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Hypertensive chronic kidney disease in African Americans: Strategies for improving care

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Abstract

African Americans have a disproportionate burden of chronic kidney disease (CKD), which tends to have an earlier onset and a more rapid progression in this population. Many of the factors responsible for the rapid progression of CKD in African Americans are detectable by screening and are modifiable with prompt therapy.

“Healthy citizens are the greatest asset any country can have.”

—Winston Churchill

Diabetes and high blood pressure take a toll on the kidneys, especially in African Americans. To prevent chronic kidney disease (CKD) and to slow or stop its progression, the same principles apply in African Americans as in other patients—ie, vigilance for the onset of proteinuria, aggressive control of blood pressure, drug treatment to block the renin-angiotensin system, and attention to lifestyle factors (TABLE 1). However, we need to try to do better in the care of African Americans.

The purpose of this article is to review recent evidence- and consensus-based recommendations and to present a practical approach for the evaluation and treatment of CKD in African Americans.

CKD DEFINED

In 2002, the National Kidney Foundation¹ defined CKD as either:

- Kidney damage for 3 or more months, as defined by structural or functional abnormalities of the kidney, with or without a decreased glomerular filtration rate (GFR), manifested either by pathologic abnormalities or by markers of kidney damage, including abnormalities in the composition of the blood or urine (eg, proteinuria), or abnormalities in imaging tests; or

- A GFR less than 60 mL/min/1.73 m² for 3 or more months, with or without kidney damage.

The definition divides CKD into five progressive stages according to the GFR:

- Stage 1 (kidney damage with normal or increased GFR): GFR ≥ 90 mL/min/1.73m²
- Stage 2 (kidney damage with mildly decreased GFR): GFR 60–89
- Stage 3 (moderately decreased GFR): GFR 30–59
- Stage 4 (severely decreased GFR): GFR 15–29
- Stage 5 (kidney failure): GFR < 15 or dialysis.

Because the definition includes markers of kidney damage such as albuminuria, it allows CKD to be detected in its earliest stages, when the estimated GFR might still be well within normal limits.

CKD APPEARS EARLIER, PROGRESSES FASTER IN AFRICAN AMERICANS

“Not everything that counts can be counted, and not everything that can be counted counts.”—Albert Einstein

CKD with or without a sustained reduction in the estimated GFR affects about one in every nine American adults.² Its course varies depending on the cause and also from patient to patient, even in those with the same cause of CKD.

In general, the prevalence of *early* CKD is comparable across racial and ethnic groups in the United States, but CKD progresses to end-stage renal disease far more rapidly in minority populations, with rates nearly four times higher in black Americans than in white Americans.³ Also, the onset of CKD is earlier in African Americans.

HYPERTENSION AND DIABETES AS REASONS FOR THE DISPARITIES

Part of the reason for these differences is that minority populations have higher rates of diabetes and hypertension, and these diseases tend to be more severe in these groups. Poverty, less access to health care, exposure to environmental toxins, and genetic variation may also contribute.^{4–7}

Compared with whites, blacks have higher rates of diabetes and hypertension and earlier onset of these diseases, poorer control, and higher rates of complications such as CKD, stroke, and heart disease.^{8,9} The higher rate of hypertension and the lower rate of blood pressure control in African Americans with CKD may contribute to the more rapid progression of CKD to end-stage renal disease.

In the Chronic Renal Insufficiency Cohort,¹⁰ a racially and ethnically diverse group of 3,612 adults with a broad spectrum of renal disease severity, 93% of African Americans had hypertension at baseline compared with 80% of whites. In addition, African Americans were 18% less likely to have their blood pressure controlled to 140/90 mm Hg (the rates of control were 76% vs 60%), and 28% were less likely to have it controlled to 130/80 mm Hg (56% vs 38%).¹⁰ These factors may partially explain the faster progression to end-stage renal disease in African Americans with CKD.

Despite the potential efficacy of strict control of serum glucose levels and blood pressure,¹¹ the high rate of poor blood pressure control has contributed to the epidemic of diabetic nephropathy, especially among African Americans. Fortunately, hypertension control in the general population, while still not ideal, has improved from 27% in 1988–1994 to 50% in

2007–2008 and is now similar across racial and ethnic groups.¹² This, hopefully, is a preface for improved hypertension-related outcomes for all Americans over the next decade.

OTHER REASONS FOR THE DISPARITIES

“There are no unnatural or supernatural phenomena, only a very large gap in our knowledge of what is natural.”—Edgar Mitchell, Apollo 14 astronaut

Proteinuria

Proteinuria is another key cardiorenal risk factor prevalent in African Americans.

