disorder affecting few people who need care by nephrologists, to a common disorder of varying severity that not only merits attention by general internists, but also needs a concerted public health approach for prevention, early detection, and management.[4–6] Although guidelines have had an important effect on clinical practice, research, and public health, they have also generated controversy.[4,7] A Series[8] in *The Lancet* emphasised early recognition and prevention of disease and described treatment recommendations. In this Seminar we review the framework and estimates of disease burden; present an overview of the assessment and management of disease; emphasise guidelines and clinical trials; and discuss the challenges that are met in the association of chronic kidney disease with ageing and vascular disease, management of clinical trials, development of guidelines, and public health. We focus on the latest data and indicate areas of uncertainty and future directions for research.[9]

Conceptual model, definitions, and outcomes

Figure 1 shows a conceptual model for the development, progression, and complications of chronic kidney disease.[1,4] The model includes antecedents associated with increased risk, disease stages, and complications including death. Risks can be categorised either as susceptibility to kidney disease because of sociodemographic and genetic factors, or as exposure to factors that can lead to disease. Early stages of disease are often asymptomatic, are detected during the assessment of comorbid disorders, and can be reversible. Rapidly progressive diseases can lead to kidney failure within months; however, most diseases evolve over decades and some patients do not progress during many years of follow-up.

The definition of chronic kidney disease is based on the presence of kidney damage (ie, albuminuria) or decreased kidney function (ie, glomerular filtration rate [GFR] <60 mL/min per 1·73 m²) for 3 months or more, irrespective of clinical diagnosis (panel 1).[1,10,11] Because of the central role of GFR in the pathophysiology of complications, the disease is classified into five stages on the basis of GFR: more than 90 mL/min per 1·73 m² (stage 1), 60–89 mL/min per 1·73 m² (stage 2), 30–59 mL/min per 1·73 m² (stage 3), 15–29 mL/min per 1·73 m² (stage 4), and less than 15 mL/min per 1·73 m² (stage 5). Findings from experimental and clinical studies have suggested an important role for proteinuria in the pathogenesis of disease progression.[12] Epidemiological studies have shown graded relations between increased albuminuria and mortality and kidney outcomes in diverse study populations, in addition to, and independent of, low GFR and risk factors for cardiovascular disease.[13–18] In view of these findings, an

Search strategy and selection criteria

We searched the database of clinical practice guidelines in adults, which are developed and maintained by Kidney Disease Improving Global Outcomes (KDIGO)[9] in collaboration with the five main groups that develop English-speaking guidelines: Australian and New Zealand Society of Nephrology, Caring for Australians with Renal Impairment, Canadian Society of Nephrology, European Renal Association/ European Dialysis and Transplant Association (ERA/EDTA) European Best Practice Guidelines (EBPG), National Kidney Foundation (NFK) Kidney Disease Outcomes Quality Initiative (KDOQI), and United Kingdom Renal Association. We included selected guidelines and consensus statements for management of cardiovascular disease risk factors and cardiovascular disease, drug dosing in kidney disease, and acute kidney injury. For our review of clinical trials, we selected high-quality, high-impact clinical trial included in the guidelines. We focused mainly on publications from 2000 to 2010, but did not exclude commonly referenced and highly regarded older publications. We also included recent trials of promising therapeutic agents.
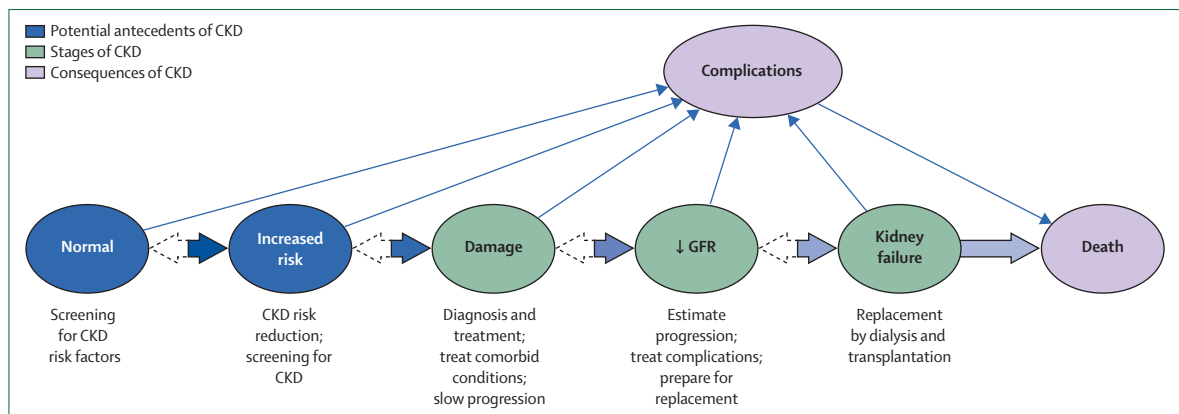
Figure 1: Conceptual model for chronic kidney disease
Continuum of development, progression, and complications of chronic kidney disease (CKD) and strategies to improve outcomes. Thick arrows between circles represent development, progression, and remission of CKD. Complications refer to all complications of CKD, including complications of decreased glomerular filtration rate (GFR) and cardiovascular disease. Complications might also arise from adverse effects of interventions to prevent or treat the disease. Horizontal arrows pointing from left to right represent the progressive nature of CKD. Dashed arrowheads signify that remission is less frequent than progression. Modified and reproduced, with permission, from references 1 and 4.

international conference recommended modification of disease classification to indicate prognosis by the addition of stages based on albuminuria, and an update of the 2002 guidelines (figure 2).[19]

Kidney failure is traditionally regarded as the most serious outcome of chronic kidney disease and symptoms are usually caused by complications of reduced kidney function. When symptoms are severe they can be treated only by dialysis and transplantation; kidney failure treated this way is known as end-stage renal disease. Kidney failure is defined as a GFR of less than 15 mL/min per 1·73 m², or the need for treatment with dialysis or transplantation. Other outcomes include complications of reduced GFR, such as increased risk of cardiovascular disease, acute kidney injury, infection, cognitive impairment, and impaired physical function.[20–24] Complications can occur at any stage, which often lead to death with no progression to kidney failure, and can arise from adverse effects of interventions to prevent or treat the disease.

Causes

In developed countries, chronic kidney disease is generally associated with old age, diabetes, hypertension, obesity, and cardiovascular disease, with diabetic glomerulosclerosis and hypertensive nephrosclerosis as the presumed pathological entities; however, exact diagnosis is often difficult.[25] Diabetic glomerulosclerosis is characterised by slowly worsening albuminuria, hypertension, and progressive decline in GFR, sometimes with nephrotic syndrome. Hypertensive nephrosclerosis has no distinct markers of kidney damage, but high-normal to high concentrations of albuminuria can occur after the onset of decreased GFR. Many patients with diabetes and chronic kidney disease do not have typical features of diabetic glomerulosclerosis, and pathological findings of hypertensive nephrosclerosis are often more severe than expected because of the level of blood pressure. The presence of red-blood-cell or white-blood-cell casts, or specific imaging abnormalities, suggest another cause of kidney disease. In developing countries, common causes of chronic kidney disease also include glomerular and tubulointerstitial diseases resulting from infections and exposure to drugs and toxins.

