Kidney Failure Stabilizes after a Two-Decade Increase: Impact on Global (Renal and Cardiovascular) Health

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After a 2-decade period of progressive increases, rates for new cases of kidney failure that are reported to the US Renal Data System seem to have stabilized in the past few years (1). During the 1980s and much of the 1990s, the number of patients who entered programs for renal replacement therapy (RRT) in the United States increased by 5 to 10% every year. Nearly 537,000 people received dialysis or a kidney transplant in 2003, and cost to Medicare peaked to $18 billion (2). On the basis of these data, estimates projected 650,000 patients progressing to ESRD and $28 million in public expenditures for RRT by the year 2010 (3). However, in 2003, for the first time, the rate for new cases of kidney failure per million people (338 *versus* 340) slightly declined compared with the previous year (Figure 1). This latest figure continued a 4-yr trend in which the yearly incidence rate has declined progressively to <1% (2). This promising development hardly reflects a chance occurrence and seems to coincide with the launch of private and government programs to increase awareness of chronic kidney disease (CKD) and to implement clinical strategies that were proved in the 1990s to delay significantly or prevent kidney failure. Actually, according to the researchers of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), "credit for recent gains goes to angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), which lower protein in the urine and are thought to directly prevent injury to the kidney's blood vessels; and careful control of diabetes and BP" (2).

The application of more strict criteria for the diagnosis and treatment of arterial hypertension and the progressive shift in class of antihypertensive agent toward a widespread use of ACE inhibitors, combined with improved metabolic control in patients with diabetes (4), most likely explain the improved outcome of CKD in recent years (Table 1). Since their introduction as antihypertensive drug therapy for treatment-resistant hypertension, ACE inhibitors have been used for an increasing number of indications, including protection of target end organs in patients with diabetes, hypertension, or proteinuria (5). In 1993, a trial of 409 patients with type 1 diabetes and overt nephropathy documented less progression to the combined end point of doubling serum creatinine, ESRD, or death in those who were on captopril compared with control subjects who were on placebo (6). In 1997, the Ramipril Efficacy In Nephropathy (REIN) study showed similar findings in patients with nondiabetic chronic renal disease (7,8). Ramipril compared with placebo reduced the rate of GFR decline and the risk for dialysis by 50% (7,8). Such benefit likely was mediated by the effect on urinary proteins, because BP was comparable in the two treatment arms, whereas proteinuria decreased on ramipril but increased on placebo. Amelioration in the rate of GFR decline was time dependent: After 3 yr of continued ramipril therapy, 10 of the 78 patients who were nephrotic at study entry showed a progressive improvement of GFR and never reached ESRD. GFR slopes in 16 additional patients stabilized or worsened so slowly that ESRD would be delayed beyond the patient's life expectancy (9). On the same line, *post hoc* analyses of the captopril study on 108 patients with type 1 diabetes and nephrotic proteinuria at study entry found that in seven of the 42 patients who were on continued ACE inhibitor therapy for at least 3 yr, proteinuria decreased to subclinical range and the GFR stabilized (10). Later studies showed that ARB may reduce proteinuria and slow disease progression in overt nephropathy of type 2 diabetes (11,12).

On the basis of these findings, a widespread use of ACE inhibitors and ARB in routine clinical practice is expected to reduce remarkably the risk for kidney failure in the general population of patients with diabetic or nondiabetic CKD. As a result of the dramatic excess cardiovascular mortality that is associated with ESRD (13), this also should translate into a substantial reduction of the overall cardiovascular risk in this population. These benefits should add to the widely known, specific cardioprotective effects of ACE inhibitors that, in patients with CKD, may be even more consistent than in those with normal renal function (14).

In theory, decreased cardiovascular mortality should translate into an increased incidence of ESRD because a larger proportion of patients with CKD may survive enough to develop kidney failure. In actuality, however, in the past 2 decades, ESRD incidence did not increase in parallel with patient survival because those treatments that so importantly contributed to limit cardiovascular events—namely ACE inhibitors and

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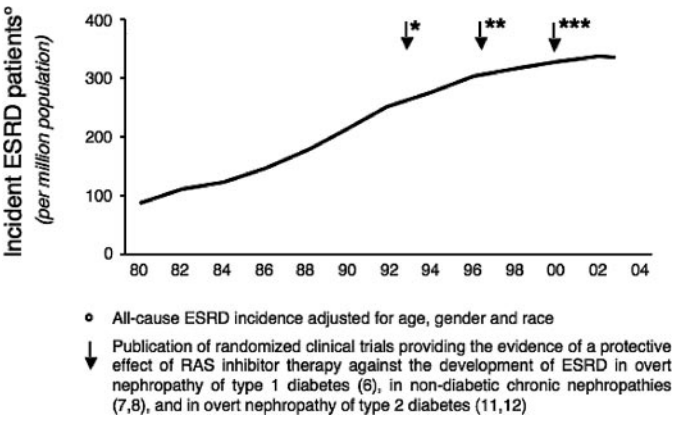

Figure 1. Annual ESRD incidence in the United States from 1980 to 2004 according to the publication of randomized clinical trials providing the evidence of a protective effect of renin-angiotensin system inhibitor therapy against the development of ESRD in overt nephropathy of type 1 or type 2 diabetes and in nondiabetic chronic nephropathies.