Knight et al,¹³ analyzing data from the Third National Health and Nutrition Examination Survey, found that people with high-normal blood pressure (systolic pressure 130–139 mm Hg or diastolic pressure 85–89 mm Hg) were twice as likely to have microalbuminuria (odds ratio 2.13, 95% confidence interval [CI] 1.51–3.01) compared with people with optimal blood pressure (systolic pressure < 120 mm Hg and diastolic pressure < 80 mm Hg). Compared with whites as the reference group, Mexican Americans had slightly but not statistically significantly higher odds of microalbuminuria (odds ratio 1.16; 95% CI 0.90–1.51), and African Americans had significantly higher odds (odds ratio 1.30; 95% CI 1.04–1.64).

The incidence of hypertension-related end-stage renal disease is nearly five times higher in African Americans than in whites, and the rate of hypertension-related end-stage renal disease is 15 times higher in African American men ages 24 to 44 than in whites of the same ages.³ The greater risk of proteinuria in African Americans at any given level of higher blood pressure is thought to contribute in part to these disparate rates.

The renin-angiotensin system

The renin-angiotensin system plays a role in modulating hypertension and mediating hypertension-related complications. Hypertensive African Americans are more likely than hypertensive whites to have low-renin, salt-sensitive hypertension. Therein lies a paradox.

Since the renin-angiotensin system promotes the progression of CKD, we would expect patients with low-renin hypertension to have a lower risk of hypertension-related end-organ damage than patients with high-renin hypertension. However, many African Americans (who as a group have high rates of sodium sensitivity and low plasma renin levels) experience more severe hypertension-related end-organ complications such as proteinuria and cardiorenal disease.¹⁴

A reason for this paradox may be that the circulating renin-angiotensin system is separate from the intrarenal one. Supporting this theory is the observation that up-regulation of the intrarenal renin-angiotensin system accompanies renal interstitial inflammation and oxidative stress in the kidneys and cardiovascular tissues of salt-sensitive rats fed a high-salt diet.¹⁵ In other experiments in salt-sensitive rats, renin-angiotensin system blockade reversed endothelial dysfunction, attenuated proteinuria, and reduced renal injury independent of blood pressure changes even though the animals had low circulating renin levels.¹⁶

These findings imply that drugs that block the renin-angiotensin system, ie, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, could still be a rational therapy for CKD patients with low-renin hypertension, particularly African Americans, in whom local up-regulation of the renin-angiotensin system in the kidney could exacerbate both diabetic and hypertensive CKD.¹⁷ Although these drugs may not lower blood pressure

as much in low-renin hypertension as in high-renin hypertension, they may still afford the same cardiorenal protection.

Genetic factors

Variations in the *MYH9* and *APOL1* genes on chromosome 22 have recently been found in genome-wide admixture mapping studies and may explain as much as 70% of the differences in the rates of nondiabetic end-stage renal disease between white and black Americans.^{7,18,19} In addition, genetic variations may modulate differences in blood-pressure response to antihypertensive medications across racial and ethnic groups,²⁰ complicating treatment recommendations and clinical outcomes in our increasingly diverse nation.

Comment—The pathophysiologic basis for the variability in the course of CKD is probably multifactorial and is still poorly understood. Nevertheless, we may be able to delay the progression of CKD and prevent its complications with specific therapeutic and lifestyle interventions.

Race and ethnicity are associated with sociocultural and biologic variations that influence the risk and progression of CKD. Understanding these factors for minority populations can help in targeting interventions to attenuate the disproportionately high rates of CKD progression and complications.

The pathophysiologic reason African Americans have a greater prevalence of end-stage renal disease and a more rapid progression of CKD is complex and probably involves the interplay of biological, behavioral, and environmental factors such as salt intake, stress levels, and exposure to heavy metals.²¹

TRIALS OF ANTIHYPERTENSIVE THERAPY IN AFRICAN AMERICANS WITH CKD

“If we knew what we were doing, it wouldn’t be called research.”—Albert Einstein

Until recently, trials of antihypertensive therapy in patients with CKD did not include adequate numbers of African American participants, but the following clinical trials have added to our knowledge (TABLE 2).^{22–26}

African American Study of Kidney Disease and Hypertension (AASK)

The African American Study of Kidney Disease and Hypertension (AASK),^{22,23} with 1,094 patients, was the largest prospective study of CKD to date designed to focus on African Americans.

AASK examined the effects of two levels of blood-pressure control:

- Standard, with a goal blood pressure of 135–140/85–90 mm Hg (mean arterial pressure 102–107 mm Hg)
- Intensive, with a goal of 120/80 mm Hg or less (mean arterial pressure 92 mm Hg).

In a two-by-two factorial design, patients were also randomized to receive one of three antihypertensive drugs as initial therapy:

- The ACE inhibitor ramipril (Altace)
- The sustained-release beta-blocker metoprolol succinate (Toprol XL)
- The calcium channel blocker amlodipine (Norvasc).

To enter the study, patients had to be African American, have at least one diastolic pressure reading of 95 mm Hg or greater during the screening period, and have a measured GFR between 20 and 65 mL/min/1.83 m². They could not have diabetes, substantial proteinuria (> 2.5 g/day), or other causes of CKD.²²

AASK was distinct from many of the larger hypertension trials in which secondary analyses of outcomes in patients with CKD were performed in that it was implicit in the design that most, if not all, study participants had substantial GFR reduction and would need diuretic therapy.