Prevalence

Many countries have surveillance programmes to monitor kidney failure treated by dialysis and transplantation (figure 3).[26] Incidence and prevalence vary because of differences in underlying diseases rates and availability of government-sponsored treatment. Incidence is now as high as 200 cases per million per year in many countries. It is nearing 400 cases per million in the USA, Taiwan, and some regions in Mexico, and has risen fastest in older individuals. Dialysis is the main treatment method in most countries. With average survival of 3–5 years in the USA, prevalence is nearing 1800 cases per million. In Japan and Taiwan, high survival translates to high prevalence nearing 2400 cases per million. Diabetes is the main cause of kidney failure in most countries, accounting for 40% or more of new patients.[26] The USA has a high incidence of disease in racial and ethnic minorities, which is probably an indicator of genetic and environmental factors in susceptibility, and disparities in treatment.[25,27,28]

Estimation of the burden of early stages of kidney disease is difficult. Prevalence estimates might be biased by limitation of the markers and methods that are used to estimate GFR and to define kidney damage. In the USA, the most accurate estimates based on estimated GFR and albuminuria of the prevalence of chronic kidney

Panel 1: Criteria for definition of chronic kidney disease

Duration >3 months on the basis of documentation or inference
Duration is necessary to distinguish chronic from acute kidney disease
- Clinical assessment can indicate duration
- Documentation of duration is not usually available in epidemiological studies

GFR <60 mL/min per 1·73 m²
- GFR is the best overall index of kidney function in health and disease
- Normal GFR in young adults is about 125 mL/min per 1·73 m²; GFR<15 mL/min per 1·73 m² is defined as kidney failure
- Decreased GFR can be detected by equations to estimate GFR that are based on serum creatinine (estimated GFR) but not by serum creatinine alone
- Decreased estimated GFR can be confirmed by measured GFR

Kidney damage as defined by structural abnormalities or functional abnormalities other than decreased GFR
Pathological abnormalities
- Clinical diagnosis is based on pathology and cause; markers of kidney damage might show pathology
- Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia)
- Vascular diseases (atherosclerosis, hypertension, ischaemia, vasculitis, thrombotic microangiopathy)
- Tubulointerstitial diseases (urinary-tract infections, stones, obstruction, toxic effects of drugs)
- Cystic disease (polycystic kidney disease)

History of kidney transplantation
In addition to pathological abnormalities in native kidneys, common pathological abnormalities include:
- Chronic allograft nephropathy (non-specific findings of tubular atrophy, interstitial fibrosis, vascular and glomerular sclerosis)
- Rejection
- Drug toxic effects (calcineurin inhibitors)
- BK virus nephropathy
- Recurrent disease (glomerular disease, oxalosis, Fabry's disease)

Albuminuria as a marker of kidney damage
Increased glomerular permeability, urine ACR >30 mg/g*
- The normal urinary ACR in young adults is <10 mg/g. Urine ACR categories 10–29, 30–300 and >300 mg are high normal, high, and very high, respectively. Urine ACR >2000 mg/g is accompanied by signs and symptoms of nephrotic syndrome (low serum albumin, oedema, and high serum cholesterol)

- Threshold value roughly corresponds to urine dipstick values of trace or 1+, dependent on urine concentration
- High urinary ACR can be confirmed by urine albumin excretion in a timed urine collection

Abnormalities in urinary sediment as markers of kidney damage
- Red-blood-cell casts in proliferative glomerulonephritis
- White-blood-cell casts in pyelonephritis or interstitial nephritis
- Oval fat bodies or fatty casts in diseases with proteinuria
- Granular casts and renal tubular epithelial cells in many parenchymal diseases (non-specific)

Imaging abnormalities as markers of kidney damage (ultrasound, CT, and MRI with or without contrast, isotope scans, angiography)
- Polycystic kidneys
- Hydronephrosis due to obstruction
- Cortical scarring due to infarcts, pyelonephritis, or vesicoureteral reflux
- Renal masses or enlarged kidneys due to infiltrative diseases
- Renal artery stenosis
- Small and echogenic kidneys (common in late stages of CKD because of many parenchymal diseases)

Renal tubular syndromes as markers of kidney damage
- Renal tubular acidosis
- Nephrogenic diabetes insipidus
- Barrter and Gittelman syndromes
- Fanconi's syndrome
- Cystinuria
- Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis

Excretion of urinary creatinine indicates muscle mass and varies with age, sex, race, diet, and nutritional status, and generally exceeds 1·0 g per day in healthy adults; therefore, the numeric value for urinary ACR (mg/g) is usually less than the rate of urinary albumin excretion (mg/day). Rates of 30–300 mg per day and >300 mg per day correspond to microalbuminuria and macroalbuminuria, respectively. Normal urine contains small amounts of albumin, low-molecular-weight serum proteins, and proteins that are from renal tubules and the lower urinary tract. In most kidney diseases, albumin is the main urine protein, comprising about 60–90% of total urinary protein when total protein is very high. Values corresponding to normal, high-normal, high, very high, and nephrotic-range total protein are about <50, 50–150, 150–500, >500, and >3500 mg/g, respectively. GFR=glomerular filtration rate. CKD=chronic kidney disease. *Conversion factor for albumin to creatinine (ACR) ratio: 1·0 mg/g=0·113 mg/mmol.

disease from 1999 to 2006 were about 11·5% (4·8% in stages 1–2 and 6·7% in stages 3–5), and 47% in people older than 70 years, mostly because of reduced GFR.[29] Prevalence seems to be increasing particularly in older individuals, and partly because of an increasing prevalence of diabetes and hypertension.[30] Reports from other countries[8] show some variation but are mostly consistent with these results.

In the USA, the ratios of prevalence of chronic kidney disease to incidence and prevalence of treated kidney

				Albuminuria stages, description, and range (mg/g)				
				A1		A2	A3	
				Optimum and high-normal		High	Very high and nephrotic	
				<10	10–29	30–299	300–1999	≥2000
GFR stages, description, and range (mL/min per 1·73m²)	G1	High and optimum	>105					
			90–104					
	G2	Mild	75–89					
			60–74					
	G3a	Mild-moderate	45–59					
	G3b	Moderate-severe	30–44					
	G4	Severe	15–29					
	G5	Kidney failure	<15					

Legend:
- No CKD
- Moderate-risk CKD
- High-risk CKD
- Very high-risk CKD

Figure 2: Prognosis of chronic kidney disease by GFR and albuminuria

Colours show how adjusted relative risk is ranked for five outcomes from a meta-analysis of general population cohorts: all-cause mortality, cardiovascular mortality, kidney failure treated by dialysis and transplantation, acute kidney injury, and progression of kidney disease. For categories with GFR >15 mL/min per 1·73 m² and albuminuria <2000 mg/g, ranks were averaged across outcomes. Mean rank numbers: 1–8=green, 9–14=pink, 15–21=orange, and 22–28=red. For categories with GFR <15 or albuminuria >2000 (corresponding to nephrotic range albuminuria), ranks were extrapolated on the basis of results from a meta-analysis of chronic kidney disease cohorts. Column and row labels are combined to be consistent with the agreed number of GFR and albuminuria stages.[22] Albuminuria=albumin-to-creatinine ratio (ACR) 1·0 mg/g=0·113 mg/mmol. Reproduced with permission from Kidney International and Kidney Disease Improving Global Outcomes.[19]

failure are about 200 to 1 and 50 to 1, respectively, which shows the high so-called competing risk of death caused by cardiovascular disease, especially in older patients. This finding emphasises the need for treatments to reduce risk of cardiovascular disease and to slow progression of chronic kidney disease. Risks of both mortality and kidney failure are associated with GFR and concentration of albuminuria. Figure 4 shows US prevalence estimates by eGFR and urinary albumin to creatinine ratio. The proportion of participants with chronic kidney disease in the groups at moderate, high, and very high risk (as categorised in figure 2) is about 73%, 18%, and 9%, respectively, representing a prevalence in the general population of about 10%, 2%, and 1%, respectively.

