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Introduction

End-stage renal disease (ESRD) is defined by the cessation of effective kidney function and the substitution of renal replacement therapy (RRT), such as hemodialysis, peritoneal dialysis, or kidney transplantation, for native kidney function to sustain life. During the last 3 decades, an epidemic of ESRD has occurred in both industrialized and developing countries [1,2]. The epidemic increase in ESRD was initially attributed to the dissemination and adoption of RRT with the attendant extension of productive life. Although there is evidence that the rate of increase in ESRD incidence has abated in the USA, continuing increases in ESRD incidence rates after access to RRT becomes available to an entire population of a particular country have been documented by registries throughout the world [3].

The public health impact of the epidemic of ESRD is substantial. In the USA, it is estimated that the lifetime risk of being treated for ESRD is 2.5% for white men, 1.8% for white women, 7.3% for black men, and 7.8% for black women [4]. Life expectancy among individuals treated for ESRD is substantially shortened, and treatment is punctuated by frequent hospitalizations and progressive disability [3]. The economic costs of the epidemic are substantial as well, and the per-patient cost of care can exceed by severalfold the costs incurred by age-, gender-, and ethnicity-matched individuals in the general population. Furthermore, these costs only partially capture the full economic burden of ESRD, which includes the costs of chronic disability, premature mortality, and diminished quality of life.

Given the population cost burden of this epidemic of ESRD, it is increasingly recognized that strategies must be designed to increase the early detection and care of the antecedent diseases that contribute to this epidemic of end-organ failure [5,6]. There are multiple causes of kidney injury that result in ESRD, and the evidence-based diagnosis and management of these conditions are discussed in detail in subsequent chapters of this textbook. Common to each, however, is a continuum of progressive decline in kidney function that leads to a syndrome of chronic kidney disease (CKD), which is characterized by hypertension, anemia, renal/metabolic bone disease, nutritional impairment, neuropathy, impaired quality of life, and reduced life expectancy and which culminates in ESRD. The purpose of this chapter is to describe the definition of CKD and the measurement of the population-based health burden of CKD across the continuum of disease, from mild impairment to ESRD, as an essential foundation for the evidence-based management of kidney disease. Problems inherent in using biomarkers and prediction equations to define kidney function and detect CKD are discussed in chapter 2. The epidemiology of CKD is discussed in chapter 4, and risk factors associated with progressive loss of kidney function can be found in chapter 3. Chapter 2 examines how surveillance systems have been used to measure and improve the care of patients receiving RRT.

Definition of chronic kidney disease

CKD can be defined as the persistence for 3 or more months of structural and/or functional abnormalities of the kidney [7]. This definition replaces previous case definitions that described variable degrees of impaired kidney function [8,9]. The rationale for adopting a uniform case definition of CKD includes the need for 1) improved comparability across observational and clinical studies, 2) an improved capability for uniform comparisons of kidney disease incidence and prevalence, and 3) improved communications about diagnosis and treatment of kidney disease. The most important anticipated benefit of a common terminology is more effective communication with patients and the public.

The "structural" abnormalities used to define CKD are 1) microalbuminuria or overt proteinuria; 2) an abnormal urinary sediment as evidenced by the presence of red blood cells (RBCs), RBC casts, white blood cells (WBCs), WBC casts, tubular cells, cellular casts, granular casts, oval fat bodies, fatty casts, or free

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Table 1.1 Prevalence of decreased kidney function and CKD in the noninstitutionalized US population

Kidney function				Albuminuria Within Each Level of GFR (%)				CKD			
Estimated GFR (mL/min/1.73 m^2)	n	Prevalence (%)	N (1,000s)	None	Micro-albuminuria	Macro-albuminuria	Persistence of Micro-albuminuria (%)	Stage	Prevalence (%)	N* (1,000s)	N† (1,000s)
>90	10,183	64.3	114,000	90.8	8.7	0.5	53.9	1	3.3	5,900	10,500
60–89	4,404	31.2	55,300	87.2	11.7	1.2	72.7	2	3.0	5,300	7,100
30–59	961	4.3	7,600	61.3	31.5	7.2	‡	3	4.3	7,600	7,600
15–29	52	0.2	400	‡	‡	‡	‡	4	0.2	400	400
<15	‡	‡	300§	‡	‡	‡	‡	5	0.2	300§	300§
Total	15,600	100	177,300	88.4	10.5	1.1	63.2	Total	11.0	19,200	25,600

NOTE: Dark shading indicates individuals with CDK, and light shading indicates CKD in a subgroup with persistent microalbuminuria. Estimates based on repeated visit of individuals with microalbuminuria ($n = 102$ for GFR > 90 mL/min/1.73 m^2, $n = 44$ for GFR of 60 to 89 mL/min/1.73 m^2). Microalbuminuria defined as albumin-creatnine ratio (ACR) of $17 \leq ACR \leq 250$ for men and $25 \leq ACR \leq 355$ for women; macroalbuminuria defined as ACR > 250 for men and ACR > 355 for women (persistence assumed to be 100%).

Abbreviations: n, number of NHANES III participants; N, estimated number of individuals in the United States.

* Estimates based on persistent microalbuminuria at two visits for CKD stages 1 and 2.

† Estimates based on albuminuria in a single spot urine sample.

‡ Denotes cells with fewer than 30 NHANES III participants.

§ Estimated from the US Renal Data System.[1]

Source: Coresh *et al.* 2003 [105].

fat; and 3) abnormal findings on imaging tests, including ultrasound, intravenous pyelogram, computer tomography, magnetic resonance imaging, and nuclear scans. Overt proteinuria is defined as an increased urinary concentration of albumin and other proteins detected by routine laboratory measures (e.g. urine dipstick test for protein), and microalbuminuria is an increased albumin excretion that can be detected only by laboratory methods more sensitive than the standard protein assay that uses the urine dipstick.

The functional component of the definition of CKD uses creatinine-based estimates of clearance derived from the Modification of Diet in Renal Disease (MDRD) glomerular filtration rate (GFR) estimating equation or the Cockcroft–Gault creatinine clearance equation [10]. The derivation and use of these multivariate prediction equations are discussed in chapter 5. At present, no single method of GFR estimation is strongly recommended. Clinicians should choose a method that is appropriate for their population to determine the estimated GFR (eGFR) and assign a stage of kidney disease, always cognizant that failing to account for the modification of the complex association between serum creatinine and GFR by age, gender, and race is likely to lead to misclassification of kidney function and attendant errors in clinical decision making.

