Lessons From Chronic Renal Diseases in African Americans: Treatment Implications

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End-stage renal disease (ESRD) is a significant public health problem in both developed and developing countries. The magnitude and patterns of renal disease vary among countries, differences that could be due, in part, to regional racial and ethnic composition. The United States is a typical example, with significant racial and ethnic differences in the magnitude and pattern of renal disease. Compared with Caucasians and Asians, African Americans, Native Americans, and Pacific Islanders are disproportionately afflicted with end-stage kidney failure. Whereas diabetes mellitus (primarily type 2) is the predominant cause of renal disease (and ESRD) in the United States, especially in Native Americans, hypertensive kidney disease is a major cause of ESRD in African Americans. Some of the lifestyle and physical characteristics that may be responsible for the increased incidence and prevalence of hypertensive kidney disease in African Americans include: 1) the higher prevalence and severity of hypertension, especially in the early years of life; 2) lower socioeconomic status leading to inadequate health care; 3) a greater propensity toward developing intrinsic renal vascular disease; 4) a greater tendency toward developing target organ damage at ''normal'' blood pressure levels; 5) illicit drug use; and 6) the use of medication that is less reno-protective to treat their blood pressure. (*Ethn Dis*. 2003;13[suppl2]:S2-118–S2-124)

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Introduction

End-stage renal disease (ESRD) is a major public health problem in the United States. The incidence rate has steadily increased over the past decade, from 219 per million population in 1991, to 334 in 2000 (rates adjusted for age, race, and gender). Similarly, the December 31 point prevalence rate has shown a steady increase from 806 per million population in 1991, to 1,311 in 2000 (rates adjusted for age, race, and gender). Striking racial and ethnic differences exist in the incidence and prevalence rates, as well as the causes, of ESRD. Data from the USRDS demonstrate that racial and ethnic minorities in the United States, especially African Americans and Native Americans (American Indians and Alaska Natives), have disproportionately greater incidence and prevalence rates.[1] Although most developed countries have reported steady increases in the incidence and prevalence rates of ESRD, differences exist in the rate of increase, probably resulting from racial and ethnic differences, and the pattern of diseases causing ESRD.

Since the early 1970s, diabetes mellitus has remained the leading cause of ESRD in the United States; however, it plays a relatively minor role in the causes of ESRD in Europe, Australia, and New Zealand. The US prevalence rate of diabetes for African-American men is nearly 50% greater than that for White men; for African-American women, the rate is approximately 100% greater than that for White women. Diabetes afflicts Hispanics (1.9 times that of non-Hispanic Whites) and Native American Indians (2.8 times that of non-Hispanic Whites) at an even higher rate.[2,3]

Hypertension is the second leading cause of ESRD in the United States. Although the rate of increase in the incidence rate of hypertensive ESRD has diminished over the past decade, it remains a major cause of ESRD in the African-American community. Among the US racial and ethnic groups, only African Americans have experienced a substantial increase in the prevalence of hypertension.[4,5] Mexican Americans, on the other hand, have demonstrated poorer control of hypertension (65% of that for African Americans or Whites), and this relatively poorer control may have implications for the future rates of ESRD development in this group.[6]

Materials and Methods

Data Source

Most of the data presented in this report come from the database of the United States Renal Data System (USRDS). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) established the USRDS in 1988. The majority of the data for the USRDS database is provided by the Center for Medicare and Medicaid Services (CMS), which receives the mandatory data collected by ESRD care providers. The data collection instrument is the standard form, SF2728, which defines specific information to be obtained by healthcare providers. In addition, data are collected from USRDS special studies, and have been used to enhance the original data provided by the CMS.