Detection and assessment

Panel 2 provides a five-step guide to the detection and assessment of chronic kidney disease, which can be accomplished by routine laboratory tests. Although GFR is difficult to measure, it can be estimated from serum creatinine. Creatinine assays are now traceable to reference methods, and estimated GFR (eGFR) is now routinely reported in more than 75% of clinical laboratories in the USA.[31] Because serum creatinine is commonly measured, reporting of eGFR allows chronic kidney disease to be detected and has led to increased referrals to nephrologists.[32,33] However, as with other diagnostic tests, reduced eGFR should be interpreted

with considerations of likelihood of disease based on the clinical setting.

Equations to estimate GFR use serum creatinine and a combination of age, sex, ethnic origin, and body size as surrogates for the non-GFR determinants of serum creatinine. These equations are more accurate for estimation of measured GFR than is serum creatinine alone.[34] The modification of diet in renal disease (MDRD) study equation[35] is reasonably accurate at eGFRs of less than 60 mL/min per 1·73 m²; however, bias and imprecision are increased at high eGFRs. The chronic kidney disease epidemiology collaboration (CKD-EPI) equation[29,36,37] has less bias at high eGFRs and is more accurate for predicting adverse outcomes than is the MDRD equation, and can be used to report eGFRs greater than 60 mL/min per 1·73 m². However, imprecision in the high range makes eGFRs less useful to classify chronic kidney disease stages 1 and 2, identify hyperfiltration, and monitor GFR decline. Both equations assign ethnic origin as either black (African American) versus white, or other. Modifications of these equations for use in individuals from China and Japan have been reported.[38] Widespread implementation of equations to estimate GFR will need assessment in other races, ethnic origins, and geographical regions. Confirmation of reduced eGFR by measurement of GFR (clearance of creatinine or exogenous filtration markers) is warranted when decisions are dependent on accurate knowledge of GFR—eg, determination of eligibility for kidney donation or dose adjustment of toxic drugs that are excreted by the kidneys.[39] Cystatin C can have more advantages compared with creatinine because its non-GFR determinants are less affected by race and muscle wasting, and because it is more predictive of subsequent cardiovascular disease and mortality.[40] The non-GFR determinants of serum cystatin C are poorly understood, and the use of two or more markers in a panel might be needed to more accurately estimate GFR.[41,42]

Although markers of kidney damage show underlying pathological changes, they are non-specific for clinical diagnosis (panel 1). The presence of one or more of these markers for 3 months or more is sufficient to identify chronic kidney disease. Albuminuria is the most frequently assessed marker in clinical practice and epidemiological studies. Historically, total urinary protein has been ascertained because of ease of measurement, especially with the urine dipstick, but cannot be standardised. Although albumin assays are expensive, measurement of an albumin to creatinine ratio in untimed spot urine has many advantages and is recommended by guidelines.[43,44] A urinary albumin to creatinine ratio of more than 30 mg/g (3·4 mg/mmol) is defined as high (panel 1); sex-specific and race-specific ratios have been proposed because of variation in creatinine excretion, but are difficult to implement. Rate of albumin excretion in a timed urine collection can be

used for confirmation when clinical diagnosis needs more accurate measurement. Although in this Seminar we use the term albuminuria rather than proteinuria, the loss of other serum proteins might be important in the pathogenesis of kidney disease and its complications.

Clinical diagnosis is categorised according to pathology and cause of disease (panel 1, panel 2). Because chronic kidney disease is mostly detected as decreased eGFR during assessment and management of other medical conditions, clinical diagnosis is generally established by recognition of the clinical setting and markers of kidney damage. A thorough review of the history, including comorbid disorders and drug use, family history, laboratory assessment, and ultrasound imaging are usually sufficient to reach a presumptive diagnosis. Biopsy of the kidney or invasive imaging procedures are usually used only for selected patients in whom a definitive diagnosis would result in a change in either treatment or prognosis.

Management

Concepts

Treatments for chronic kidney disease can prevent development, slow progression, reduce complications of decreased GFR, reduce risk of cardiovascular disease, and improve survival and quality of life. Data from the US renal data system[25] show a decreasing incidence of kidney failure in some high-risk groups—eg, in young people with diabetes—suggesting beneficial effects of these interventions. Despite these remarkable advances, the detection, assessment, and management of chronic disease are not fully understood.

Disease management is based on clinical diagnosis and stage according to GFR and albuminuria. Identification of clinical diagnosis allows for specific therapy that is directed at the cause and pathological processes. Thereafter, disease stage can be used to guide non-specific therapies to slow progression and reduce the risk of complications. Stage-based recommendations are cumulative—ie, recommendations for late stages include recommendations for early stages. Guidelines for stage-based recommendations have simplified the management of chronic kidney disease (table 1, webappendix pp 1–10); however because of an inadequate evidence base, thresholds for stage-based testing and treatment are uncertain. Despite many clinical trials, important clinical questions are unanswered (table 2, webappendix pp 11–19). Many trials have been underpowered or have relied on surrogate rather than clinical outcomes. Other trials have been difficult to interpret because of findings for both benefits and harms.

Practice models for the care of patients with chronic kidney disease will probably vary according to the availability of nephrologists and other specialists. Not all patients need referral to nephrologists; many common problems can be managed with existing guidelines by
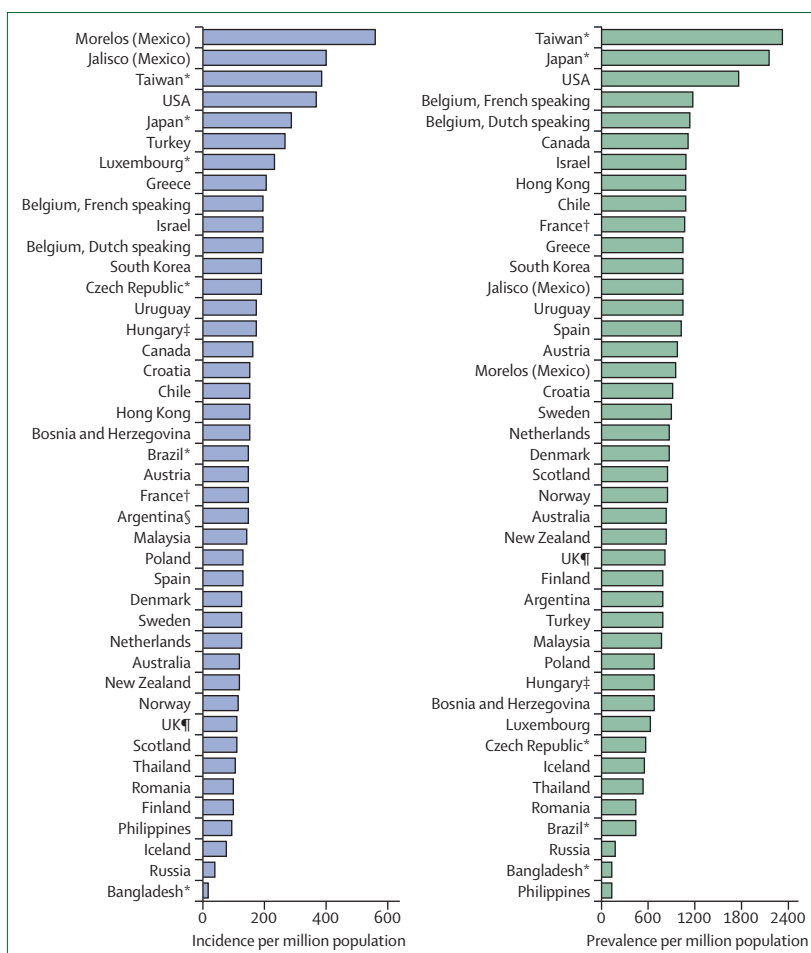