The available estimating equations are imprecise at higher levels of GFR, and there is great interest in revising them or identifying better filtration markers that will improve our ability to measure kidney function across the continuum of kidney performance from normal to ESRD [10]. The inherent imprecision of all methods of estimating GFR led to the decision to rank the degree of impaired kidney function into more global stages (levels) by the eGFR in the following manner:

Stage 1: eGFR >90 mL/min/1.73 m^2 (with structural abnormalities)
Stage 2: 60–90 mL/min/1.73 m^2 (with structural abnormalities)
Stage 3: 30–59 mL/min/1.73 m^2
Stage 4: 15–29 mL/min/1.73 m^2
Stage 5: <15 mL/min/1.73 m^2

In addition to these eGFR ranges, the persistence of structural abnormalities for at least 3 months is necessary to assigning CKD stages 1 and 2, and stages 3–5 of CKD are defined by persistent impairments for greater than 3 months in the eGFR alone.

This staging algorithm is illustrated by using data from the US population aged 20 years and older (Table 1.1). The prevalence of CKD based on eGFR and presence and degree of proteinuria CKD is estimated to be 11% of the US population [7]. Over 50% of the prevalent disease is due to the presence of proteinuria among individuals with stage 1 (3.3%) and stage 2 (3.0%) CKD, and this proteinuria is largely due to microalbuminuria. Among individuals with stages 3–5 CKD, which are defined by eGFR alone, 85% of individuals have stage 3 disease (4.3%).

Kidney disease: improving global outcomes

The definition of CKD was reviewed at the 2004 "Kidney Disease: Improving Global Outcomes (KDIGO)" Controversies Conference [11]. Two further modifications were proposed to better

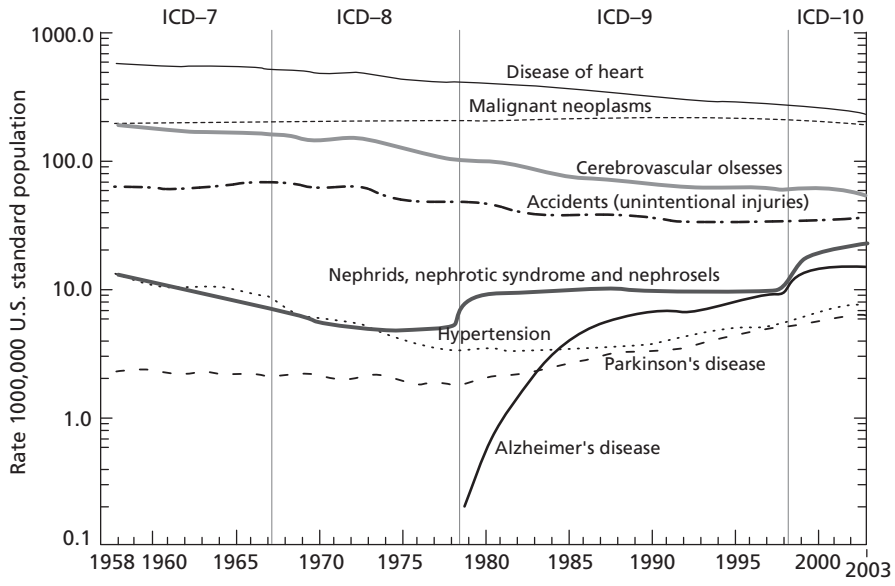

Figure 1.1 Secular trends in mortality attributed to various causes illustrating discontinuities in trends with changes in ICD classification of cause of death. (Reprinted with permission [13].)

adapt the staging algorithm for international use: 1) clinical judgment should be used to decide the relevance of nonproteinuric markers of kidney damage prior to diagnosing CKD in individuals without either proteinuria or reduced GFR; 2) individuals with a transplanted kidney should be considered as having CKD irrespective of other structural or functional markers. The KDIGO modified the CKD risk stratification by adding the letter T to denote CKD in a transplanted kidney and recommended that stage 5 CKD be modified by the letter D to denote RRT by dialysis [11].

International Classification of Diseases and kidney diseases

The *International Classification of Diseases* (ICD) classifies each condition that has given rise to the chain of events leading to death (underlying cause of death) as recorded on death certificates. The ICD is used by national vital statistics registries. At present, it provides the only uniform population-based case definition for international comparisons of the burden of disease attributable to earlier stages of CKD and, as such, is an important actuarial tool in defining the health burden of CKD across populations and, with certain limitations described below, temporally. The Ninth Revision of the ICD (ICD-9), used between January 1, 1979 and December 31, 1998, was replaced by ICD-10 on January 1, 1999 [12].

Revisions of the ICD reflect the evolution of disease classification and emergence of new diseases, and they resolve administrative issues that have stemmed from a particular version of the codes. Clinicians should be aware that ICD revisions often introduce changes in the classification of an underlying cause of death. Comparisons of death rates due to specific causes, such as kidney disease, across different ICD revisions can be facilitated by using comparability ratios that relate rates from different time periods. The comparability ratio relating rate computed from ICD-9 (ICD-9 codes 580–589) and ICD-10 (ICD-10 codes N00–N07, N17–N19, and N25–N27) data is estimated to be 1.23, indicating that the new ICD-10 coding will result in a 23% increase in classification of deaths due to kidney disease compared with the ICD-9 codes [12]. This version-to-version difference is due, in part, to a change in the classification of ESRD from an unspecified disorder of the kidney in ICD-9 to ESRD (N18.0), a subcategory of kidney failure (N17–N19) in ICD-10.

Secular trends in kidney disease as an underlying cause of death need to be interpreted with these changes in mind. This can be illustrated by trends in kidney disease as a cause of death in the USA (Figure 1.1), which declined between 1958 and 1978 and then increased substantially until the end of the century [13]. The transition from ICD-9 to ICD-10 in 1998 is represented by the discontinuity in the trend line for deaths due to nephritis, nephrotic syndrome, and nephrosis.

