Kidney International, Vol. 68, Supplement 99 (2005), pp. S30–S38

Chronic kidney disease: A European perspective

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Chronic kidney disease: A European perspective. There is an exponential growth worldwide of patients with end-stage renal disease (ESRD). Prevalences, outcomes, and underlying causes of ESRD are relatively well documented through different organizations. It is, however, clear that a large part of the bad outcome of ESRD patients is due to deficient follow-up during the earlier chronic kidney disease (CKD) stages. Data on CKD, prevalence of the different stages, and the evolution to ESRD are rather scant, and available data are conflictive. This is at least partly due to the lack of an international standard for measurement of renal function. In addition, there is compiling evidence that presence of proteinuria, even with a normal renal function, predisposes to ESRD. Most authors now prefer the term "kidney injury" rather than "kidney failure" to indicate people at risk for evolution to ESRD or for complications of CKD. Detection of these patients at risk is important to implement measures to slow down progression of CKD and avoid secondary complications. As it is clear that most of these CKD patients die before they reach ESRD, it might be that by taking the necessary preventive measures, the number of ESRD patients might still further increase exponentially.

The global population of end-stage renal disease (ESRD) patients treated with renal replacement therapy (RRT) was estimated to have reached almost 1.7 million at the end of 2003, and continues to grow at a significantly higher rate than the world population. Of the 1.7 million ESRD patients, 1.3 million were undergoing dialysis treatment, and over 300,800 people were living with kidney transplants.

El Nahas and Bello have recently discussed this global challenge [1]. In developed countries, it is estimated that the number of those with ESRD will continue to rise at an annual rate of around 5% to 8%—a growth driven by an aging population, increased incidence of diseases involving renal failure, particularly diabetes mellitus, improved technology, and better access to treatment.

About 90% of treated ESRD patients come from more developed countries that can still afford the cost of RRT [2]. In the United States, the annual expenditure on ESRD is estimated to increase to more than US $28 billion by 2010 [3]. In Europe, dialysis alone takes up about 2% of health care budgets, with only a small proportion (<0.1%) of the population needing treatment [2].

In numerous countries, mainly in the Western hemisphere, renal registries and other official bodies are valuable sources of extensive information on various aspects of ESRD demographics, treatment practices, and outcomes.

Table 1 (taken from the European Renal Association/European Dialysis and Transplant Association Registry) shows that the number of new RRT patients in the 25 countries of the European Union can be estimated at 63,000 per year [4]. Currently, there are approximately 360,000 RRT patients in the European Union, with 66% of them being treated by dialysis and the remainder living with a functioning graft.

Studies of acceptances to RRT from registry data are biased, however, because they include only patients believed to be suitable for treatment, given available health care resources. A better understanding of the epidemiologic characteristics of chronic kidney diseases (CKD) in the stages before RRT is required to develop strategies to identify and manage these patients. It is difficult, however, to get precise epidemiologic data about CKD. This is mainly because of a tendency to extrapolate data from the RRT population (assuming that CKD is a precursor to ESRD in most patients), the only recent introduction of precise epidemiologic and clinical definitions of CKD and the relatively high mortality rate of this group of patients. It is therefore highly probable that the number of patients with ESRD underestimates the entire burden of CKD, because the numbers with earlier stages of disease (stages 1 to 4) are likely to exceed by as much as 50 times those reaching stage 5 (ESRD) according to the United States Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) [5].

EPIDEMIOLOGY OF CKD OUTSIDE EUROPE

The limited amount of available data, mainly derived from registries in the United States, suggests that CKD is also a significant epidemiologic problem in the

Key words: chronic kidney disease, economic, end-stage renal disease, prevention, diabetes, hypertension.