Figure 3: Incidence and prevalence of end-stage renal disease[26]
Incidence and prevalence of kidney failure treated by dialysis or transplantation (end-stage renal disease) in 2008. Data are only for countries for which relevant information was available. All rates are unadjusted. Average survival with treated kidney failure in each country can be computed from the ratio of prevalence to incidence. *Data from Bangladesh, Brazil, Czech Republic, Japan, Luxembourg, and Taiwan are dialysis only. †Data for France are from 13 regions in 2005, 15 in 2006, 18 in 2007, and 20 in 2008. ‡Latest data for Hungary are from 2007. §Data for Argentina from before 2008 are dialysis only. ¶UK=England, Wales, and Northern Ireland (data for Scotland are reported separately).

generalists and non-nephrology specialists. Referral is generally recommended for stage 4 disease, but early referral is recommended for patients with very high concentrations of albuminuria or with complications of decreased GFR that are difficult to manage.[45]

See **Online** for webappendix

Slowing progression of chronic kidney disease and reduction of albuminuria

The mean rate of age-related decline in GFR is 0·75–1·00 mL/min per 1·73 m² every year after the age of 40 years.[34] The decline in chronic kidney disease is highly variable—fast rates are noted in patients with high concentrations of albuminuria, diabetes, or hypertension, and racial and ethnic minority groups in the USA.[1] No generally accepted definition of fast progression is available. We believe that a decline of more than

				Albuminuria stages, description, and range (mg/g)				
				A1		A2	A3	
				Optimum	High-normal	High	Very high	**All**
				<10	10–29	30–299	>300	
GFR stages, description, and range (mL/min per 1·73m²)	G1	High and optimum	>105	23·6%	5·7%	1·9%	0·1%	**31·4%**
			90–104	20·0%	4·7%	1·7%	0·3%	**26·7%**
	G2	Mild	75–89	17·3%	4·1%	1·6%	0·2%	**23·0%**
			60–74	8·2%	2·7%	1·3%	0·1%	**12·2%**
	G3a	Mild-moderate	45–59	2·5%	1·1%	0·8%	0·2%	**4·7%**
	G3b	Moderate-severe	30–44	0·6%	0·4%	0·4%	0·2%	**1·5%**
	G4	Severe	15–29	0·1%	0·1%	0·1%	0·1%	**0·4%**
	G5	Kidney failure	<15	0·0%	0·0%	0·0%	0·1%	**0·1%**
		All		72·2%	18·8%	7·8%	1·3%	**100·0%**

Figure 4: **Prevalence of chronic kidney disease in the USA by GFR and albuminuria**
Grey shading=CKD defined by glomerular filtration rate (GFR) or albuminuria (13·8%). Cells show the proportion of adult population in the USA. Data from the National Health and Nutrition Examination Survey (NHANES III 1999–2000, 2001–02, 2003–04, and 2005–06 (N=18 026). GFR is estimated with the CKD-EPI equation and standardised serum creatinine. Albuminuria is established by one measurement of albumin-to-creatinine ratio (ACR); thus proportions for GFR >60 mL/min per 1·73 m² exceed those reported elsewhere.[29] Values in cells might not total to values in margins because of rounding. Category of very high albuminuria includes nephrotic range. For eGFRs of 45–59 ml/min per 1·73 m², percentages estimated with the CKD-EPI equation for urine ACR categories <10, 10–29, 30–299, and >300 mg/g (2·5%, 1·1%, 0·8%, 0·2%, and 4·7% [subtotal], respectively) are lower than for the same categories in the MDRD study equation (3·6%, 1·4%, 0·9%, 0·2%, and 6·1% [subtotal], respectively).

4 mL per min per year is fast; at this rate, the interval from onset of chronic kidney disease stage 3 to kidney failure would be 12 years or less. Mechanisms of progression probably differ according to clinical diagnosis (eg, diabetic kidney disease *vs* non-diabetic kidney disease, disease with *vs* without proteinuria, and genetic *vs* acquired diseases). Nonetheless, substantial evidence from experimental models shows that some mechanisms are independent of the initial cause of disease, and provide several biomarkers and treatment targets for interventions to slow progression, induce remission of disease, and potentially regenerate healthy tissue.[12,46–48] Consistent with these findings are several interventions that slow progression in human beings.

The most consistent benefit is noted with use of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), usually in association with diuretic drugs, in patients with high concentrations of albuminuria. Some trials show favourable effects of a lower than usual target blood pressure (<130/80 mm Hg *vs* <140/90 mm Hg) in patients with high concentrations of albuminuria. Unfortunately, these trials included few participants older than 70 years; therefore, the generalisability of their findings to the large number of older patients with chronic kidney disease is not known.[49] Clinical trials of these interventions for risk reduction of cardiovascular disease in older populations who were not selected for kidney disease

have not shown beneficial effects on disease progression, and some have suggested an increased risk of acute kidney injury. The absence of benefit probably indicates the low risk of progression to kidney failure corresponding to lower concentrations of albuminuria in studies of cardiovascular disease than in studies of chronic kidney disease.[50–52] Until further studies are done, these interventions should be recommended for patients with high concentrations of albuminuria (threshold for urinary albumin to creatinine ratio between 30 mg/g and 300 mg/g). ACE inhibitors and ARBs in high doses or with other agents that inhibit the renin-angiotensin system are effective to reduce albuminuria, but have not been tested in long-term trials in populations with chronic kidney disease.[53–56]

Previous clinical trials of intensive glycaemic control (mean achieved glycosylated haemoglobin [HbA$_{1c}$] 7%–8%) showed a benefit in slowing the development of diabetic kidney disease, but did not enrol sufficient patients with kidney disease at baseline to assess the effect on disease progression. Clinical trials of high-intensity therapy (target HbA$_{1c}$ <6·0% or <6·5%) have included increased numbers of patients with kidney disease at baseline and have shown a slow rise in albuminuria, but inconclusive effects on GFR decline, and an increased risk of hypoglycaemia. Despite much interest in restriction of dietary protein (<0·8 g/kg per day), clinical trials have so far been inconclusive.