Statistical Analysis

Survival probabilities were estimated using age, gender, race, and cause of

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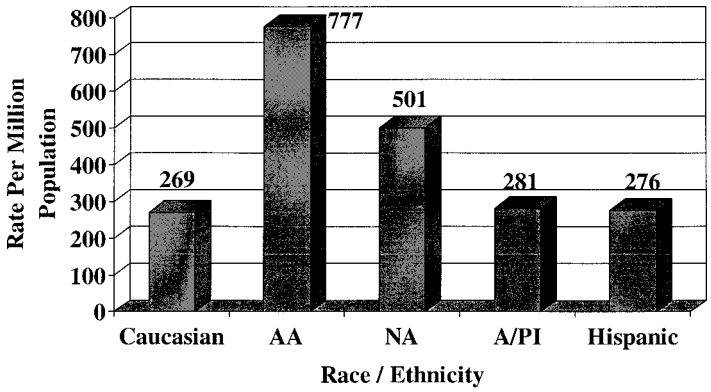

Fig 2. Incidence rate (per million population) of ESRD by race, adjusted for age and gender, 2000. AA=African Americans; NA=Native Americans; A/PI=Asian and Pacific Islanders; Hispanic=Hispanic Americans. The highest incidence rate of ESRD in the year 2000 was in African Americans. Data from the USRDS 2002 Annual Data Report

ESRD adjusted (according to the methods of Breslow et al[7]) Kaplan-Meier survival curves, starting 91 days after first treatment for ESRD, for each calendar year's incident cohort of patients.[8] The reference population was the 1997 incident cohort of ESRD patients.

Mortality rates were estimated using the person year method, in which days at risk of dying are calculated for each patient prevalent at the beginning of each of the years. Total time at risk was summed and divided by 365 to provide the number of patient years at risk. The total number of deaths observed was computed. The cause-specific death rate per 1,000 patient years at risk was estimated as the number of deaths per number of patient years at risk.

The Cox proportional hazards regression model[9] was used to estimate the independent effect of a variable on time to death. Variables in the regression model included age, race, gender, cause of ESRD, the presence of congestive heart failure, left-ventricular hypertrophy, cirrhosis, coronary artery disease, peripheral vascular disease, chronic obstructive pulmonary disease, cardiomegaly, neoplasm, active or unknown smoking status, obesity, serum albumin level, cholesterol level, and bilirubin level.

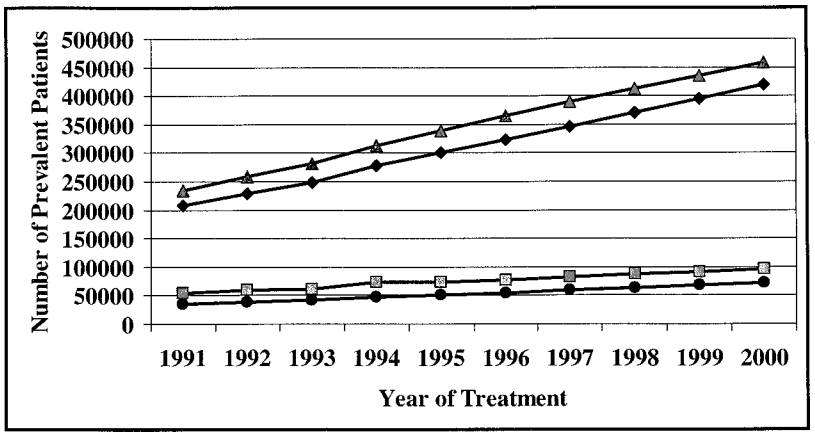

Fig 1. Time trends in the incidence, point and period prevalence, and death of ESRD patients in the US, 1991–2000. Incidence count (-□-), period prevalence count (-▲-), point prevalence count (-♦-), and death (-●-) all have shown progressive increase during the decade. Data from the USRDS 2002 Annual Data Report

RESULTS

ESRD Incidence Rates

The incidence rate of ESRD in the United States has steadily increased (exponentially) from 1991 to 2000 (Figure 1), a pattern seen for all racial and ethnic groups, all age groups, and in all disease categories. The 2 racial groups that seem most severely affected have been African Americans and Native Americans (including Alaskan Natives), and, to some extent, Hispanics. The incidence rate of ESRD in African Americans is 4 times that for Caucasians, with the rate for Native Americans being almost 3 times that for Caucasians (Figure 2).