Table 1. Incidence and prevalence of RRT in countries and regions included in the ERA-EDTA Registry (source ERA-EDTA Registry—Annual Report 2002)

	Incidence at day 1 of RRT (pmp)	Prevalence of RRT on December 31 (pmp)
Austria	131	781
Belgium, Dutch-speaking	170	882
Belgium, French-speaking[a]	170	802
Bosnia-Herzegovina	110	400
Croatia	118	699
Czech Republic	172	695
Denmark	129	711
Estonia	—	273
Finland	92	636
France, Limousin	177	810
France, Lorraine	148	822
Germany	174	918
Greece	165	841
Iceland	77	438
Latvia	59	266
Macedonia	73	522
Norway	93	641
Poland	99	405
Portugal	200	1097
Russia	15	79
Serbia and Montenegro	137	493
Slovakia	139	488[b]
Spain, Basque country	99	893
Spain, Catalonia	147	1018
Spain, Valencia region	155	1081
Sweden	125	759
The Netherlands	100	658
Tunisia	112	539
UK, England, Wales	95	601
UK, Scotland	108	700
25 European Union countries (estimate)	137	786

Abbreviations are: RRT, renal replacement therapy; ERA-EDTA, European Renal Association/European Dialysis and Transplant Association Registry; pmp, per million population.

[a]Based on 2001 data.

[b]Dialysis patients only.

stages before RRT. The Third National Health and Nutrition Examination Survey (NHANES III), collecting data among a large representative sample of the United States population (18,723 participants of different age, sex, and ethnic groups examined between 1988 and 1994), still represents the most comprehensive source of epidemiologic data regarding CKD in the conservative phase [6]. This survey estimated that up to 11% of the general adult population (19 million) could have some degree of CKD, including more than 8 million individuals with glomerular filtration rates (GFR) of less than 60 mL/min [5]. The percentage of the overall United States population with serum creatinine (SCr) values >1.5 mg/dL was 9.74% in men and 1.78% in women; it was also found that older age, together with male sex, was associated with higher SCr levels. More than 30% of men and nearly 10% of women aged >70 years were estimated to have SCr levels >1.5 mg/dL in this survey [6]. This analysis also estimated that 5.9 million people could have stage 1 CKD with normal renal function [5].

A recent article by Coresh et al [7] quantifies the pool of CKD patients in 1999 to 2000 and compares it with that in 1988 to 1994. It was found that the prevalence of moderately or severely decreased kidney function (GFR 15 to 59 mL/min per 1.73 m^2) remained stable over the past decade ($4.4 \pm 0.3\%$ in 1988 to 1994 and $3.8 \pm 0.4\%$ in 1999 to 2000). At the same time, the prevalence of albuminuria (albumin to creatinine ratio (ACR) ≥30 mg/g) in single spot urine significantly increased from $8.2 \pm 0.4\%$ to $10.1 \pm 0.7\%$. Overall CKD prevalence was similar in both surveys (9% using ACR >30 mg/g for persistent microalbuminuria; 11% in 1988 to 1994, and 12% in 1999 to 2000 using gender-specific ACR cutoffs). In contrast to the dramatic increase in treated kidney failure, overall CKD prevalence in the US population has been relatively stable. The estimated prevalence of ESRD (KDOQI stage 5) in the US population is 344,000 [8]. This could suggest that less than 2% of the US CKD population progresses to RRT. Relatively little is known about the 98% of patients with CKD who do not advance to ESRD or are not taken into RRT. However, in 1996, the Kaiser Permanente health plan identified 27,998 patients with an estimated GFR of less than 90 mL/min/1.73 m^2 on two separate measurements at least 90 days apart [9]. The patients were followed up from the index date of the first GFR of less than 90 mL/min per 1.73 m^2 until RRT, death, disenrollment from the health plan, or June 30, 2001. The data showed that the rate of RRT over the 5-year observation period was 1.1%, 1.3%, and 19.9%, respectively, for the KDOQI stages 2, 3, and 4, but that the mortality rate was 19.5%, 24.3%, and 45.7% for the same stages. During this observation period, it appeared thus that only 3.1% of patients with stage 2 through stage 4 disease progressed to RRT, while 24.9% died. Thus, death was far more common than dialysis at all stages. In other words, these data indicate that RRT patients in registries are not representative for patients with CKD [9].