Treatments to slow the decline in GFR also reduce albuminuria, and the relation between albuminuria reduction and subsequent GFR decline is strong. Nonetheless, whether albuminuria is on the causal pathway to GFR decline and whether targeting albuminuria is important in modification of therapy is uncertain.[57–59] In practice, serial measurements of albumin to creatinine ratio and eGFR can be used to monitor disease progression and guide therapy. However, variability can occur over time because of fluctuations in disease activity and treatment; therefore, a long period of observation might be needed to assess the rate of progression. Development of risk prediction instruments for kidney failure might be helpful to guide clinical decisions, but few instruments are available.[60–62]

Prevention of complications from decreased GFR
Threats to patient safety
Chronic kidney disease has been recognised as a potential risk factor for medical errors.[63] Furthermore, acute kidney injury is a frequent complication of medical errors and can potentially accelerate progression to kidney failure.[20,21]

Decreased GFR is associated with altered pharmacokinetics and pharmacodynamics of many drugs, leading to an increased risk of toxic effects if the dose is not appropriately adjusted. Patients with decreased GFR are also at an increased risk of complications from administration of intravenous fluid—eg, fluid overload

and electrolyte disturbances—and of complications from agents that are used in diagnostic angiography, including iodinated contrast (acute kidney injury) and gadolinium (nephrogenic systemic fibrosis). Guidance for adjustment of drug doses has traditionally been based on serum creatinine or creatinine clearance as estimated by the Cockcroft-Gault equation.[64] A study[65] has suggested that GFR estimates from the MDRD study equation would be as accurate; however, estimates that are adjusted for body surface area should be unadjusted for accurate dosing in patients with very large or small body size. Recognition of decreased GFR is fundamental to appropriate drug dosing. Several studies[66] have investigated the value of linking laboratory reporting of serum creatinine or eGFR to computerised entry of prescription orders, with variable success.

Many commonly used drugs and procedures can potentially cause acute kidney injury, and patients with decreased GFR have an increased risk of drug-induced injury.[67] Avoidance of non-steroidal anti-inflammatory drugs (NSAIDs), phosphorus-based enemas, and iodinated contrast is recommended if possible. Acute kidney injury is a risk after iodinated contrast is aggravated by depletion of extracellular fluid, and guidelines recommend administration of saline or bicarbonate, with or without N-acetylcysteine, before contrast procedures.

Uraemic complications
Many of the disorders associated with uraemia are generally asymptomatic and can first be identified at GFRs of less than about 60 mL/min per 1·73 m².[1] These disorders are more common as GFR declines, and when GFR is 15–30 mL/min per 1·73 m² the frequency is about 75% for hypertension; 50% for anaemia; 20% for hyperparathyroidism, hyperphosphataemia, and acidosis; and 5–10% for hypocalcaemia and low serum albumin.[1,25,45,68] Fatigue, weakness, frailty, and decreased health-related quality of life are common but non-specific, and might be caused by comorbid disorders.

Impairments in renal excretory and endocrine function parallel reductions in GFR, leading to complex disorders that are characterised by solute retention, hormone deficiencies or resistance, and compensatory responses in other organ systems.[69] For each disorder, these abnormalities are markers of disease severity and targets for intervention. Observational studies[1] provide strong evidence for associations of markers with clinical outcomes. Clinical trials have shown that several interventions are successful in ameliorating the abnormalities in the markers (table 2), but evidence is scarce for long-term effectiveness for clinical endpoints for many therapies.

Hypertension is attributed to salt retention and increased vascular tone due to a failure to suppress the sympathetic nervous system and renin-angiotensin system, inhibition of sodium-potassium ATPase, and

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Panel 2: **Five-step guide for the detection and assessment of chronic kidney disease**

1 Recognition of increased risk of CKD
- Increased susceptibility to CKD (ie, old age, family history, history of acute kidney injury, member of ethnic or racial minority in the USA, reduced nephron mass [history of nephrectomy, low birthweight], genetic traits)
- Exposure to diseases or conditions that cause CKD—ie, risk factors for CVD (hypertension, diabetes, obesity), CVD, autoimmune disease (systemic lupus erythematosus, vasculitis), infections (bacteria, HBV, HCV, HIV, schistosomiasis, malaria), drugs or toxins (NSAID, iodinated radiographic contrast, aristolochic acid)

2 Testing for CKD
- Measure serum creatinine to estimate GFR
- Measure urinary albumin
- Search for other markers of kidney damage that are specific to the risk (urine sediment, imaging abnormalities, or renal tubular syndromes)
- Confirmatory tests (if indicated)

3 Detection of CKD
- GFR <60 mL/min per 1·73 m² (measured or estimated)
- Kidney damage (pathological abnormalities, markers, or history of kidney transplantation)
- Duration >3 months (documented or inferred)

4 Evaluation of clinical diagnosis for implementation of specific therapy
- Diabetic kidney disease (type 1 or type 2)
- Non-diabetic kidney disease (glomerular diseases other than diabetic kidney disease, vascular diseases, tubulointerstitial diseases, or cystic diseases)
- Kidney disease in recipients of kidney transplants

5 Assessment of stage for implementation of stage-based non-specific therapy
- GFR stages
- Albuminuria stages

CKD=chronic kidney disease. CVD=cardiovascular disease. HBV=hepatitis B virus. HCV=hepatitis C virus. NSAID=non-steroidal anti-inflammatory drug. GFR=glomerular filtration rate.

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nitric-oxide deficiency.[70] Although restriction of dietary sodium reduces blood pressure in experimental models, adherence is low in clinical practice. All antihypertensive drugs seem to be effective in lowering blood pressure, but several agents, including a diuretic, are usually necessary to reach the target level. The optimum level of blood pressure and selection of antihypertensive agents to reduce risk of cardiovascular disease are controversial. Guidelines suggest a lower than usual target for blood pressure (<130/80 mm Hg *vs* <140/90 mm Hg), but no adequately powered randomised trials of chronic kidney disease have been done to test this hypothesis.[51,52] The main findings from the action to control cardiovascular

	Rationale	Target population	Examples*
Reduction of the risk of CKD	Interventions for modifiable factors that can cause or increase susceptibility to kidney disease	All adults	Prevention, detection, and treatment of hypertension and diabetes
Early detection of CKD	Laboratory testing to detect presence of asymptomatic disease	Adults at increased risk of CKD (hypertension, diabetes, clinical CVD, family history of kidney failure, or age ≥60 years)	Urinary albumin-to-creatinine ratio as a marker of kidney damage, serum creatinine to estimate GFR
Identification of the clinical diagnosis (cause and pathology)	Specific therapy directed at the clinical diagnosis	All patients with CKD	See panel 1
Slowing the progression of CKD and of albuminuria	Non-specific therapies, irrespective of the cause of CKD	All patients with CKD (high priority in patients with high-risk CKD)	ACE inhibitors or ARBs for patients with albuminuria, low blood-pressure goal
Prevention of complications of decreased GFR: threats to patient safety	Avoiding toxic effects of drugs and drug-induced AKI	Patients with CKD stages 3–5	Drug dosing based on eGFR; avoiding NSAIDs, iodinated radiographic contrast, phosphate-based bowel preparation, gadolinium (CKD stages 4–5); prevention of contrast AKI with isotonic saline or bicarbonate
Prevention of complications of decreased GFR: uraemic complications	Therapy directed at altered pathophysiology	Patients with CKD stages 3–5 (more often in stages 4–5)	ESA and iron for anaemia; vitamin D and phosphate binders for CKD-MBD; appropriate energy intake for malnutrition; referral to nephrologists
Treatment of the nephrotic syndrome	Non-specific therapies, irrespective of the cause of CKD	Patients with urine ACR >2000 mg/g	ACE inhibitors or ARBs, restriction of dietary sodium, diuretics, statins, consider anticoagulation
Improvements in the outcomes of dialysis and transplantation	Preparation and timely initiation of kidney replacement therapy	Patients with CKD stages 4–5 (more often in stage 5)	Modality selection for dialysis; access placement for haemodialysis; recipient selection for transplantation; donor selection for transplantation; adequate dialysis dose; improved immunosuppression for transplantation; complications associated with decreased GFR and albuminuria after transplantation
Reduction of the risk of CVD	Treatment of CVD risk factors and clinical CVD	All patients with CKD (high priority in patients with high-risk CKD)	CKD as the highest risk group for blood pressure, lipids

For references see table 1, webappendix pp 1–10. CKD=chronic kidney disease. CVD=cardiovascular disease. GFR=glomerular filtration rate. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. AKI=acute kidney injury. eGFR=estimated GFR. NSAID=non-steroidal anti-inflammatory drug. ESA=erythropoietin-stimulating agent. CKD-MBD=CKD-mineral and bone disorders. ACR=albumin-to-creatinine ratio. *References to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[9] if available, and to other guidelines and consensus statements if no KDIGO guideline is available.