The Clinical Modification of ICD-9 (ICD-9-CM) is used administratively in the USA and was modified in 2005 to reflect the new nomenclature for CKD. ICD-9-CM code 585, "Chronic renal failure," was dropped, and seven new four-digit codes were introduced to code for the presence of CKD [14]. These new codes reflect the National Kidney Foundation (NKF) CKD staging definitions:

585.1: Chronic kidney disease, stage 1
585.2: Chronic kidney disease, stage 2 (mild)
585.3: Chronic kidney disease, stage 3 (moderate)
585.4: Chronic kidney disease, stage 4 (severe)
585.5: Chronic kidney disease, stage 5
585.6: End-stage renal disease
585.9: Chronic kidney disease, unspecified

Furthermore, in 2006, the ICD-9-CM nomenclature for codes 403 and 404, denoting kidney complications of hypertension, were changed from "renal disease" to "kidney disease" and from "renal failure" to "chronic kidney disease." A revision of the clinical modification of ICD-9 to reflect the ICD-10 coding conventions is currently being developed.

The standardized ICD nomenclature provides some uniformity of data that allows descriptions of population-to-population differences in death rates attributed to kidney disease. This standard nomenclature stands in contrast to the information reported by national ESRD registries that collect and report information on the occurrence of stage 5D CKD (see chapter 2). A report by Maisonneuve *et al.* found substantial variability in the definition and classification of primary causes of ESRD throughout the world [15]. Comparisons of the burden of CKD based on ICD-related mortality statistics also avoid the skewing of prevalence rates based on ESRD rates that would be introduced by the variable coverage of ESRD registries in economically developing countries.

The use of international comparisons of kidney disease burden can be illustrated by considering the proportionate mortality attributed to kidney disease throughout the world. Kidney disease is the 9th leading cause of death in the USA [6] and the 12th leading cause of death worldwide [16]. The burden of mortality due to kidney disease in different world regions was recently reported by the Global Burden of Disease Report [17]. Age- and gender-adjusted proportionate death rates for genito-urinary diseases, which include nephritis and nephrosis, benign prostatic hypertrophy, and other genito-urinary system diseases, vary from less than half of to 50% greater than those observed in high-income regions of the world (Figure 1.2) [17].

There are multiple potential explanations for this region-to-region variability in the overall mortality burden due to kidney disease. Regional differences in the prevalence of risk factors for kidney injury and progressive loss of kidney function, access to health care, detection and treatment of kidney disease, and diagnostic convention could contribute to the observed variability. The main point of international comparisons is that a better understanding of the source of variation is essential for better control of CKD and its risk factors through public health measures and may lead to important generalizable insights into the reasons for the occurrence and progression of CKD.

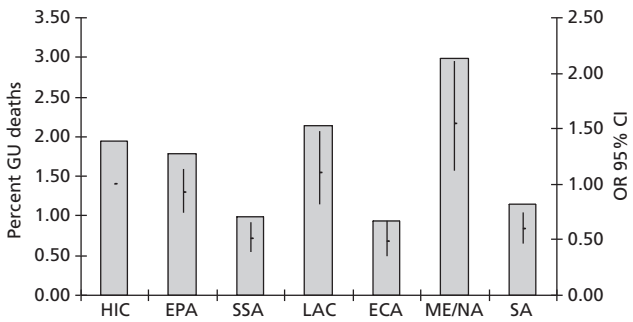

Figure 1.2 Proportion of all deaths attributed to genito-urinary causes (ICD-9 codes 580–611 and 617–629 or ICD-10 codes N00–N64 and N75–N98). These codes include nephritis and nephrosis, benign prostatic hypertrophy, and other genito-urinary system diseases. Regions in the Global Burden of Disease study were defined as high-income countries (HIC), East Asia and Pacific (EPA), sub-Saharan Africa (SSA), Latin America and the Caribbean (LAC), Europe and Central Asia (ECA), Middle East and North Africa (ME/NA), and South Asia (SA). Data were derived from regional tables for deaths by cause, sex, and age. (Reprinted with permission [17].)

Functional and etiologic diagnoses for CKD

CKD is a nonspecific diagnosis that describes the presence and degree of structural and functional abnormalities of the kidney. CKD does not identify the cause for the injury and/or impaired kidney function. Thus, the stage of CKD is an incomplete clinical description of the underlying disease process, and identification of CKD should also lead to a clinical diagnosis that includes a cause (etiology) for the kidney disease and the stage of CKD. For example, a diagnosis for CKD might be stated as "stage 3 CKD due to diabetes," "immunoglobulin A nephropathy with stage 4 CKD," or "stage 2 CKD of unknown etiology."

At present, the best estimates for the relative contributions of specific etiologies to the total burden of CKD within populations are derived from the proportionate, cause-specific incidence of ESRD within a population (see below). These estimates, however, have a number of limitations. Most important is the possibility that variations in survival and progression to stage 5 CKD among individuals with kidney disease due to different causes might alter the patterns of disease and the proportionate health burden over the course of CKD. It is also likely that there are substantial regional and ethnic variations within and between groups with respect to specific causes of initial kidney injury. It is likely that many individuals with prevalent kidney disease will have a number of competing risk factors associated with the initiation and progression of kidney disease, and the precise temporal relationship between these and the etiology of the initial kidney injury remains obscure. Finally, systematic studies to estimate the risk of kidney injury among individuals with less common forms of stage 5 CKD remain to be conducted.

Prognostic importance of the stage of CKD

As discussed in chapter 2, the classification of CKD using the NKF stages provides substantial prognostic and diagnostic information concerning 1) outcomes (progression to ESRD and mortality) [18,19] and 2) ocurrence of intercurrent morbidity (ischemic heart disease, stroke, and peripheral vascular disease) [20–28]. Further, the stage of CKD is predictive of the prevalence of complications associated with impaired kidney function (anemia, bone disease, and nutritional and functional status) (Table 1.2).

Table 1.2 CKD stage characterizations and risk factors associated with progressive kidney disease

Characteristic or risk factor	**Stages 1 and 2**	**Stage 3**	**Stage 4**	**Stage 5**
CKD stage characterization				
Description	Chronic kidney damage with normal to mildly decreased GFR	Moderate GFR loss	Severe GFR loss	Kidney failure
GFR (mL/min/1.73 m^2) [2]	≥60	30–59	15–29	<15 or dialysis
Prevalence [7]	6.6%	4.3%	0.2%	0.2%
Proteinuria [45]	8.1%	23.3%	63.4%	–
Cardiovascular risk factors				
Hypertension [7]	40%	55%	77%	75%
Diabetes [45]	3.1–6.5%	16.8%	22.8%	–
C-reactive protein >0.21 mg/dL [44]	25–30%	48.7%	57.7%	–
Nutritional risk factors	–	2%	20%	50%
Albumin <3.5 g/dL [44]	1.7–2.2%	6.2%	8.2%	–
Bicarbonate <22 mmol/L [44]	1.3–1.6%	2.3%	19.1%	–
Risk factors for bone disease				
PO_4 >4.5 mg/dL [7,32]	–	<5%	20%	50%
Ca <8.5 mg/dL [7,32]	–	<5%	8%	28%
25(OH)-vitamin D ≤75 nmol/L [32]	–	71%	83%	
iPTH (pg/mL) (<70 CKD-3 or <110 CKD-4) [32]	–	35.4%	31%	–
Quality of life				
Difficulty walking [7]	5%	8%	22%	30%
Hemoglobin <13 g/dL [38]	4%	7%	29%	69%
Outcomes				
5-year ESRD rate [18]	1.1%	1.3%	19.9%	–
5-year mortality rate [18]	19.5%	24.3	45.7%	–
3-year CVD rate [18]	2.1%	4.8%	11.4%	14.1%

Abbreviations: iPTH, intact parathyroid hormone; CVD, cardiovascular disease.