Diabetes mellitus and hypertension cause approximately 70% of all new adult ESRD cases in the United States. Glomerulonephritis and cystic kidney diseases contribute to about 10% of the cases (Figure 3). However, other, relatively rarer diseases, such as the Human Immunodeficiency Syndrome Virus (HIV), are also important contributors to ESRD, especially in the African-American community.

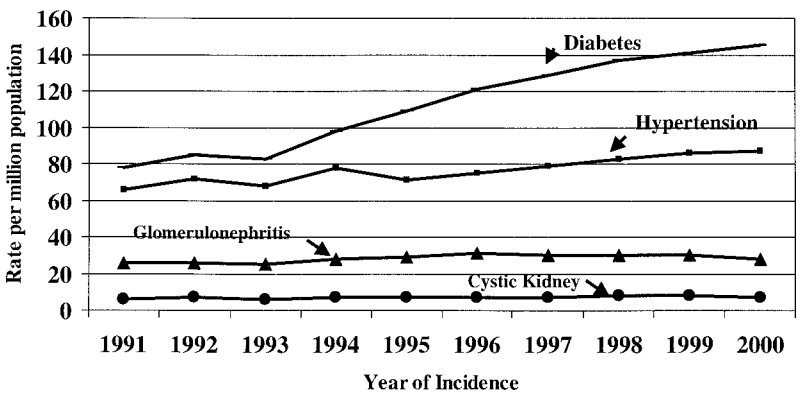

Fig 3. Time trends in the causes of ESRD, 1991–2000. The rates (per million population) are adjusted for age, gender, and race. The highest rate has been in diabetic ESRD. Data from the USRDS 2002 Annual Data Report

DIABETES MELLITUS

Diabetes mellitus is the primary cause of ESRD in all racial and ethnic groups, but at a much higher rate in Native Americans and African Americans (USRDS, 2002) (Figure 4). In African Americans, it was the second leading cause of ESRD prior to 1995. The age distribution is similar for all races, with the highest prevalence rates being in the 65–79-year age group, except for Native Americans, where the highest prevalence rate is in the 60–69-year age group. Curiously, although ESRD is unusual in children, primarily because of the time it takes the established disease to cause sufficient injury to the kidneys to progress to end-stage, diabetic ESRD has been diagnosed with increasing frequency in African-American, Native American, and Hispanic girls, and, to a lesser extent, in Caucasian children. The gender difference is not the same for all races. For Caucasians and Asians, men have a higher incidence rate of diabetic ESRD. In African Americans, American Indians, and Alaska Natives, women have a higher incidence rate.

HYPERTENSION

The incidence of hypertensive end-stage renal disease is extremely high among young African Americans, nearly 20 times the incidence for Caucasians in the 20–44-year-old group.[10] As illustrated in Figure 3, the incidence rates of hypertensive ESRD have increased steadily over the past 2 decades, but less dramatically in the last 5. This increase has occurred at the greatest rate in African Americans. Hypertension was the leading cause of ESRD prior to 1995 in African Americans, but is currently the second leading cause. In 2000, 24,566 (25.5%) of the 96,192 new cases of ESRD were reportedly caused by hypertension. During 1997–2000, the incidence rates (per million population) of hypertensive ESRD by race were 55.4 for Caucasians, 77.8 for Native Americans, 103.6 for Asians and Pacific Islanders, and 330.2 for African Americans, with a Black/White ratio of approximately 6:1 (Figure 5); the rate was higher in men for all races. Patients older than 80 years had the highest incidence rates of hypertensive ESRD.[1]

ESRD Prevalence Rates

In 2000, racial and ethnic minority groups constituted about 28% of the US population, but represented 37% of the ESRD patient population. African Americans and Native Americans have the greatest proportional representation in the ESRD patient population; while constituting only 14% of the total US population, they comprise nearly 34% of the ESRD patient population (Figure 6).