Table 1: Overview of strategies for prevention, detection, evaluation, and management to improve outcomes of chronic kidney disease in adults

risk in diabetes (ACCORD) trial did not show an advantage of low systolic blood pressure on cardiovascular disease events in patients with type 2 diabetes, but analyses in the subgroup with chronic kidney disease are not yet available. The systolic blood pressure intervention trial (SPRINT) will test this hypothesis in non-diabetic patients with chronic disease.

Anaemia is caused mainly by decreased production of erythropoietin by the peritubular cells, and bone-marrow unresponsiveness to erythropoietin, indicating systemic inflammation, increased hepcidin production by the liver, and decreased iron availability for erythropoiesis.[71] Treatment with exogenous erythrocyte-stimulating agents (ESA) raises haemoglobin, reduces the need for transfusions, and improves quality of life and exercise capacity.[72,73] However, treatment with ESA to target haemoglobin concentrations of 130 g/L or more (achieved mean concentrations >110 g/L or 120 g/L) has been consistently associated with high rates of cardiovascular disease, especially in patients who are ESA-hyporesponsive.[74–81] Clinical decision making should balance risks and benefits and usually favours ESA administration in patients undergoing dialysis in whom haemoglobin concentrations are lower, quality of life is poorer, and transfusion is needed more often than for patients with earlier stages of chronic kidney disease.[82]

Mineral and bone disorders in chronic kidney disease are characterised by abnormalities in serum concentrations of calcium, phosphorus, 1,25-dihydroxycholecalciferol, and parathyroid hormone; abnormalities in bone morphology; and vascular calcification.[83] Phosphate retention and deficiency of 1,25-dihydroxycholecalciferol seem to be the main causes of hyperparathyroidism and hypocalcaemia, and can be treated by decreased phosphorus intake (with restriction of dietary protein) and phosphate-binding drugs (calcium carbonate, lanthanum carbonate, and sevelamer). Hyperparathyroidism can also be treated by exogenous 1,25-dihydroxycholecalciferol and vitamin D analogues, and calcimimetics. Although these measures can reduce the severity of osteitis fibrosa cystica, they do not reduce the incidence of fractures. 1,25-dihydroxycholecalciferol and calcium-containing phosphate binders have a greater risk of hypercalcaemia than do non-calcium-containing phosphate binders, and might induce low-turnover osteomalacia and vascular calcification. However, the long-term consequences of these effects are not known. Fibroblast growth factor (FGF)-23—a bone-derived

phosphaturic hormone—is secreted in response to phosphorus intake, inhibits production of 1,25-dihydroxy-cholecalciferol, and is associated with cardiovascular disease. Increased FGF-23 in chronic kidney disease might be an alternative mechanism for mineral and bone disorders and a new target for interventions.[84]

Malnutrition and inflammation frequently coexist in chronic kidney disease.[85,86] Decreased energy intake is an important causal factor, but dietary interventions are usually not sufficient to increase intake. Inflammation might be partly due to underlying systemic vascular disease and to retained solutes. Clinical trials are underway with exercise training and agents to promote anabolism, such as human growth hormone and ghrelin.[87–90] Signs of peripheral nervous system and CNS disorders include peripheral neuropathy, restless leg syndrome, sleep disorders, and cognitive impairment.[69] Retained toxins are thought to have a role

	Surrogate outcomes*		Clinical outcomes	
	Measures	Trial results	Measures	Trial results
Kidney disease progression in CKD stages 1–4				
ACE inhibition and ARB vs other antihypertensive regimens	Decline in GFR and albuminuria	Slow decline in GFR (strong effect in patients with high baseline albuminuria); reduction in albuminuria	Time to kidney failure	Beneficial effect in patients with high baseline albuminuria
Low vs usual blood pressure target	Decline in GFR and albuminuria	Slow decline in GFR in patients with high baseline albuminuria; reduction in albuminuria	Time to kidney failure	Beneficial effect after long-term follow-up in patients with high baseline albuminuria; harm for target SBP<120 mm Hg in type 2 diabetes
More vs less intensive glycaemic control in diabetes	Decline in GFR and albuminuria	Inconsistent effects on GFR decline; reduction in albuminuria	Time to kidney failure	Not enough events; harm for target HbA$_{1c}$<6·0–6·5% in type 2 diabetes
Low protein diet with or without aminoacid or ketoacid supplements vs usual protein diets	Decline in GFR and albuminuria	Inconclusive effect on GFR decline; reduction in albuminuria	Time to kidney failure	Insufficient events
Statins vs placebo	Decline in GFR and albuminuria	Slow decline in GFR in some trials; reduction in albuminuria	Time to kidney failure	Insufficient events in small trials, generally non-significant outcomes in largest trial
Sodium bicarbonate vs standard care	Decline in GFR, nutritional status	Slow decline in GFR; improved nutritional status	Time to kidney failure	Beneficial effect in one small trial
Paricalcitol vs placebo	Decline in GFR and albuminuria	No effect on GFR decline; greater decline in albuminuria	Time to kidney failure	Not tested
Somatostatin vs placebo in PKD	Decline in GFR, cyst growth	No effect on GFR decline; small effect on cyst growth	Time to kidney failure	Not tested
mTOR inhibitors vs placebo or standard care in PKD	Decline in GFR and cyst growth	No effect on GFR decline; small effect on cyst growth	Time to kidney failure	Not tested
Anaemia in CKD stages 4–5				
ESA with high vs low haemoglobin target	Need for blood transfusions	Decreased need for transfusions	CVD and mortality, quality of life	No benefit for mortality; probable harm for CVD
ESA vs placebo	Need for blood transfusions	Decreased need for transfusions	CVD and mortality; quality of life	Beneficial effect on quality of life; no benefit for mortality; probable harm for CVD
Mineral and bone disorders in CKD stages 4–5				
Vitamin D or analogues vs other agents	Parathyroid hormone	Lower concentrations of parathyroid hormone	Fractures	Not tested
Cinacalcet vs other agents	Parathyroid hormone	Lower concentrations of parathyroid hormone	Fractures	Not tested
Sevelamer vs calcium-containing phosphorus binders	Vascular calcification	Reduced increase in vascular calcification	CVD and mortality	No beneficial effect
Dialysis delivery in CKD stage 5D†				
Early vs usual initiation of dialysis	Uraemic symptoms	Few symptoms	Mortality	No benefit
High vs low dialysis dose	Hospital admissions	No difference	CVD and mortality	No benefit
High vs low dialysis membrane flux	Hospital admissions	No difference	CVD and mortality	No benefit
Short daily (6 days per week) vs usual (3 days per week) haemodialysis	Left ventricular mass	Improved left ventricular mass	Quality of life	Beneficial effect on self-assessed physical function