Complications of CKD and CKD stages

Complications that develop in CKD are listed in Table 1.2. The diagnosis and management of these complications are discussed in greater detail in the sections Prognostic importance of the stage of CKD and Complications of CKD and CKD stage of this text. Some of the important CKD-specific associations between the development of comorbidities and CKD stage that have emerged from epidemiologic studies are described in brief below.

Disordered metabolism of 25(OH)-vitamin D, phosphorous and calcium balance, and serum parathyroid hormone levels are well-documented for stage 5 CKD [1] and are noted to begin at or before stage 3 CKD. LaClair *et al.* studied patients with stage 3–5 CKD and found that 25(OH)-vitamin D deficiency was present in 71% and 83% of these patients, and parathyroid hormone levels outside of the recommended normal range were present in 64.6% and 69% of individuals with stages 3 and 4 of CKD [32]. Interestingly, geographic locations characterized by lower latitudes were inversely associated with an intact parathyroid hormone level. A recent study by Binkley *et al.* questioned the role of sun exposure on 25(OH)-vitamin D deficiency because deficiency remains relatively common even in sun-exposed individuals [33]. The prevalence of elevated serum phosphorous levels and low albumin-adjusted serum calcium levels increases with increasing stage of CKD. Analyses of data from a cohort study of left ventricular hypertrophy and anemia by Levin *et al.* estimated that the prevalence of a serum phosphorous level greater than 4.5 mg/dL increased from less than 5% among individuals with stage 3 CKD to 20% of those with stage 4 CKD; comparable prevalence estimates for a serum calcium level of less than 8.5 mg/dL were less than 5% and 8% [34]. In contrast to these observations, Hsu *et al.* found that age-, gender-, and race-adjusted femoral bone density among National Health and Nutrition Survey III (NHANES III) participants was unchanged among individuals with mild and moderate kidney disease [35].

Abnormalities of calcium and phosphorous metabolism are associated with increased risks of death and cardiovascular disease. Kestenbaum *et al.* reported that patients with CKD in the Veterans Affairs medical system with an elevated serum phosphorous level were at increased risk for all-cause mortality (hazard ratio [HR] per 1 mg/dL increase, 1.33; 95% confidence interval [CI],

1.15–1.54) [36]. Menton *et al.* reported that, after adjusting for other risk factors, cardiovascular disease but not all-cause mortality rates were marginally associated with increased serum phosphorous among participants in the MDRD study (adjusted HR per 1 mg/dL increase, 1.27; 95% CI, 0.94–1.73) [37]. Similarly, the calcium–phosphorus product was marginally associated with cardiovascular disease, but not all-cause mortality (HR, 1.22; 95% CI, 0.89–1.66; $P = 0.23$) in the MDRD participants. Among individuals with stage 5 CKD, the association between disorders of mineral metabolism, including elevated serum phosphorus and calcium levels and hyperparathyroidism, are well-documented and are estimated to account for 17.5% of the population attributable risk for proportionate mortality.

Astor *et al.* used the NHANES III data to determine the association between GFR and the prevalence of anemia, defined as hemoglobin less than 12 g/dL for men and less than 11 g/dL for women [38]. The prevalence of anemia increased from 1% among individuals with no CKD to 5.2% of individuals with stage 3 CKD and 44.1% of those with stage 4 CKD.

As the stage of CKD increases, functional impairment and magnitude of diminished quality of life reported by patients increase as well [39,40]. A recent report from the Chronic Renal Insufficiency Cohort study compared standard disease-specific measures of quality of life, the Kidney Disease Quality of Life Short Form 36, and general measures, including the SF-12 Physical and Mental Health Short Form, the Health Utilities Index 3, and the Time Trade-Off score among individuals with CKD [39]. The Chronic Renal Insufficiency Cohort study investigators observed a strong inverse association between stage of CKD and baseline measures of disease-specific and general quality of life. Furthermore, among individuals with CKD of stage 4 or greater who were tested sequentially over 2 years, progression of CKD was associated with further impairment of quality of life [40].

There is also evidence that the prevalence of cognitive impairment increases with increasing stage of CKD and that individuals with impaired kidney function at any level are at increased risk of developing cognitive impairment [41–43]. A report from the Health, Aging, and Body Composition study found that baseline cognitive function measured by the Modified Mini-Mental State Exam was inversely associated with degree of impaired kidney function, which declined from a total score of 87.5 among individuals without CKD to 86.9 among those with a GFR between 45 and 59 mL/min/1.73 m^2 and to 84.7 for those with a GFR less than 45 mL/min/1.73 m^2, with a score of less than 80 indicative of cognitive impairment [42]. After controlling for other risk factors, both individuals with a GFR between 45 and 59 mL/min/1.73 m^2 (odds ratio [OR], 1.32; 95% CI, 1.03–1.69) and those with a GFR of less than 45 mL/min/1.73 m^2 (OR, 2.43; 95% CI, 1.38–4.29) were at an increased risk of developing dementia during follow-up.

Individuals in the Cardiovascular Health Cognition Study underwent a three-stage evaluation for dementia that included an assessment of dementia risk, neuropsychological testing on high-risk patients (and a sample of other study subjects), and neurological and psychiatric evaluation for those classified as abnormal on the neuropsychological tests [42]. Subjects with an increased serum creatinine of $\geq$1.3 mg/dL for women and $\geq$1.5 mg/dL for men were found to be at increased risk of developing incident dementia during follow-up (OR, 1.37; 95% CI, 1.06–1.78). Of interest from this study, these associations were observed only among individuals who were healthy at baseline and were observed for vascular-type but not Alzheimer's-type dementia.