The point and period prevalence rates of ESRD have also shown a steady increase over the past decade in the United States (Figure 1). During 2000, the period prevalence, or the number of ESRD patients treated in the United States, was 458,113. The December 31 point prevalence for the year was 419,835, giving the point prevalence rate of 1,311 per million population, adjusted for age, race and gender. As was

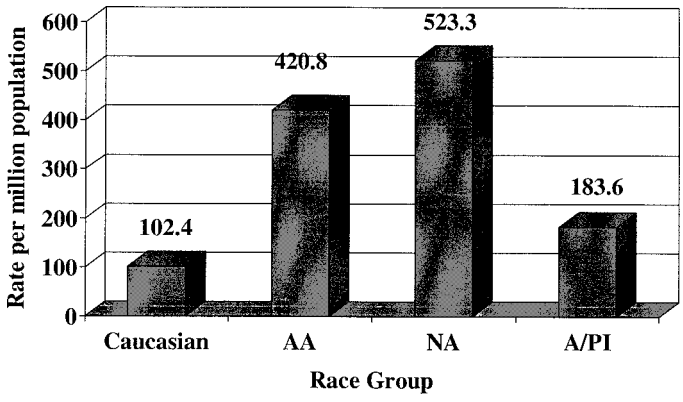

Fig 4. Incidence rate (per million population) of diabetic ESRD by race, 1997–2000; rates adjusted for age and gender. AA=African Americans; NA=Native Americans; A/PI=Asian and Pacific Islanders; Hispanic=Hispanic Americans. The highest incidence rate of diabetic ESRD in the period 1997–2000 was in Native Americans. Data from the USRDS 2002 Annual Data Report

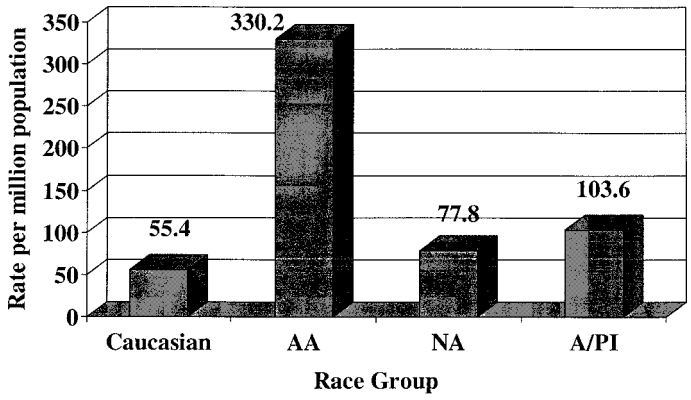

Fig 5. Incidence rate (per million population) of hypertensive ESRD by race, adjusted for age and gender, 1997–2000. AA=African Americans; NA=Native Americans; A/PI=Asian and Pacific Islanders. The highest incidence rate of hypertensive ESRD in the period 1997–2000 was in African Americans. Data from the USRDS 2002 Annual Data Report

the case with the incidence rates, in 2000, African Americans and Native Americans had the highest point prevalence rates, at 4,240 and 3,287 per million population, respectively, compared with 943 for Caucasians, and 1,623 for Asian Americans and Pacific Islanders. For the cause of ESRD category, diabetes mellitus (primarily type 2) had the highest point prevalence rate at 456 per million population, compared with 304 for hypertension, 205 for glomerulonephritis, and 57 for cystic kidney diseases. Individuals older than 65 years also had the highest prevalence rates, at more than 4,000 per million population.

Modalities of Therapy

In 2000, of the 96,192 incident patients, 83,635 (87%) received hemodialysis as the initial modality of therapy. African Americans represented 29% of the incident dialysis patient population, and 38% of the prevalent dialysis population, compared with Caucasians, who represented 63% of the incident dialysis population, and only 54% of the prevalent dialysis population.[1] The decrease in the proportion of Caucasians in the prevalent population is mainly due to their referral for renal transplantation.

The 2 predominant modes of peritoneal dialysis in the United States are chronic ambulatory peritoneal dialysis (CAPD), and continuous cycling peritoneal dialysis (CCPD). In general, there has been a gradual decrease in the use of peritoneal dialysis in the United States. A decade ago, approximately 14% of the incident ESRD patients were treated with peritoneal dialysis; however, by 2000, only 7.8% received this modality of treatment. Racial differences exist in peritoneal dialysis use, with Whites and Asian Americans being more likely to choose peritoneal dialysis, compared with African Americans and Native Americans.