ARB—also were extremely effective in slowing the progression of CKD, in particular in patients with type 1 diabetic nephropathy (6,10) and in those with nondiabetic chronic nephropathies (7–9). Surveys of European series (15,16) show that increasing use of ACE inhibitors substantially contributed to the decreasing rates of kidney failure and cardiovascular mortality observed in young patients with type 1 diabetes (Figure 2) despite the approximately 2.4% annual increase in type 1 diabetes prevalence in the general population during the past 3 decades (17). Consistently, the most striking trends in the NIDDK report (1,2) were found in white patients who were younger than 40 yr and had type 1 diabetes, for whom rates for new cases of kidney failure were the lowest since the late 1980s. Data of the US Renal Data System registry show a similar trend also for new cases of ESRD from nondiabetic chronic nephropathies that progressively decreased during the past 2 decades (18), possibly in parallel with the increasing use of renin-angiotensin system (RAS) inhibitors. This is in stark contrast to rates in older patients—mostly with type 2 diabetes—and in black patients, who did not decrease to a comparable extent. Population growth, rapidly rising prevalence of type 2 diabetes, and, possibly, a less consistent benefit of RAS inhibitor therapy in patients with type 2 diabetes and black patients (19,20) may contribute to the increasing rates in the United States, as well as in Western Europe and worldwide (18,21). The high rate of progression of these patients, who currently represent the large majority of those who are on RRT in the United States, also may explain the excess ESRD risk in American compared with European series. The gap is particularly striking, with rates of progression to ESRD three times higher in the United States than in Norway, Finland, or Great Britain and two times higher than in Germany in 2003 (22,23). Indeed, data show that the higher risk for ESRD in the United States is not due to a remarkably higher prevalence of CKD—which currently ranges from 10 to 11% in both the United States and western Europe—but rather to a higher rate of progression from CKD to ESRD (24). Similarly, among American patients, black patients experience a three times higher incidence of ESRD compared with white patients, despite similar prevalence of CKD stages 3 to 4—a difference that is explained only partially by higher prevalence of diabetes, hypertension, and other conventional risk factors in black patients (25). Although differences in genetic or clinical characteristics might account for different responses to treatment (26,27), underdosing of RAS inhibitors and suboptimal control of hypertension, hyperglycemia, or dyslipidemia also might contribute. A survey of 602 patients with CKD in the Boston area found that 65% of them had BP above the target level of 140/90 mmHg recommended in the fifth report of the Joint National Committee on Detection, Evaluation and Treatment of high BP in 1993 (28). Moreover, only 49% received an ACE inhibitor at some point during the follow-up. On the same line, a study of hospitalized Medicare patients in Atlanta found that <35% of patients with diabetes, hypertension, and renal insufficiency had been prescribed an ACE inhibitor at discharge (29). A more recent survey found that 81% of patients with diabetes, CKD, and proteinuria had prescriptions for ACE inhibitors or ARB but that only 57% were effectively prescribed these medications (30). This suggests that impressive results from clinical trials on progression of CKD have not been translated fully into clinical practice, even in nephrology practices. Indeed, although the use of RAS inhibitors has doubled since 1993 (1,2), only 32% of patients who are older than 60 yr and have CKD and <50% of those with specific indications such as type 2 diabetes, hypertension, or congestive heart failure receive these medications (2). Consistently, a recent study that examined a population of 742 people who were 55 yr or older and had type 2 diabetes and at least one additional guideline indication (hypertension, proteinuria, cardiovascular disease, or congestive heart failure) found that only 43% received ACE inhibitors or ARB (31), a figure that only slightly exceeded 50% in those who presented all of the indications. Of note, among those with proteinuria, black patients were significantly less likely than white patients to receive RAS inhibitor therapy (31).

A provocative explanation is that differences in health care access and systems may result in different standards of care that eventually contribute, at least in part, to the excess renal risk in American patients, particularly in patients with type 2 diabetes and black patients. Free access, earlier nephrology referral, and greater number of predialysis nephrology visits seem to indicate a better predialysis therapy in Western Europe than in the United States (32). Financial cost to the patient also is a key factor that hampers proper use of ACE inhibitors and ARB in eligible patients, in particular in older patients with type 2 diabetes (33) and in those with lower incomes or without health insurance (34). Progressive shifting of costs back on patients as a disincentive for resource overuse also may provide a financial disincentive to recommended healthy actions, as demonstrated by studies that show a negative correlation between copays and compliance (33). This may have major implications, because undertreatment of these high-risk patients may translate into a substantial excess of renal and cardiovascular events.