(Continues on next page)

	Surrogate outcomes*		Clinical outcomes	
	Measures	Trial results	Measures	Trial results
(Continued from previous page)				
Cardiovascular disease in CKD stage 5D†				
Antihypertensive agents *vs* placebo or conventional agents	..	..	CVD and mortality	Beneficial effect in a meta-analysis
Statins *vs* placebo	..	..	CVD and mortality	No benefit on total mortality; beneficial effect on atherosclerotic CVD events
Folic acid and B vitamins *vs* placebo	..	..	CVD and mortality	No benefit
Graft survival in CKD stages 1–5T†				
Tacrolimus *vs* ciclosporin	Acute rejection	Few acute rejections	Long-term graft survival	Not tested
Antilymphocyte antibodies and low-dose calcineurin inhibitor *vs* standard-dose calcineurin inhibitor for induction	Acute rejection	Few acute rejections	Long-term graft survival	Not tested
Mycophenolate mofetil *vs* placebo or azathioprine	Acute rejection	Fewer acute rejections	Long-term graft survival	Not tested
mTOR inhibitors *vs* calcineurin inhibitors	Acute rejection, GFR	Equivalence for acute rejection, higher GFR	Long-term graft survival	Not tested
Costimulatory blockade (betalacept) *vs* calcineurin inhibitors	Acute rejection, GFR	Equivalence for acute rejection, higher GFR	Long-term graft survival	Not tested

For references see table 2, webappendix pp 11–19. CKD=chronic kidney disease. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. GFR=glomerular filtration rate. SBP=systolic blood pressure. PKD=polycystic kidney disease. ESA=erythropoietin-stimulating agent. CVD=cardiovascular disease. mTOR=mammalian target of rapamycin. *GFR decline that is ascertained from doubling of baseline serum creatinine is accepted as a surrogate for progression of kidney disease in clinical trials to slow progression. This doubling roughly corresponds to halving of baseline GFR with new onset of CKD stage 3 in patients with CKD stages 1–2 at baseline, or new onset of CKD stage 4 in patients with CKD stage 3 at baseline. Acute rejection ascertained from biopsy is accepted as a surrogate for graft failure in clinical trials of transplant immunosuppression. Surrogate outcomes do not include direct effects of interventions (eg, effects of blood pressure for antihypertensive agents, serum urea nitrogen for low protein diets or higher dialysis dose, LDL cholesterol for statins, haemoglobin for ESA or iron, phosphorus for phosphorus binders, middle-molecular-weight solutes for high-flux dialysers, homocysteine for folic acid, or immunological measures for immunosuppressive therapy). †D or T after CKD stage refers to treatment with dialysis or transplantation.

Table 2: **Summary of selected randomised trials for chronic kidney disease**

in these disorders, and intensive dialysis is sometimes associated with amelioration. No specific therapies have yet been developed for these neurological manifestations.

Treatment of nephrotic syndrome

Nephrotic syndrome is one of the main clinical presentations of glomerular disease (panel 1), indicating the pathophysiological effects of losses of large quantities of urinary albumin and other serum proteins, such as immunoglobulins, growth factors, components of the complement, and coagulation cascades. The clinical manifestations are related to the underlying clinical diagnosis and severity of proteinuria.[91–93] Irrespective of cause, patients with nephrotic syndrome might have disabling symptoms from fluid retention, and are at increased risk of infectious, metabolic, and thrombotic complications, and acute kidney injury. Non-specific therapy includes ACE inhibitors or ARBs to reduce proteinuria, restriction of dietary sodium and diuretics for oedema, statins to reduce hypercholesterolaemia, and possibly anticoagulants to reduce the risk of deep-vein thrombosis.

Dialysis and transplantation

The high cost of dialysis and transplantation restrict their availability worldwide, and many patients with kidney failure die without treatment. In 2008, Medicare payments in the USA were US$77 506 for haemodialysis, $57 639 for peritoneal dialysis, and $26 668 for transplantation per person per year.[94] Observational studies suggest that referral to nephrologists before the onset of kidney failure is associated with an increased rate of transplantation, and reduced mortality and cost after the onset of dialysis; however, findings from a clinical trial[95] did not show a benefit of early initiation of dialysis. Early referral also enables informed decision making about modality by patients, creation of vascular access for haemodialysis, and identification of living donors for transplantation before the onset of kidney failure.

First-year survival with a functioning graft after deceased donor transplantation now exceeds 90%. However, the rate at 10 years is less than 40%, which is caused partly by nephrotoxic effects of calcineurin inhibitors and death with graft function attributed to cardiovascular disease.[25] Clinical trials focus on low doses of these agents in combination with other

immunosuppressive agents to reduce nephrotoxic effects and risk of cardiovascular disease, and to prevent graft rejection. Observational studies show that reduced GFR and albuminuria are risk factors for graft loss and mortality in recipients of kidney transplants.[96,97] Guidelines for non-specific therapy to slow progression of kidney disease and to prevent complications of decreased GFR and albuminuria are based largely on observational data and extrapolation of trials of diseases in the native kidneys. Transplantation is mostly limited by a scarcity of donor organs. Although preliminary experience with donor exchange programmes or recipient desensitisation shows promising results in overcoming ABO and HLA incompatibilities, logistical obstacles need to be overcome before these activities can be used worldwide.[98,99]

Patients' survival in long-term dialysis is substantially lower than survival for transplant recipients, even after selection and case-mix bias have been accounted for. Improvements in age-adjusted survival of patients on dialysis have occurred during the past decade in association with adoption of new technologies and measures of clinical performance, including increased doses of dialysis, partial correction of anaemia, and control of hyperphosphataemia.[25] However, clinical trials of single interventions have not shown improved survival. One trial[100] showed improvement in left ventricular mass and physical function with frequent haemodialysis, perhaps indicating improved fluid and blood-pressure control. Cardiovascular disease is the leading cause of death, but the relation of traditional risk factors—such as blood pressure, serum LDL cholesterol, and body-mass index—to mortality is complex, with increased risk at both low and high levels. These paradoxical relations seem to indicate confounding by disease severity, malnutrition and inflammation, and unmeasured comorbid disorders. Although a meta-analysis[101] of trials of antihypertensive agents has shown reduced mortality, the optimum agents and blood pressure targets were not identified. Two moderately large trials of statins[102,103] did not show reduction in total mortality despite substantial lowering of serum LDL cholesterol; however, the study of heart and renal disease protection (SHARP) trial[104] showed reduced atherosclerotic events. The failure of statins to reduce overall mortality could indicate heart failure or arrhythmias as the main mechanism for death from cardiovascular disease, rather than atherosclerosis. Improvements in mortality in patients on dialysis will probably need several interventions.