In the United States, the Kidney Early Evaluation Program was a free, community-based screening that took place in 21 cities in 1997. The objective was to identify persons at risk for kidney disease by screening persons with first-order relatives with diabetes, hypertension, or kidney disease, or those with a personal history of diabetes or hypertension [10] Six hundred thirty-six (71.4%) of the 889 screened individuals had abnormal test values and were encouraged to follow-up. Three hundred ninety-four individuals (44.3%) had two or more values outside the normal range, and 514 (57.8%) learned of at least one new condition. There were 420 individuals identified with markers for kidney disease, some of whom had more than one abnormality: 114 had an elevated SCr, 171 had microalbuminuria, 137 had pyuria, and 165 had hematuria. From this preliminary report, it was concluded that

Table 2. Selected studies on the epidemiology of CKD in Europe

Reference and country	Study type total sample	Timing of study	Inclusion criteria	Number of studied cases	Incidence and/or prevalence of CKD pmp	Remarks
Feest 1990 UK [38]	Selected population (lab tests): 451	1986–1988	SCr >500 μmol/L	210	Incidence: 148 (128–168)	Age related prevalence: 54% referral
Khan 1994 Scotland [39]	Selected population (lab tests): 757	1/7/89–30/6/1990	SCR ≥300 μmol/L	304	Incidence: 450	Age-related: 35.8% referral
Lupi 1997 [33] Locatelli 2003 [85] Lombardy	Selected population (lab tests)		SCr 1.5–3 mg%	2248	Annual incidence: 336.6	
Magnasson 2002 [42] Iceland	Population-based (lab tests): 18,912	1967–1991	SCr >150 μmol/L		Prevalence: 41 220/100000 (0.22%)	Progression in the 41 with CKD: 27 = 66%
Drey 2003 UK [40]	Population-based (lab tests): 382,936	1/7/1992–30/6/1994	SCr >1.7 mg%	1076	Incidence rate ≥1.7 mg%: 1330 ≥3.4 mg%: 140 ≥5.7 mg%: 51 Overall: 1700	Mortality 69% after mean of 5.5 years
John 2004 UK [41]	Population-based (lab tests): 13,658	1/10/2000–30/9/2001	SCr >180 μmol/L (men) SCr >135 μmol/L (women)	3822	Prevalence: 5554	Unreferred: 84.8%
Ejerblad 2004 [37] Sweden	Population-based (lab tests) effect of smoking Matched control vs. smoking cohort	20/5/1996–31/5/1998	SCr ≥300 μmol/L (men) SCr ≥250 μmol/L (women)	926 CKD 998 controls	Prevalence: 926/5.3 million = 207	
Cirillo 2004 [35] Italy	Population-based Gubbio study 1684			1632	Prevalence: GFR <60 mL/min: 3.6% (men); 4.4% (women)	
Otero Giz, personal communication, 2005 (Spain)	Population-based (lab tests) total adult population: 382,936		GFR by CG and MDRD	1069	Prevalence <60 mL/min CG: 17.8% MDRD: 13%	
Verhave 2004 [72] Groningen (Netherlands)	Population-based: 8592 (with albuminuria?)	Started 1997 with FU: 4 y	GFR by CG or MDRD (known GFR <60 mL/min and abnormal urine: excluded)	6022	At baseline: GFR <60 mL/min: 3.6% at FU: Incidence: GFR <60 mL/min:4.2%	Baseline albuminuria strong predictor for CKD
Bruno 2003 [44] Italy	Type 2 diabetes total: 1565 all normal SCr	Started 1991–1992 FU till 31/12/2001		1408	ESRD: 1.04/1000 pt yrs CKD: SCr >2 mg%: 7.6/1000pt yrs SCr >1.5: 13.1/1000pt yrs	
Kissmeyer 1999 [86] UK	Selected population hypertensives: diabetics 50–75 yrs total: 16,855		SCr >125 μmol/L	2561	150 (11%) 110,000 in this population	28% referred

Abbreviations are: CKD, chronic kidney disease; pmp, per millions population; SCr, serum creatinine; GFR, glomerular filtration rate; CG, Cockcroft-Gault; MDRD, Modification of Diet in Renal Disease (study); FU, follow-up; ESRD, end-stage renal disease.

targeted screenings are an effective means of identifying persons at risk for kidney disease, and can identify individuals at risk early enough in the course of their disease to allow for effective intervention

The interpretation of the epidemiologic data on CKD in the United States has been subject to some debate.