A great racial and ethnic disparity remains in rates of renal allograft transplantation in the United States. Of the 49,963 kidneys transplanted between 1997 and 2000, 35,531 (71%) were transplanted in Caucasians, 11,667 (23%) in African Americans, 625 (1%) in Native Americans, and 2,130 (4%) in Asian/Pacific Islanders. In addition, 60% of the kidneys were transplanted in males. Although diabetic patients constituted 36% of the (period) prevalent ESRD patient population, only 26% of the kidneys were transplanted in diabetic ESRD patients. Living donor kidney transplants were carried out predominantly in Caucasians, with approximately 58% of these being in males.

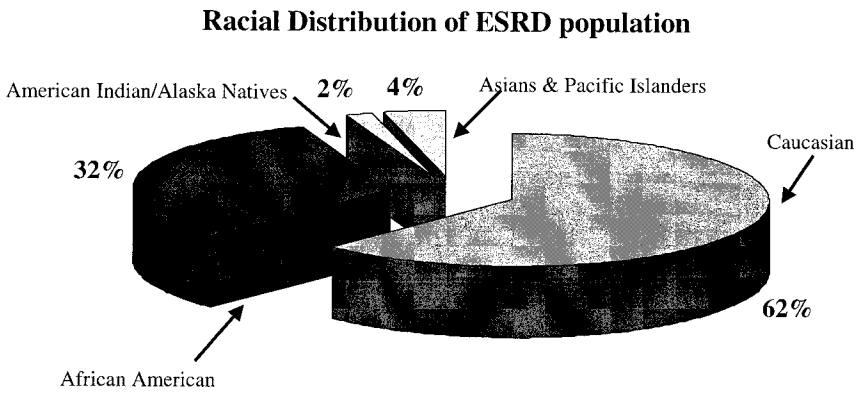

Fig 6. Racial distribution of the prevalent ESRD population in 2000. Data from the USRDS 2002 Annual Data Report

Morbidity and Mortality in ESRD Patients

Morbidity in patients treated for ESRD is defined in terms of all-cause and cause-specific hospitalization. Events such as acute myocardial infarction, and problems with vascular access, are frequent causes for hospitalization. In general, peritoneal dialysis patients spend more days in the hospital than do transplant patients. Overall, there is no significant difference between African Americans and Caucasians in the rate of first hospitalization for all ESRD patients. However, in dialysis patients, African Americans have a lower rate of first hospitalization, but spend more

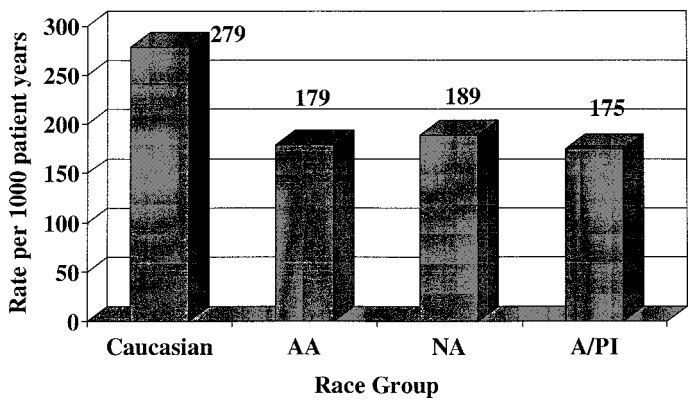

Fig 7. Death rate (per 1000 patient years) of dialysis patients by race, adjusted for age, gender and primary cause of ESRD, in 2000. AA=African Americans; NA=Native Americans; A/PI=Asian and Pacific Islanders. The highest incidence rate of hypertensive ESRD in the period 1997–2000 was in African Americans. Data from the USRDS 2002 Annual Data Report

time in the hospital when they receive renal transplants.[1]