Descriptive epidemiology of CKD

Prevalence of Stage 1–4 CKD

The epidemiology of CKD is not well understood. NHANES is an ongoing series of surveys of representative samples of the US population conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. These surveys are cross-sectional, complex, random samples of the US population, and they have been analyzed to provide CKD prevalence estimates. The prevalence of CKD among adults aged 20 years and older in the USA based on NHANES III data is estimated as 11%, with 6.3% of the population in the combined stages 1 and 2 CKD, 4.3% in stage 3 CKD, and 0.2% of the population in each of stage 4 and stage 5 CKD (Table 1.1).

Microalbuminuria, defined as an albumin–creatinine ratio of 17–250 mg/g in men and 25–355 mg/g in women, is present in 10.5% of the population on initial screening and persists over time on repeated measures in the same individual in 63.2%, whereas overt proteinuria (albumin–creatinine ratio of >250 mg/g for men and >355 mg/g for women) is present in 1.1% of the population [45]. Proteinuria increases in prevalence with decreasing GFR and is found in 0.5% of individuals with an estimated GFR greater than 90 mL/min/1.73 m^2, 1.2% of those with stage 3 CKD, and 7.2% of those with stage 4 CKD.

There is substantial heterogeneity in the prevalence of stage 3 and 4 CKD across subgroups of the US population. CKD stages 3 and 4 are more prevalent among women (5.3%) than men (3.6%), and prevalence increases from 0.2% among individuals age 20–39 years to 7.5% of individuals age 60–69 years. The non-Hispanic white population has the highest prevalence of stage 3 and 4 CKD in the US population (5.0%), compared with the non-Hispanic black population (3.3%) and Mexican–Americans (1.0%). CKD stage 3 and 4 prevalence is higher among individuals with diabetes (15.1%) and those with treated (17.5%) and untreated (7.9%) hypertension.

Comparisons of CKD estimates between the US population and other countries are difficult to make for several reasons. The measure of kidney function needs to be based on a standardized measure of kidney function that has been validated within each population. A standard classification needs to be applied to each population. Estimates need to be adjusted for differences in the underlying demographic characteristics (age, gender, and ethnicity) of the respective populations.

CKD prevalence estimates currently available in the literature are shown in Table 1.3 [46–57]. There is substantial variability

Table 1.3 Prevalence estimates for Stage 3 and 4 CKD by world region

Region [reference]	*N*	Ages (yrs)	Sample	Prevalence (%) with indicated stage(s)		
				Stage 3	Stage 4	Total, stages 3 and 4
North America						
USA [105]		≥18	Random, stratified national	4.3	0.2	4.5
Morelia, Mexico [46]	3564	≥18	Random sample clinic patients	8.1	0.3	8.4
Mexico City (diabetes) [47]	1586	35–64	Random, stratified Mexico City	23.8	0.7	41.2
Europe						
Norway [48]	65,181	≥20	Total population, Nord-Trondelag County	4.5	0.2	4.7
Groningen, Netherlands [49]				5.7	0.1	5.8
Galicia, Spain [50]	237	≥20	Random community	5.3	0.4	5.7
Reykjavik, Iceland [51]	19,381	≥30	Total population, Reykjavik area	3.7 (M)		
				11.0 (F)	0.0–0.3	–
Switzerland [52]	1778	55–65	Random national	7.1 (M)		
				23.5 (F)	–	–
East Asia/Pacific						
China [53]	15,540	35–74	Random, stratified national	2.4	0.1	2.5
Australia (diabetes) [54]	11,247	≥25	Random, stratified national	10.9	0.3	22.4
Hisayama, Japan [55]	2634	≥40	Community survey	10.2	–	10.2
South Asia					–	
Karachi, Pakistan [56]	262	≥40	Random, stratified community	29.4	–	29.4
India* [57]	4972	≥30	Random, stratified, regional (Delhi)	–	0.8	0.8

* Serum creatinine >1.8 mg/dL.

across the studies in the age strata studied, classification methods, and methods of estimating GFR. Despite these variations, it is possible to discern the substantial drop-off in prevalence between stage 3 and stage 4 CKD across these varied populations; the estimated prevalence of CKD stage 4 is consistently less than 0.5% among nondiabetic populations. It is also evident that stage 3 and 4 CKD is a substantial public health problem across the world, exceeding 4% prevalence in all but one population. Finally, the population-to-population variability in prevalence suggests that, similar to the risk for cardiovascular disease, population-specific risk factors for CKD may exist.

CKD and race

The lifetime risks of incidence of ESRD, based on 1993–1995 US Renal Data System (USRDS) data, for 20-year-old white men has been estimated to be 1.98%, 1.67% for white women, 5.49% for black men, and 6.31% for black women, and these cumulative incidences increased further during the 1990s [4]. The racial disparity is reflected in age-adjusted ESRD rates, which are 3.8- to 4-fold higher among black people compared with white people [3]. The excess ESRD incidence for the black population stands in stark contrast to the prevalence data of stage 3 and 4 CKD estimated from the NHANES III population-based sample of the US population [58]. These studies report that CKD among adults age 20 years and older is found in 5.0% of the white population and 3.4% of the black population [58]. These racial disparities persisted after controlling for age, hypertension, and diabetes. Analyses of the REGARDS cohort study showed that these disparities are particularly evident in stage 3 CKD. As GFR declines, the black–white prevalence gap diminishes and crosses in stage 4 CKD such that the prevalence among Black people with advanced stages of CKD becomes consistent with the observed ESRD incidence rate disparities [59].

The disparity in black and white population ESRD incidence rates persists after accounting for differences in the prevalence of hypertension [60] and diabetes [61] in the at-risk population. Factors associated with these racial disparities in ESRD incidence include access to health care, poverty, and community poverty [62–64]. Tarver-Carr and her associates used follow-up data from NHANES II to examine risk factors associated with racial differences in the incidence of all-cause ESRD [65]. They reported a 2.7-fold-higher ESRD incidence for black people compared with white people. Adjustment for a number of sociodemographic factors (poverty status, educational attainment, and marital status) explained 12% of the excess ESRD risk among black people, and adjusting for life-style factors (smoking status, physical activity, alcohol use, and body mass index) explained an additional 24% of the excess risk. Models that adjusted for prevalent diabetes mellitus, hypertension, and cardiovascular disease and baseline values of systolic blood pressure and serum cholesterol levels explained 32% of the excess risk. When all of these factors were controlled, the adjusted relative risk was 1.95 (95% CI, 1.05–3.63), accounting for 44% of the excess risk. Furthermore, the excess risk among black people for ESRD reported by Tarver-Carr and her colleagues was much greater among middle-aged than among older adults [65].