Improved predialysis therapy therefore is of paramount im-

Table 1. Clinical studies showing a benefit of specific interventions on the onset and progression of chronic renal disease and related complications[a]

Year	Study (Reference)	Setting	Intervention	Main Outcome
1983	Parving *et al.* (40)	Type 1 diabetes, overt nephropathy	BP control	Slowed GFR decline
1993	Collaborative Study (6)	Type 1 diabetes, overt nephropathy	ACE inhibition	Reduced incidence of ESRD
	DCCT (6)	Type 1 diabetes	Intensified metabolic control	Reduced incidence of microvascular complications
1994	European Microalbuminuria Captopril Study (41)	Type 1 diabetes, microalbuminuria	ACE inhibition	Reduced incidence of macroalbuminuria
	MDRD Study (42)	Nondiabetic chronic nephropathies	Intensified BP control	Slowed GFR decline
1997	REIN Study (7)	Nondiabetic chronic nephropathies	ACE inhibition	Slowed GFR decline, reduced incidence of ESRD
1998	REIN Follow-Up Study (8)	Nondiabetic chronic nephropathies	ACE inhibition	GFR stabilization or improvement
	UKPDS 33 (43)	Type 2 diabetes	Intensified metabolic control	Reduced incidence of microvascular complications
	UKPDS 38 (44)	Type 2 diabetes	Intensified BP control	Reduced mortality Reduced incidence of micro- and macrovascular complications
2001	IRMA 2 Study (45)	Type 2 diabetes, microalbuminuria	Angiotensin II blockade	Reduced incidence of macroalbuminuria
	RENAAL Study (11)	Type 2 diabetes	Angiotensin II blockade	Reduced incidence of ESRD
	IDNT Study (12)	Overt nephropathy		
2004	BENEDICT (46)	Type 2 diabetes	ACE inhibition	Reduced incidence of microalbuminuria

[a]ACE, angiotensin-converting enzyme; BENEDICT, Bergamo Nephrologic Diabetic Complications Trial; DCCT, Diabetes Control and Complications Trial; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA, Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients; MDRD, Modification of Diet in Renal Disease; REIN, Ramipril Efficacy In Nephropathy; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; UKPDS, UK Prospective Diabetes Study.

portance, in particular in those who are at increased risk. Patients with diabetes and hypertension account for 44 and 28% of all new cases of kidney failure, respectively (2) and among patients on renal replacement therapy are those with the highest cardiovascular mortality and treatment costs (35). Therefore, to meet the Healthy People 2010 goal of reducing new cases of CKD and its complications, disability, death, and economic costs (20), efforts to increase awareness, diagnosis, and treatment of CKD are needed, in particular in those who are at increased risk and lowest adherence.

Data that were generated from clinical studies and randomized trials in developed countries have demonstrated that prevention of progression of renal disease and related complications is feasible. This justifies and should encourage future funding of research into renal diseases, because the investment is already reaping financial and health care dividends. However, this is true largely for patients in Western countries, whereas the majority of patients in developing countries do not benefit (36). Moreover, the large majority of renal patients who progress to ESRD in emerging countries do not have access to RRT. In an effort to face this situation, the Commission for the Global Advancement of Nephrology (COMGAN) of the International Society of Nephrology was established on 1993 to implement the translation of results of clinical research into clinical practice on a global basis and to provide opportunities of research also in emerging countries in which Western expertise could be applied to local problems. Indeed, in parallel with population aging, shift from an active life as farmers to a less active lifestyle that is associated with urbanization, and increased consumption of sugar and fat, the prevalence of high BP and diabetes is increasing rapidly also in these countries, where both conditions contribute in a significant way to the rising burden of global morbidity and mortality from renal and cardiovascular disease. Therefore, screening programs that use simple, cheap, and reliable tests, such as measurement of body weight, BP, blood glucose, and dipstick urinalysis for protein,

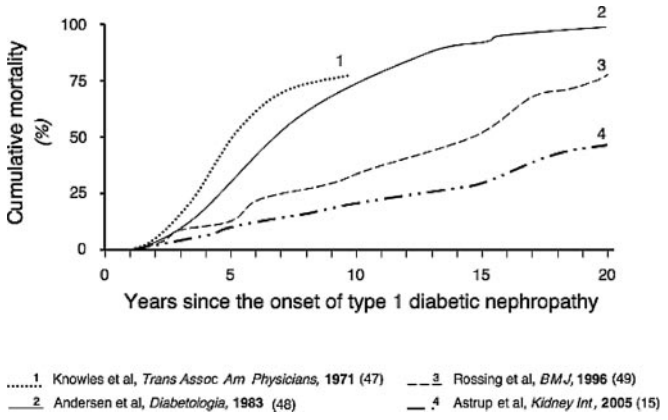

Figure 2. Cumulative death rate from the onset of overt nephropathy in different series of patients with type 1 diabetes reported since 1971. Adapted from reference (15).

should be implemented to identify early and treat those who are at risk (37–39). Quite soon, drug patents should expire for ACE inhibitors, making it feasible to implement more vigorous preventive programs even in less favorable settings. Because of the enormous social and economic costs of RRT, these interventions would be extremely cost-effective and might eventually save millions of lives.

Disclosures

None.

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