Clase et al [11] applied four equations that predict GFR from measurements of SCr, with SCr values obtained in 13,251 normal, nondiabetic adults in the NHANES III. They arrived at the rather startling conclusion that CKD was as much as a log factor more common than previously predicted; for example, 13% of the population had GFR below 60 mL/min/1.73 m^2, and these figures were significantly higher in the elderly. Clase et al conclude by recommending that predictive equations to calculate GFR should not be routinely applied by laboratories that measure SCr until further research is done to determine the meaning of their observations. The authors reported a prevalence of reduced GFR that is approximately fivefold greater than previous estimates. In a worst-case scenario, their results suggest that approximately half of the ambulatory, adult US population have a reduced GFR. If this assessment of the prevalence of CKD is valid and all of these patients survived to develop ESRD, the American health care system would be financially overwhelmed.

The prevalence of CKD in the study by Clase et al [11] contradicts that reported in the KDOQI. [12]. Using NHANES III, the KDOQI group estimated that 64% of US adults aged 20 years or older had an estimated GFR ≥90 mL/min by the Modification of Diet in Renal Disease (MDRD) equation. Only 31% of the population was estimated to have a GFR between 60 and 89 mL/min, and 4.3% with a GFR between 30 and 59 mL/min. Conversely, the KDOQI group noted that only 0.2% of the population had an estimated GFR of 2 mg/dL versus >1.5 mg/dL [12]. Many of the epidemiologic studies on prevalence of CKD did not take into account two important sources of bias (i.e., the lack of standardized serum creatinine methodology and the age-related decline in renal function) [13–33]. Performing an age-stratified analysis, Jungers et al recorded a striking increase in the annual incidence of CKD together with the increase of age, with incidence rates in patients aged >75 years being almost seven times higher than those of patients aged 20 to 39 years (619 per million population [pmp] vs. 92 pmp) and more than twice those of patients aged 40 to 59 years (619 pmp vs. 264 pmp) [32]. In a recent Italian regional epidemiologic analysis, in which data were collected from the local dialysis and transplantation registry, hospital discharge abstracts, and ambulatory and laboratory databases, the prevalence of patients with CKD (defined as SCr >1.5 mg/dL) was estimated to be about 0.8% of the general population, with 75% of these patients being unknown by nephrologists [34].

A more recent Italian study [35] analyzed the presence of overnight urinary albumin excretion with prevalence of coronary heart disease and low renal function in a population sample of 1632 men and women aged 45 to 64 years. Coronary heart disease prevalence was 8.2% in the whole sample. Prevalence of low renal function was 4% in the total group, and 4.8% in the hypertensive group. Age-related incidence rose from 58 pmp per year in those aged 20 to 49 years to 588 pmp per year in those aged 80 years or older. Only 54% of these patients were referred to a nephrologist; 120 patients (57%) needed dialysis or died within three months of presenting without receiving dialysis, and 187 (89%) died or needed dialysis within three years. After patients unsuitable for further treatment had been excluded, the authors calculated that 78 patients pmp per year younger than 80 years of age needed to start long-term RRT.

In a Spanish general population study, it was found that the prevalence of stages 2 and 3 CKD increased with age (especially > 65), and this more in women than in men. Using the Cockroft-Gault method, almost half the older women had a stage 3 CKD as opposed to a third of the men, whereas if the abbreviated MDRD study was used, there were very few differences between the sexes. This difference was most pronounced in stage 2 (60% as opposed to 36%) [36].

Khan et al [39] calculated an annual incidence of chronic renal failure (CRF) (SCr ≥300 μmol/L) as 450 pmp, and persistent advanced CRF (SCr ≥500 μmol/L) as 132 pmp. After excluding those aged >80 years and those with advanced malignancy, the corresponding incidence figures were 240 pmp per year and 81 pmp per year. Only 109 patients (35.8%) were referred to a nephrologist.