The unexpected reversal of prevalence of CKD among black individuals compared with the white population and the failure of multiple risk factors to explain the observed disparities in ESRD incidence are consistent with observations that black people with the same degree of impaired kidney function are at increased risk of progressive kidney failure [62–69]. Hsu *et al.* recently examined this possibility in an ecologic analysis of NHANES III and USRDS data [70,71]. They estimated that, despite a comparable prevalence of CKD, 5% of black people and 1% of white people in the US population will develop ESRD over a 5-year period, which is consistent with the progression hypothesis.

Incidence and prevalence of stage 5 CKD

Stage 5 CKD is defined by a GFR of <15 mL/min/1.73 m^2 and has two phases. The first phase is treated conservatively without dialysis, and the second, slightly later phase involves the initiation of RRT—either dialysis or kidney transplantation. The latter has been called stage 5D, or ESRD, which is defined by its treatment [11]. Whereas there is ample information available about patients treated with RRT, epidemiological information about stage 5 prior to starting dialysis is quite limited.

During the earlier phase of stage 5 CKD, conservative therapy includes the same factors discussed in chapter 3 for stage 4 but requires much closer monitoring of laboratory data and clinical symptoms of uremia. Symptoms or laboratory abnormalities are the main indications for starting dialysis. The optimal time for initiation of dialysis therapy has been a focus of many debates, as reports appear to be conflicting. Collins *et al.* showed that late stages of CKD are associated with a high risk of mortality even before starting dialysis [72]. Therefore, it appears reasonable that early initiation of dialysis will save lives. Retrospective analyses of mortality risk after initiation of dialysis, by level of kidney function at the start of dialysis, suffer from a major bias: patients who are started on dialysis with relatively higher levels of kidney function tend to be older and frailer, whereas those who start with poorer kidney function tend to be otherwise healthier with relatively few comorbidities. Thus, due to selection bias, retrospective data may falsely suggest that a later start is associated with better survival on dialysis. Prospective studies that randomize patients to early versus late start are scarce, but they appear to suggest that earlier start of dialysis is associated with better outcomes after dialysis [73]. Such studies must consider the lead time bias, which can be avoided by studying survival not from the start of dialysis but from the time of randomization to early versus late start. This takes into account mortality risk while being treated without dialysis for those randomized to a later start. As with stage 4, various causes of CKD have different rates of loss of kidney function, which needs to be considered in such studies, for example, by stratified randomization. The contributors to the recent NKF Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines reviewed the available evidence on optimal RRT start time in great detail [7]. These guidelines do not offer a specific level of GFR to indicate the need for starting dialysis but suggest that impairment of nutritional status is one of several key indications for the initiation of dialysis therapy. The evidence regarding when to initiate dialysis therapy and what dialysis modality results in the best outcomes is reviewed in detail in chapters 7 and 8 of this textbook.

There is a wealth of epidemiologic information available about the later stage 5D of CKD (i.e. for patients who have started RRT, usually with dialysis). Numerous national and regional registries have relatively complete information on patients undergoing RRT. Patients initiating dialysis should be viewed as survivors of stage 4 CKD and the earlier phase of stage 5 CKD. This applies to numerous retrospective studies on patient management during the months prior to the start of dialysis.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) inquired from patients how long they had seen a nephrologist prior to starting dialysis and found (among those surviving to dialysis) that, for each of the 12 DOPPS countries, about 66.8–82% had seen a nephrologist for more than 4 months and 8.4–20.6% had seen one for less than 1 month prior to starting dialysis. Patients who received longer pre-ESRD nephrology care were sixfold more likely to have a permanent vascular access rather than a catheter in use, and they were more likely to have an arteriovenous fistula rather than a graft [74].

Incidence

The number of patients starting RRT per year has been increasing steadily since maintenance dialysis became available in 1960, with roughly a doubling in the annual number of new patients during each decade in the 1970s, 1980s, and 1990s [75]. Thus, the incidence has been growing at an exponential rate. Each registry has shown clearly that this rate of growth has been substantially lower for younger patients and highest for the oldest age group. This epidemic of dialysis-requiring CKD may have several causes, although it may be difficult to quantify the role of each contributor. Causes may be categorized into three major groups: 1) patient selection, 2) competing risk, and 3) increased incidence of advanced CKD.

Selection of patients to RRT

The steep increase in incidence for older age groups suggests that very elderly patients and those with particularly severe comorbid conditions were likely not offered dialysis therapy in earlier years and have been increasingly offered RRT in each subsequent decade. In fact, in the early 1970s, a common exclusion for dialysis was age over 60 or 65 years and presence of any systemic disease, such as diabetes or lupus erythematosus. Such patients did have stage 5 CKD but were not counted in registries because registries dealt only with patients who actually received dialysis therapy. The "epidemic" of ESRD was defined only by its treatment.

Competing risks

There is clearly a high mortality risk among patients with earlier stages of CKD, and most individuals with stage 3 and 4 CKD die before starting RRT [18,19]. In fact, impaired kidney function is now recognized as one of the most important risk factors for coronary artery disease, and these risks persist into stage 5 CKD [20].

Substantial improvements in the treatment of heart disease and in survival have occurred in recent decades, which may have allowed such patients to survive to advanced stages of CKD and to the need for dialysis, whereas in earlier eras, these same patients would have died from heart disease during an earlier stage of CKD. A recent analysis by Muntner *et al.* investigated the possibility that the increase in ESRD between 1978 and 1991 could be attributed to increased survival among individuals with diabetes, myocardial infarction, and stroke [76]. They estimated that changes in the numbers of persons in the US population with these conditions could account for slightly over 40% of the increased ESRD incidence (diabetes, 27.6%; myocardial infarction, 4.8%; stroke, 7.9%). These results suggest that some, but not all, of the increase in ESRD in the USA is due to improved care and survival among high-risk groups.