Despite advances in dialysis technology and transplantation, long-term survival rates for ESRD patients are very low. In 2000, the annual death rate for all ESRD patients (per 1000 patient years) was 192.6 for Caucasians, 157.3 for African Americans, 155.8 for Native Americans, and 130.4 for Asians. For hemodialysis patients, the annual death rate was 284.7 for Caucasians, 181.1 for African Americans, 192.8 for Native Americans, and 179.8 for Asians[1] (Figure 7). In general, kidney transplantation is associated with better survival rates and quality of life. Although African Americans have poorer survival rates than Caucasians, irrespective of graft function, there is a substantial survival benefit when compared with patients on the waiting list or on dialysis. Diabetic ESRD patients, in general, have worse survival rates than do patients with other diseases, especially hypertension. This increased risk of death for diabetic ESRD patients is present regardless of the modality of therapy.

DISCUSSION

End-stage renal disease is a major public health problem in the United States, as well as in all developed countries. Where sufficient data are available, it is apparent that ESRD is becoming a major public health problem in developing countries, as well. Within each country, there appears to be significant differences in the patterns of renal disease among various racial and ethnic populations. In addition, the magnitude and patterns of renal disease appear to vary from country to country. The differences among the various countries may, therefore, be partly explained by the racial and ethnic mixes.

In the United States, racial and ethnic minorities, particularly African Americans and Native Americans, have significantly higher incidence and prevalence rates of renal disease, compared to Caucasians. The incidence rates of renal disease also significantly increase with advancing age. However, in racial and ethnic minorities, the median age and the mean age for the development of end-stage renal disease are lower than in Caucasians. The earlier onset and more severe renal disease in racial and ethnic minority populations may be partly explained by the lifestyle factors and lesser access to health care, compounded by lower socioeconomic status.

The causes of renal disease, especially end-stage renal disease, also differ among racial/ethnic groups. Diabetes mellitus (predominantly type 2) is the most frequently reported cause of ESRD in the United States. However, the magnitude of diabetes' contribution to ESRD varies by racial and ethnic groups. In Caucasians, the prevalence rate of diabetic ESRD is nearly double that of any other cause of ESRD. Caucasians also have the highest rate of ESRD due to type 1 diabetes mellitus. On the other hand, in Native Americans, the rate for diabetic ESRD (primarily due to type 2 diabetes mellitus) is nearly 5 times that of any other cause of ESRD.

It has been postulated that the continuing rise in the incidence of diabetic ESRD is due to a combination of increasing incidence rates of diabetes in the United States, and ineffective therapy to retard progression of diabetic renal disease in the early stages of development. The early effects of diabetes on the kidneys include microalbuminuria and hyperfiltration. Subsequently, the damage progresses to gross proteinuria and a relentless decrease in the glomerular filtration rate to end stage. Many investigators suggest that intervening early in the course of the disease would be more effective than doing so after the disease has been established.

Recently, 3 landmark studies in the nephropathy of type 2 diabetes were completed and published. One of the studies was conducted in the early phase of type 2 diabetic nephropathy, and showed that treatment with angiotensin receptor blockers (ARBs) resulted in reduction of microalbuminuria, and/or progression to gross proteinuria.[11] The other 2 clinical trials were conducted in type 2 diabetic patients with gross proteinuria and reduced glomerular filtration rate. Both studies demonstrated the effectiveness of using ARBs in the late stages to reduce, albeit not to prevent, the progression of the disease.[12,13]

It is possible to conclude that diabetic ESRD can be delayed if patients in the advanced stages of the disease are

treated with ARBs. There are also indications that treatment in the early stages of the disease with ARBs has the potential to reduce the incidence, and eventually the prevalence, of the disease.

Hypertensive kidney disease has been an important cause of ESRD in the United States and other countries. However, its contribution to the magnitude and pattern of renal disease in African Americans is significantly different from that for any other US racial/ethnic population. Although type 2 diabetes mellitus is the predominant cause of ESRD, hypertensive kidney disease has remained a major leading cause of ESRD in this group, and is present in African Americans of all ages, from the pediatric age group (uncommon in the other racial/ethnic groups), through the geriatric population.