In the Southampton and Southwest Hampshire Health Authority population base of 405,000, a retrospective cohort analysis was performed on all new cases of CKD determined by a persistently increased SCr level ≥1.7 mg/dL for 6 months, identified from chemical pathology records [40]. The annual incidence rate of detected CKD was 1701 pmp and 1071 pmp in those younger than 80 years. The median survival was 35 months. Only 4% of patients were accepted to RRT.

John et al [41] identified patients in a predominantly Caucasian UK population who were unknown to renal services, and followed up with them to establish survival, rate of referral, and change in GFR. The prevalence of CKD defined by SCr cutoff values of ≥2.03 mg/dL in men and ≥1.53 mg/dL in women was 5554 pmp. Median-calculated GFR of the cohort was 28.5 mL/min/1.73 m^2, and median age was 83 years. A total of 84.8% of patients were unknown to renal services. During a mean follow-up of 31.3 months, 8.1% of these patients were referred. The median survival of the unreferred population was 28.1 months. The majority of unreferred patients had stable renal function. The incidence of new unreferred CKD

during the first year of follow-up was 2435 pmp, such that the prevalence remained stable at 4910 pmp. It was concluded that referral of all patients with CKD is unrealistic and inappropriate. Management strategies aimed at improving adverse outcomes need to take account of this and be developed and implemented through collaboration between primary and secondary health care services.

It is generally believed that once CRF is established, it progresses to ESRD irrespective of its original cause. However, longitudinal data on the natural course of CRF are sparse.

One of the few studies to evaluate the prevalence of CRF in an unselected population and look into the problem of progression of kidney disease has recently been performed in Iceland [42]. The study sample comprises a large fraction of the Icelandic population, which totaled 286,275 individuals on December 1, 2001. The authors studied 18,912 adult patients between 1967 and 1991. Patients with SCr levels of ≥1.7 mg/dL were considered to have CRF. The crude prevalence of CRF, as well as age-standardized prevalence for 5-year age groups, was determined. Progression of CRF was defined as a decrease in estimated GFR greater than 1 mL/min/1.73 m^2/year. Of 49 individuals who had an SCr of ≥1.7 mg/dL at entry, 41 individuals had a persistent elevation in SCr levels. Thirty-four individuals had mild CRF (SCr, 1.7 to 2.8 mg/dL), 6 individuals had moderate CRF (SCr, 2.8 to 5.6 mg/dL), and 1 individual had ESRD. The crude prevalence of CRF was 0.22%; 0.15% among women and 0.28% among men. Only 27 patients had progressive renal failure, 17 of whom progressed to ESRD during a median of 7 years (range, 3 to 21 years). It was concluded that the prevalence of CRF is markedly low in Iceland and that 27% of patients did not show progression of their renal failure during a median of 11 years of follow-up.

The definition of progression used in the Icelandic study as a decline in estimated GFR in excess of 1 mL/min/1.73 m^2/year is somewhat arbitrary. It is based on traditional beliefs that an age-related decline in GFR may be as high as 1 mL/min/1.73 m^2/year [43]. Four of the eight patients in the Icelandic study with an estimated GFR decline between 1 and 2 mL/min/1.73 m^2/year developed ESRD, which suggests that with time, a significant number of patients with such a modest decline in renal function are at risk for developing ESRD. It is of interest to note that the majority of patients with an unknown cause of CRF did not progress. Their indolent course may have led to a more conservative approach to their management, so that diagnostic procedures were not pursued.