True increase in incidence of CKD

It is also possible that the increased incidence of ESRD reflects increases in the underlying prevalence of CKD. There are potential reasons for more CKD to occur, but these are somewhat speculative. The incidence of type 2 diabetes mellitus has doubled from the 1970s to the 1990s, according to the Framingham study [77]. The availability of nonsteroidal anti-inflammatory drugs without prescription has likely increased their widespread use and the potential for nephrotoxic injury. Greater intensity of medical care may have led to greater exposure to potentially nephrotoxic agents, such as antibiotics and chemotherapeutic agents. Specifically, the growth in nonrenal organ transplantation has been associated with a substantial incidence of CKD and ESRD [78].

Influence of race on incidence of ESRD

Incidence rates for newly treated ESRD differ markedly by race and ethnic group. Incidence is highest among African Americans and among indigenous populations of North America, Australia, and New Zealand [7,78]. Diabetes as the cause of ESRD is also particularly high in these populations. Low incidence rates are recorded in developing countries, but this may reflect more limited availability of dialysis therapy, rather than less CKD. Japan and the USA have relatively high overall incidence rates. The USA also has a particularly high fraction of incident patients with diabetes as the cause of their kidney failure. It is surprising that incidence rates of RRT and of the fraction with diabetes are substantially lower among Europeans than among white Americans, since the latter are mostly of European descent [7,79]. As ESRD incidence rates continue to rise everywhere, European rates have been similar to those observed in the USA nearly a decade earlier. As the rates of increase gradually level off in the USA, one may speculate that rates in Europe and the USA will eventually become more similar.

Trends in incidence

The first indication of a significant slowing of the rate of rise in the incidence of stage 5D CKD was noted by Wolfe and Port for nondiabetic patients, according to USRDS data for the year 1997 [80]. More recent USRDS data confirm the earlier change in trend for nondiabetic patients and show that, for patients with diabetic ESRD, the annual rise in incidence rates has also significantly slowed in more recent years. This is shown in Figure 1.3 by the evidence that, since 2001, annual incidence rates for diabetic patients have been below the projected 95% CI of prior years. USRDS data

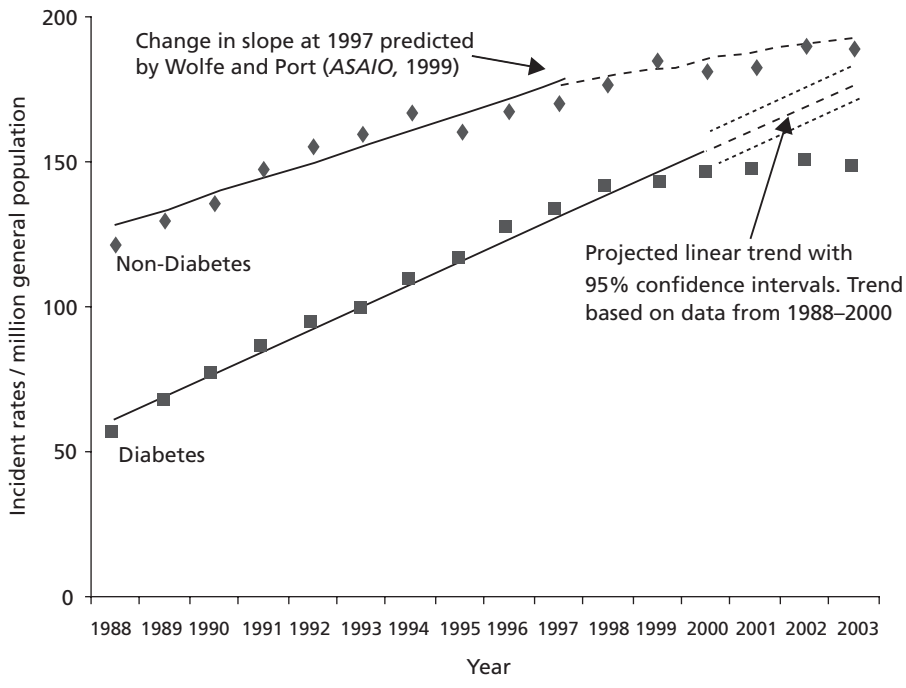

Figure 1.3 USRDS data showing trends for non-diabetic and diabetic patients.

Table 1.4 Comorbid conditions for representative samples of prevalent and incident hemodialysis patients by geographic region in 2002–2003 based on DOPPS-II

Comorbid condition	Prevalent cross-section (%)			Incident prevalent cross-section (%)[a]		
	Europe ($n = 3938$)	Japan ($n = 1805$)	US ($n = 2260$)	Europe ($n = 230$)	Japan ($n = 75$)	US ($n = 162$)
CAD	44.3	25.2	61.1	40.8	14.9	60.7
Cancer	12.9	6.0	11.9	18.9	10.4	15.8
Cardiac (other than CAD or CHF)	40.1	31.7	31.1	31.1	17.5	29.7
Cerebrovascular	16.5	14.6	19.1	13.8	14.3	15.4
CHF	24.5	16.4	40.1	24.7	25.6	44.0
Diabetes	25.6	26.8	51.4	34.8	33.8	52.5
GI bleed	5.6	4.1	6.5	8.6	0.8	3.7
HIV/AIDS	0.5	0.1	1.0	1.5	0.0	0.6
HTN	74.2	63.9	87.8	75.6	67.5	87.0
Lung disease	11.3	2.2	12.9	15.4	0.0	15.3
Neurological	11.7	6.8	14.2	11.3	9.5	13.2
Psychiatric	20.2	3.4	25.5	15.4	1.9	33.0
PVD	28.5	11.7	29.3	26.7	10.7	26.9
Recurrent cellulitis, gangrene	7.2	3.1	10.2	5.0	4.3	9.5

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure

[a] Defined as entering the DOPPS study within 90 days of their first-ever hemodialysis treatment.

Note: Analyses are weighted for dialysis facility size.

also show that the age group of patients that shows essentially no increase in incidence now extends beyond childhood and adolescence to also include young adults [80]. Despite these encouraging trends, it is important to note that there continues to be an increase in the incidence rate overall, even in the USA. The epidemic may have slowed in the USA, but it continues to be a major concern. Recent reports from non-US ESRD registries indicate that similar trends may be emerging throughout the world [81].