Reductions in risk of cardiovascular disease
Cardiovascular disease is considered separately from other complications of chronic kidney disease because it is the most frequent outcome of chronic kidney disease, and because chronic kidney disease is a risk factor for cardiovascular disease.[105–107] Studies of several populations show that low GFR and high albuminuria

are associated with an increased risk of cardiovascular mortality, de-novo and recurrent cardiovascular events, and subclinical cardiovascular disease. Pathophysiological links between cardiovascular and chronic kidney disease include a high prevalence of traditional and non-traditional risk factors, including hypertension; fluid overload; electrolyte, acid-base, and mineral disorders; anaemia; dyslipidaemia; inflammation; increased oxidative stress; and prothrombotic stimuli.[108–110] However, these associations do not prove causation. Other possible explanations are the high prevalence of shared risk factors for both diseases, and reverse causation, because cardiovascular disease is now recognised as a risk factor for GFR decline.[111,112]

Many guidelines now recommend that patients with chronic kidney disease be considered in the highest-risk group for subsequent cardiovascular events, and that most effective interventions for reducing the risk of cardiovascular disease in the general population should also be applied to patients with chronic kidney disease. Few clinical trials have been specifically designed to assess clinical outcomes after interventions for risk factors for cardiovascular disease and for clinical cardiovascular disease in people with chronic kidney disease. However, treatment for patients with risk factors for cardiovascular disease is effective in early stages of chronic kidney disease, and in trials of cardiovascular disease, the subgroup with chronic kidney disease seems to benefit as much or more than the subgroup without disease from intensive reduction in risk factors for cardiovascular disease and intensive management of clinical disease.[113–115] These findings suggest that patients with early stages of chronic kidney disease might be more similar to the general adult population, in whom one intervention for cardiovascular disease can improve mortality, than to patients with kidney failure treated by dialysis.

Controversies and challenges
Association with ageing and vascular disease
Ageing and vascular disease are associated with low GFR and high albuminuria, and whether the present definition leads to overdiagnosis of chronic kidney disease has been questioned, particularly for older individuals.[116,117] The magnitude and cause of these associations are not well understood and are important topics for research; however, some evidence suggests that low GFR and high albuminuria are not normal and that the term kidney disease is appropriate. First, the age-related decline in GFR is associated with abnormalities in kidney structure and function, which cannot be distinguished from abnormalities caused by disease.[118–120] Second, the kidney is a highly vascular organ; therefore kidney disease cannot be distinguished from kidney involvement in a systemic vascular disease as has been suggested.[121] Third, increased evidence has indicated that decreased GFR and albuminuria are associated with high risks of mortality and kidney outcomes in both old and young individuals.[15–18]

As in diabetes, hypertension, or hypercholesterolaemia, the selection of the threshold value for disease definition should balance the risk of identification of low-risk individuals versus the benefit of early detection of high-risk individuals. Although studies of risks and benefits are necessary, they are limited by insufficient knowledge about the full range of complications and effectiveness of interventions to treat chronic kidney disease.[122]

Clinical trials
To improve outcomes for chronic kidney disease, new treatments will need to be translated into clinical practice and public health.

Nephrology has the fewest number of clinical trials of major specialties[123] and, not surprisingly, few treatments have been shown to enhance clinical outcomes (table 2). These factors are the substantial challenges in clinical trials of chronic kidney disease. First, the average rate of progression of most kidney diseases is slow, needing a long period of follow-up or a large study population to test the effectiveness of interventions to slow progression. Death from cardiovascular disease is a competing event, especially in older patients with early stages of chronic kidney disease in whom the rate of death far exceeds the rate of kidney failure. Second, the high prevalence of comorbid disorders in patients with chronic kidney disease suggests that multifaceted interventions and coordination of medical care might be needed to improve outcomes. The design, management, and interpretation of trials of complex interventions is difficult; however, some have been reported.[124–126] Third, despite the large number of uraemic complications in chronic kidney disease, most patients do not have specific symptoms until late stages of disease, and few studies have recorded patient-reported outcomes.[127] However, pivotal clinical trials for drug development need a clinical endpoint that is an indicator of how a patient survives or feels. A doubling of serum creatinine has been accepted as surrogate endpoint for progression of chronic kidney disease, but a change in GFR that is smaller than this change in serum creatinine is not accepted.[57,59] Changes in serum creatinine are not sensitive to the early decline in GFR, which limits drug development to patients with severe disease. Re-evaluation of whether some asymptomatic disease complications might be considered as clinical endpoints in chronic kidney disease could be worthwhile.

Guidelines
Clinical practice guidelines are systematically developed statements that assist practitioners and patient decisions about appropriate health care for specific clinical circumstances. Implementation of rigorously developed evidence-based guidelines can reduce variability of care, improve patient outcomes, and ameliorate deficiencies in health-care delivery.[128,129] The first guidelines in nephrology were developed in 1993 and focused on the delivery of adequate doses of haemodialysis.[130,131] Many guidelines now target all stages of chronic kidney disease and the most common clinical diagnoses (table 1), and many recommendations have been incorporated into measures of clinical performance in patients undergoing dialysis.[132] The main responsibility for developing guidelines for chronic kidney disease has now been assumed by Kidney Disease Improving Global Outcomes (KDIGO)—a global not-for-profit foundation dedicated to improving the care and outcomes of patients with kidney disease worldwide.[133,134] KDIGO guidelines rate the strength of recommendations and evidence with rigorous and well accepted methods.[135] The rationale for worldwide development of guidelines is that chronic kidney disease is a global health problem, methods need to be standardised for guideline development, and the scientific and evidence-base are independent of geographical location or national borders. However, guidelines should be implemented locally because of variations in cause and prevalence of disease, standards of medical practice, and public health priorities for resource allocation.

Chronic kidney disease as a public health problem
The increased prevalence of kidney failure and early stages of chronic kidney disease, and the high costs and poor outcomes of treatment constitute a worldwide public health threat. Costs for dialysis and transplantation are increasing alongside costs for other chronic diseases.[136] The ageing of the population and the obesity epidemic mean that this disease will probably be a threat to both developed and developing nations for the foreseeable future. Through remarkable progress in laboratory investigation and clinical trials, treatment is now available that can be tailored to the risk of adverse outcomes on the basis of GFR and albuminuria. Testing can detect early stages of disease, and the same methods that are used in clinical practice can be used to screen populations at increased risk. Public health interventions are available to improve the treatment and prevent the development of hypertension and diabetes. Thus, methods to reduce the burden of chronic kidney disease are available, and many countries are beginning to develop public health strategies for this disease.

Recommendations for prevention include improvements in surveillance, screening, education, and awareness, which are directed at three target populations: people with or at increased risk of chronic kidney disease; providers, hospitals, and clinical laboratories; and the general public.[137,138] Low awareness of chronic kidney disease in all three groups probably indicates the absence of symptoms and low familiarity with the new guidelines for definition and classification. To increase awareness, the International Society of Nephrology and International Federation of Kidney Foundation inaugurated World Kidney Day in 2006,[139] to be marked in March every year to communicate that kidney disease is common, harmful, and treatable. Screening

programmes for kidney disease have been launched in many locations, which confirm a high prevalence of decreased GFR and albuminuria in association with a high burden of risk factors for cardiovascular disease.[140] However, studies[141–144] have suggested that screening is not cost effective for reducing kidney failure or all-cause mortality except in high-risk populations—eg, old people with diabetes or hypertension. With a wide range of outcomes and a focus on high-risk target populations, cost-effectiveness of screening might be improved.

Chronic kidney disease is one of several chronic diseases affecting mostly older people and leading to a substantially increased risk of cardiovascular disease. Coordination of public health efforts for chronic kidney disease and other chronic diseases will probably be the most efficient strategy. Reorganisation of delivery of care to treat older people and others with various chronic diseases efficiently will probably be necessary, as will cooperation at all levels of governmental and private organisations. Assessment of the effectiveness of public health strategies will be important to guide progress.

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