Data on the incidence of ESRD and CRF from population-based studies in Caucasian type 2 diabetic patients are lacking. To provide such data, a population-based cohort of type 2 diabetic patients was identified in Casale Monferrato, Italy, and prospectively examined from 1991 to 2001 [44]. The authors followed up 1408 of 1540 (91.4%) patients (average follow-up time 6.7 years); 10 new cases of ESRD and 72 of CRF (plasma values of creatinine ≥2.0 mg/dL) were identified, giving incidence rates per 1000 persons per year of 1.04 and 7.63, respectively. Cumulative risks for CRF adjusted for competing mortality were 6.1% and 9.3% after 20 and 30 years from diagnosis of diabetes, respectively. Incidence rates and cumulative risks of CRF defined by plasma creatinine values >1.5 mg/dL increased to 13.1 per 1000 persons per year, 8.6% and 14.8%, respectively. It was concluded that the individual risk of ESRD and CRF in type 2 diabetes is low, and that albumin excretion rate and diastolic blood pressure are independent predictors of progression.

In the outpatient diabetic care unit of the University of Torino (Italy), approximately 25% of the type 2 diabetics of a 900,000-inhabitant city were followed up [45]. At the time of the study (1998–1999), the unit followed up with 5182 type 2 diabetics whose SCr and proteinuria were tested at least yearly. A total of 3826 prevalent and 478 incident patients with one or more analyses in the same laboratory were included in the study. The authors also calculated the stepwise need for nephrologic follow-ups calculated according to their usual policy (4–12 evaluations per year on SCr and proteinuria and 30 minutes per evaluation). The prevalence of increased SCr ≥1.5 mg/dL was 8.1%; of proteinuria 0.3 g/day was 25.2%; of SCr ≥3 mg/dL was 1.2%; and of nephrotic proteinuria, it was 3.4%). Projecting this data to the entire unit, with adherence to their usual evaluation protocol, it was estimated that early nephrologic follow-up of type 2 diabetics would require approximately 1300 hours per year (one full-time nephrologist); 5 nephrologists would be needed for the whole city of Torino, and 24 nephrologists would be required for the region of 4,350,000 inhabitants. It was concluded that early nephrologic referral and follow-up of type 2 diabetics is time-consuming, expensive, and that meeting this type of outpatient care requires considerable resources.

Population-based programs to promote screening for CKD are intended to increase the rate that persons with previously undetected renal injury are identified and linked to further evaluation and disease-modifying intervention [46].

It is the expectation that early intervention for patients with CKD will delay, if not prevent, subsequent progression to ESRD. There are interventions to delay and prevent the progression of CRF [47–71], and national guidelines have recommended that all patients with evidence of reduced renal function (e.g., SCr level >1.7 mg/dL or GFR 60 mL/min/1.73m^2) should be sent to a nephrology unit when these values are confirmed at the second evaluation. In multivariate analysis, urinary albumin excretion was independently predictive for the risk of developing an impaired GFR [72]. Measurement of urinary albumin excretion may thus prove to be a valuable

Table 3. Population-based study of the epidemiology of CKD in Belgium and the mortality in the different stages of CKD, with results based on MDRD staging (mL/min/1.73m^2), and on Cockroft-Gault staging (mL/min)

	Total number of individuals	% Total mortality	Total number of individuals	% CVD mortality	Total number of individuals	% CHD mortality
GFR						
>60	7630	6.6	7267	1.98	7198	1.04
30–60	1458	12.2	1345	4.8	1323	3.3
15–30	16	25	13	7.7	13	7.7
<15	2	50	2	50	2	50
Creatinine clearance						
>60	7816	5.8	7494	1.72	7439	0.99
30–60	1259	18.4	1105	7.1	1069	3.9
15–30	17	41.2	14	28.6	14	28.6
<15	0	—	0	—	0	—

Abbreviations are: CKD, chronic kidney disease; CHD, coronary heart disease; MDRD, Modification of Diet in Renal Disease (study); GFR, glomerular filtration rate. Mortality is given as total mortality, CVD mortality, and mortality due to CHD 10 years after screening.

tool to detect patients at risk for later development of renal failure, independent of the presence of other cardiovascular risk factors.