Prevalence

Data on the true prevalence of stage 5 CKD are lacking, except for the detailed registry data on those treated with dialysis or transplant. The number of patients undergoing RRT at the end of a year (point prevalence) and the number at any time during a year (period prevalence) are much higher than the number starting RRT during the year (incidence). Prevalence rates have been rising steeply over time. Prevalence of a disease increases if patient survival increases at a constant incidence rate or if the incidence rises at a constant survival rate. Thus, the prevalence rate corresponds to the product of the incidence and survival rates. For RRT, both a rise in the incidence (Figure 1.1) and an improvement in survival have been well-documented in the USA [82]. The issues described above related to incidence also apply to prevalence of treated ESRD, except where modified by differences in survival for certain groups. Because of the lower survival rates for the oldest age groups, their relative rate of rise in prevalence is not as steep as that observed for incidence. Worldwide, more than a million patients were undergoing ESRD therapy at the beginning of the millennium, and this number continues to grow.

Comorbidity in stage 5D CKD patients

Patients starting RRT usually have numerous comorbid conditions. International data from the DOPPS indicate that, at the initiation of hemodialysis, the vast majority of patients carry a diagnosis of hypertension. Heart disease, particularly coronary artery disease and congestive heart failure, lead the list of serious conditions. Other major factors are noted in Table 1.4 both for incident and for a cross-section of prevalent hemodialysis patients. With diabetes as a leading cause of ESRD, it is noteworthy that the prevalence of comorbidities is even higher in diabetic patients than in nondiabetic patients. Compared with patients on dialysis for over 1 year, incident hemodialysis patients (<30 days) are more markedly anemic [82], and almost half of them have phosphorous levels above the guideline level of <5.5 mg/dL (DOPPS unpublished information). Patients starting ESRD with peritoneal dialysis may have a positive selection because greater independence and ability to learn self-care may select healthier patients. On the other hand, difficulties with vascular access or lack of prior nephrologic care may select higher-risk patients to peritoneal dialysis [84]. Transplant recipients have substantially less comorbidity, largely due to patient selection. This has been documented by the finding that the mortality risk for wait-listed transplant candidates on dialysis is substantially lower than for all dialysis patients who are not (yet) wait-listed [85].

Comparisons of treatment modalities for ESRD and for patient groups need to consider differences in case mix (i.e. comorbidities and demographics). This can be accomplished in part through statistical adjustment for those factors that are recorded. The DOPPS and other studies showed that a long list of factors needs to be considered to allow meaningful comparisons between treatments,

patient groups, regions, or centers. Some factors, such as age, cancer, and diabetes, may be considered as givens, whereas others, such as control of anemia, phosphorus, and malnutrition, may be modifiable. Studies of the latter factors, while adjusting for the former, have the potential to identify ways to improve patient care and longevity. This has been the focus of observational studies, such as the DOPPS, and of panels that review evidence to develop practice guidelines, such as the K/DOQI.

Survival after initiation of RRT

Morbidity and mortality are high in late stages of CKD and remain high among those who survive to the start of dialysis therapy. After initiation of dialysis, mortality depends largely on patient characteristics and comorbid conditions, particularly age and diabetes. Comparative studies of treatment modalities have clearly identified that kidney transplantation provides superior outcomes [85], and even more so when from a living donor [86]. Studies of the mortality risk for peritoneal dialysis versus hemodialysis have been somewhat inconclusive, as no large randomized studies of these dialytic treatment options have been performed and patient selection may influence the outcomes. Age may serve as an example for important differences in patient selection; compared with patients treated with hemodialysis, those treated with peritoneal dialysis are on average younger in the USA and older in Italy [87]. Thus, selection practice may explain some of the conflicting comparative survival results of peritoneal dialysis versus hemodialysis from different countries. In the USA, peritoneal dialysis appears to be associated with lower mortality risk in the first 1 or 2 years of dialysis, followed by a higher mortality risk. This early benefit of peritoneal dialysis, particularly among nondiabetic patients, may be related to greater preservation of residual kidney function with peritoneal dialysis [88]. These issues are reviewed in detail in the chapters in part 6 (hemodialysis) and in part 7 (peritoneal dialysis) of this textbook.

Differences in ESRD patient survival for Europe, Japan, and the USA have been found to be based largely on registry data, after adjusting for age and diabetes [89]. Subsequent study of hemodialysis patients, based on the DOPPS, confirmed these significant differences, albeit of a lesser magnitude, when allowing for greater adjustments for case mix and achieving better death ascertainment [90]. A more recent analysis of the DOPPS II data indicated that the mortality difference between the USA and Europe was confirmed but suggested that it could be largely explained by differences in vascular access [91].

Further studies of hemodialysis patients have indicated that several treatment factors are associated with mortality risk. The DOPPS pointed to a large number of factors that may be modifiable. Specifically, significantly lower mortality risk was associated with less catheter use and greater arteriovenous fistula use [92] as well as greater compliance with guidelines for Kt/V, hemoglobin, albumin, phosphorus, and calcium and avoiding large interdialytic fluid weight gains [93]. Additionally, the DOPPS analyses suggest that better quality of life indicators [94], less depression [95], and better nutrition [96] are strongly associated with longer survival.

The mortality risk has been shown to be relatively high in the early phase after initiation of dialysis. According to the DOPPS, this risk is elevated for the first 4 months and then appears to level off [97]. Among survivors to subsequent years, the mortality risk appears to show a gradual increasing trend by the fifth year compared with the second year [98].

Among causes of death, those related to atherosclerotic heart disease and congestive heart failure are dominant. Infection deaths are strongly associated with catheter use for vascular access. Withdrawal from dialysis precedes death in about 20% of deaths in the USA, about half of them due to failure to thrive and half following acute complications [99]. Withdrawal from dialysis is practiced differently in different countries; for example, much lower rates have been reported in Japan and Italy and much higher rates have been reported in the USA [100].

Hospitalization may serve as a proxy for morbidity. On average, dialysis patients are hospitalized nearly twice yearly [7]. Modifiable factors associated with higher case mix-adjusted hospital admissions include more severe anemia and hyperphosphatemia [83,101]. Cardiac problems account for most admissions, and these same laboratory abnormalities are associated more prominently with cardiac admissions. Catheter use for vascular access is strongly associated with greater risks of hospitalization for infections [102].

Dialysis therapy is successful overall in prolonging life. However, survival of patients on dialysis is similar to survival of patients with serious malignancies, such as colon or prostate cancer [103]. A greater focus on modifiable practices may influence better outcomes. A recent study strongly suggested a causal relationship between practice and outcomes by showing that dialysis facilities that improved their compliance with guidelines for dialysis dose and anemia control had improvements in their patients' survival during the same time period compared with those with little change in treatment, where outcomes did not improve [82]. Transplantation clearly provides a better quality of life [104] and longer survival than dialysis in virtually all patient groups [85].

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