The major reasons for the increased incidence and prevalence of hypertensive renal disease are not clearly defined. Some investigators have suggested that the magnitude of hypertensive ESRD in African Americans may be exaggerated due to misdiagnosis, since diagnosis is based primarily on clinical impression, and not usually confirmed histologically. Although this may be true in some instances, a recent study, the pilot phase of the African-American Study of Kidney Disease and Hypertension (AASK), confirmed the diagnosis. In the AASK study (pilot phase), the results of the renal biopsies performed in 50% of participants (all with the clinical diagnosis of hypertensive kidney disease) confirmed the renal histology to be almost exclusively arterio- and arteriolo-nephrosclerosis.[14,15]

Further, it is unclear whether the high incidence of hypertensive kidney disease, especially among African Americans, is a result of damage from severe essential hypertension potentiated by environmental nephrotoxins, use of illicit or prescribed drugs, or other factors.[16–19] Several other reasons have been suggested for the disproportionate presence of hypertensive renal disease in the African-American population, including the fact that this group also exhibits the highest prevalence rate of hypertension, for all ages.[20] However, the excess prevalence of hypertension does not completely explain the disproportionate prevalence of hypertensive renal disease. Some argue that because of their lower socioeconomic status, in general, African Americans are less likely to receive early and adequate medical care. Also, a greater proportion of African Americans arrive at ESRD without receiving early and adequate pre-ESRD care. However, there is no documentation that African Americans in the lower socioeconomic strata have higher incidence rates of hypertensive renal disease, compared to African Americans in the higher strata. It is also noteworthy that a significant proportion of other racial and ethnic groups in the United States, including Caucasians, arrive at ESRD with inadequate pre-ESRD care.

Two other reasons frequently suggested for the increased incidence and prevalence of hypertensive renal disease in African Americans include the level of blood pressure treatment, and the type of anti-hypertensive medication used. The normal level of blood pressure (<140/90 mm Hg), defined as the blood pressure level at which target organ damage is minimized, was established in the Caucasian population. Some investigators suggest that this level may not be appropriate for all racial groups. Indeed, a recent recommendation from a national task force suggests that African Americans with renal dysfunction should be treated to a lower level of blood pressure.[21] Secondly, certain anti-hypertensive medication groups, such as calcium channel blockers and diuretics, are more efficacious in controlling blood pressure in African Americans than are those that block the renin-angiotensin-aldosterone axis; however, the former groups have been demonstrated to be less reno-protective. Therefore, it is argued, African Americans often do not get the benefit of renal protection in hypertension treatment. The ongoing AASK clinical trial, funded by the US National Institutes of Health, was designed to address both of these issues.[22]

The AASK clinical trial has demonstrated that progression can be slowed, even in the advanced stage of the disease, by the use of angiotensin converting enzyme inhibitors (ACEI).

Until recently, we knew of no effective way to halt progression to end stage once the disease developed. However, the results of the recently completed African-American Study of Kidney Disease and Hypertension (AASK) clinical trial have demonstrated that progression can be slowed, even in the advanced stage of the disease, by the use of angiotensin converting enzyme inhibitors (ACEI). In that study, patients without significant proteinuria showed no significant worsening of the disease with adequate blood pressure control. In the presence of proteinuria, however, even at the level of 300 mg per 24 hours, the disease progresses more rapidly unless ACEI are used.[23–25] There are no reported studies on the effects of intervention in the early phases of the disease; however, some investigators suggest that treatment of hypertension in the early phases of the disease will result in prevention of ESRD. The presence of proteinuria mandates the use of ACEI.

In summary, several recent studies have demonstrated that the relentless progression of renal disease in African Americans, whether due to diabetes, hypertension, or other causes, can be slowed through the use of appropriate medications, and the effective control of blood pressure. In proteinuric renal dis-

eases, drugs that modify the renin-angiotensin-aldosterone axis, such as ACE inhibitors and angiotensin receptor blockers, can slow progression. Some investigators even speculate that the use of these drugs early in the course of renal disease may prevent progression altogether. Primary care providers for patients with renal disease, particularly African Americans, Native Americans, and other indigenous populations worldwide, should offer these patients state-of-the-art care, in order to reduce their disproportionate burden of renal disease.

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