A preliminary analysis of the distribution of CKD in a population study in Belgium has recently been performed, and the data are summarized in Table 3. The results are based on observations made in men and women who took part in the Belgian inter-university research on nutrition and health study. This study, in which baseline measurements were made in the years 1981 to 1984, focuses on the distribution of cardiovascular risk factors and nutritional habits in Belgium and their relation to total and cause-specific mortality. An age- and sex-stratified population sample of patients 25 to 74 years of age was selected at random from 42 of the 43 Belgian geographic districts. To achieve a sufficient sample size under circumstances in which little pressure was put on invited eligible patients, a sample of more than 30,000 persons was selected. The participation rate was 36.5%, resulting in 11,302 patients taking part in the study (5949 men and 5353 women). A 10% random sample of nonparticipants was selected and invited to answer a number of questions related to smoking and nutritional habits, which revealed that no differences existed between participants and nonparticipants with respect to lifestyle. GFR was estimated by both the simplified MDRD formula or by Cockcroft-Gault (CG) formula. This population database also contains information on the evolution of mortality 10 years after the initial screening. For all participants, biochemical measurements were performed with a nonfasted blood sample analyzed in one central laboratory. Levels of SCr were measured on an SMAC Technicon (Technicon Instruments Corp, Tarrytown, NJ, USA).

Table 3 shows the 10-year total mortality and mortality due to cardiovascular diseases in the different stages of CKD based on the CG and MDRD estimated GFR. Although there was a prevalence of a GFR >60 mL/min by CG and MDRD of 84.3% and of 83.2% of the studied population, respectively, total cardiovascular disease mortality and mortality due to coronary heart disease increased inversely with the estimated GFR, which confirmed recent results obtained from the Hoorn Study [73] in the Netherlands and Go et al [74] in the United States.

It has been shown that the prevalence of CKD increases to 50% to 60% when at-risk individuals are screened [10], and the early identification of such individuals and prevention of progressive CKD are likely to be key factors in alleviating the future burden of ESRD and its associated mortality.

HIGH-RISK SCREENING OR POPULATION-BASED INTERVENTION STRATEGIES?

Although there is no well-defined method of identifying "high-risk" populations, the KDOQI guidelines identify demographic groups characterized by high incidence or prevalence of CKD as populations that should be targeted for screening and intervention [12]. Note that similar high-risk disease control strategies for cardiovascular disease have been criticized. Rose et al have argued that most cases of cardiovascular disease arise not from the "high-risk" tail of the population but from the general population [75, 76], and a similar situation may pertain to ESRD.

Are there populations of patients wherein the practicality of a population-based screening strategy for CKD might be easily studied? Two studies have recently reported suggesting this possibility [77, 78]. These studies involve family members of patients with ESRD and patients who are hospitalized for cardiovascular problems.

Family members of ESRD patients were recruited for CKD screening. Of 221 family members of patients with ESRD screened between 1999 and 2001, 13.9% had an estimated creatinine clearance of 2.0 mg/dL. These results indicate that CKD is both prevalent among patients with congestive heart failure and confer substantial increased risk of mortality in this population.

COST-EFFECTIVENESS ANALYSIS

The cost-effectiveness of screening is one of the most relevant criteria for advocating systematic screening for

renal disease. Unfortunately, extremely limited data on the cost, as well as the effect of the early detection of renal disease, are available. Indeed, the few publications that have attempted to address this issue have used computer simulation models, rather than performing randomized clinical trials evaluating the efficacy of systematic screening. In addition, the majority of these analyses are limited to studying the efficacy of microalbuminuria screening in the context of the prevention of diabetic nephropathy. For example, a recent review by Scheid et al [79] identified seven such cost-effectiveness analyses, only two of which focused on type 2 diabetes mellitus [80, 81]. In both these analyses, screening for microalbuminuria appeared to be a cost-effective approach. However, it was the systematic treatment of all newly diagnosed patients with type 2 diabetes mellitus that appeared to be most associated with the highest life expectancy, as illustrated by a marginal cost-effectiveness ratio of US $7500 per quality-adjusted life year gained when all patients were treated with angiotensin-converting enzyme (ACE) inhibitors compared with systematic screening for microalbuminuria [81]. It was further argued that the routine treatment of all patients with type 2 diabetes mellitus using ACE inhibitors would potentially bypass current concern for low rates of microalbuminuria screening by primary care physicians. However, these analyses were limited by strict assumptions as to the efficacy of ACE inhibitors in preventing the progression of normoalbuminuria to microalbuminuria. Furthermore, the marginal cost-effectiveness ratio was extremely sensitive to factors such as age at diagnosis of diabetes mellitus, cost of ACE inhibitors, and side effects of the chronic use of these drugs.

In the only analysis evaluating the cost-effectiveness of screening for nondiabetic renal disease, Craig et al [67] recently questioned the feasibility of mass screening for detection of CKD based on Australian data. ESRD develops in about 1500 Australians each year. Of these, about 1000 are more than 50 years of age (an incidence of about 200 pmp per year). Proteinuria, which is present in about 5% of the general population, confers an approximately 15-fold increased risk for ESRD. Twelve randomized trials of ACE inhibitors, in 1943 patients with varying degrees of renal impairment, hypertension, and proteinuria, showed that the risk of developing ESRD can be reduced by about 30% over a 2- to 3-year period. In a general practice-based screening model involving: (1) an opportunistic single dipstick test for protein, (2) a confirming 24-hour urine test for protein, and (3) commencement of ACE inhibitors in appropriate individuals, 20,000 people 50 years of age or older would need to be screened to prevent one case of ESRD. To achieve this, approximately 100 people would need to be treated with ACE inhibitors for 2 to 3 years, and 1000 would need to have a 24-hour urine protein test (and, of these, 700 would be false positives). Such a strategy may save health dollars, but some critical research questions are still unanswered. What is an individual's risk of developing ESRD, given values for proteinuria, blood pressure, and renal function? What is the benefit of ACE inhibitors in screen-detected cases, which are at low risk of ESRD? What psychologic and physical harm is caused by screening, including the specific renal investigations and treatments that follow proteinuria detection?

The authors concluded that given available data, screening middle-aged and older Australians for proteinuria and treating some with ACE inhibitors is, at best, a promising primary prevention strategy for preventing ESRD. However, a large population-based cohort study, with nested trial of ACE inhibitors, is still required to evaluate whether this model of screening for renal disease does more harm than good [67].

However, this analysis, as in other simulation models, is subject to the limitations of the model assumptions such as those the authors made regarding the reliability and reproducibility of screening tools and the natural history of renal disease progression. Indeed, the authors note uncertainty about the risk of progression to ESRD among patients with proteinuria, the risks and benefits of ACE inhibitor therapy among patients at low risk for ESRD, and the adverse psychologic and physical consequences of the screening process. Thus, although these indirect evaluations of the effectiveness of screening with simulation models suggest its usefulness, these findings only emphasize the dearth of definitive studies that examine the effectiveness of screening for renal disease.

CONCLUSIONS

This article summarizes the scarce information on the epidemiology of CKD before stage 5 in Europe. From the data available, we can derive that the prevalence of undetected (or unreferred) CKD in our continent is at least as high as in the United States.

In addition, the utility of screening for patients at risk of CKD is briefly discussed.

People with hypertension, diabetes, cardiovascular disease, autoimmune disease, and their family members are at high risk and should be screened by urinalysis and by testing for SCr. Conversely, the utility of unselected population screening for renal disease (e.g., by dipstick) is very low [82, 83] and should at present not be recommended.

The use of estimating GFR by the available equations should be limited to identifying patients with low GFR [5], although there are compelling arguments against this recommendation [11]. Applying estimating equations universally will lead to the "labeling" and referral of many patients who would not otherwise have been identified as having renal failure. These patients will have different demographic characteristics (older age, more women,

higher proportion with nonproteinuric renal disease) and probably a lower risk of progression than those identified on the basis of SCr level [5, 11]. The benefits of nephrologic intervention in such patients are unclear. Moreover, current nephrology resources could not possibly handle the potential referrals [84]. A clinical trial is urgently needed to address whether referral triggered by identification of low estimated GFR leads to cost-effective therapy. In the absence of clear evidence of benefit, it may be premature to advocate a strategy with such major resource implications.

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