At baseline, after blood pressure medications had been tapered to define eligibility and then reintroduced before randomization, 20.0% of the patients in the intensive blood pressure goal group had pressure lower than 140/90 mm Hg, and this increased to 78.9% by 14 months after randomization. In the standard goal group, the numbers were 21.5% at baseline but only 41.8% at 14 months.²³ In spite of this difference, the rate of decline in GFR (the main clinical outcome measure) was the same in both groups.

However, the class of drug did make a difference. Secondary clinical outcomes, including the composite end point of development of end-stage renal disease, doubling of serum creatinine, or death, were less frequent in the ACE inhibitor group than in the beta-blocker and calcium channel blocker groups. As anticipated and consistent with real world practice, nearly 90% of all participants received concomitant diuretic therapy to achieve target blood pressure levels.

Comments—AASK showed that blood pressure can be controlled in African Americans who have CKD and that clinical cardiorenal outcomes can be improved by using an ACE inhibitor as initial therapy rather than a beta-blocker or calcium channel blocker, with diuretics and other agents added as needed.

AASK cohort phase

After completing the trial phase, patients were invited to enroll in a cohort phase in which the blood pressure target was less than 130/80 mm Hg. The combined follow-up period was 8.8 to 12.2 years.²⁴

During the trial phase, the mean blood pressure was 130/78 mm Hg in the intensive group and 141/86 mm Hg in the standard group. During the cohort phase, the mean blood pressures were 131/78 mm Hg and 134/78 mm Hg, respectively, in these groups.

In both phases, there was no significant difference between groups in clinical outcomes (hazard ratio in the intensive-control group 0.91, $P = .27$). However, the groups differed when stratified by baseline level of proteinuria ($P = .02$ for the interaction), with a potential benefit of a blood pressure target lower than 130/80 mm Hg in patients with a protein-to-creatinine ratio of more than 0.22 (hazard ratio 0.73, $P = .01$).²⁴

Comment—Given that many African Americans with hypertension and CKD have a protein-to-creatinine ratio of more than 0.22, these findings support a practical approach in clinical practice for a target blood pressure less than 130/80 mm Hg, using a first-line combination of a renin-angiotensin system inhibitor and a diuretic.

RENAAL study

The Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL) study²⁵ included 1,513 patients, of whom 15% were African American and 18% were Hispanic; all had type 2 diabetes mellitus and nephropathy. They were randomized to

receive the angiotensin II receptor antagonist losartan (Cozaar) or placebo in addition to other antihypertensive drugs.

At 3.4 years, the blood pressure was about 141/74 mm Hg in both groups. A post hoc analysis found lower rates of albuminuria and end-stage renal disease in the group treated with losartan,²⁵ with no racial or ethnic differences in its renoprotective effect.

Comments—While these findings support the recommendation of inhibiting the renin-angiotensin system for improving clinical outcomes in diabetic nephropathy in racial and ethnic minorities, the AASK study also proved a second important point. These patients required intense blood pressure management for several years in a clinical trial environment, which may be difficult to do in many clinical practice models.

To be cost-effective in today's health care environment, such care will likely be limited to larger group practices or health care plans with large comprehensive covered populations. Payers and providers need to be willing to invest in intense early care in such high-risk subgroups with the understanding that they could recognize downstream gains from long-term improved outcomes. However, even in these settings, the ability to provide effective care to high-risk subgroups without generating significant financial losses remains a concern.

ALLHAT

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)²⁶ enrolled more than 33,000 hypertensive patients at high risk, of whom 32% were black, 16% were Hispanic, and 36% had diabetes. Their mean serum creatinine level was 1 mg/dL. Follow-up was for up to 8 years. At year 5, the mean blood pressure was 135/75 mm Hg.

In a secondary analysis, patients were stratified by GFR:

- Normal (> 90 mL/min/1.73 m²; n = 8,126)
- Mild reduction (60–89 mL/min/1.73 m²; n = 18,109)
- Moderate-severe reduction (< 60 mL/min/1.73 m²; n = 5,662).

In all three groups, amlodipine, lisinopril (Zestril), and chlorthalidone were equivalent as initial monotherapy in reducing the rate of the composite end point of end-stage renal disease or 50% or greater decrement in GFR.

Comments—The combined AASK, RENAAL, and ALLHAT findings are consistent with the practical recommendation of a diuretic, renin-angiotensin system inhibitor, or both, as initial therapy for blood pressure control in African American patients who have CKD, with a target blood pressure of less than 130/80 mm Hg.

A COMPREHENSIVE APPROACH TO CHRONIC KIDNEY DISEASE CARE

“It is much more important to know what sort of a patient has a disease, than what sort of disease a patient has.”—William Osler

Many of the risk factors for cardiovascular disease in African Americans are behavioral and modifiable. These include too much salt and fat in the diet, too little physical activity, excessive alcohol intake, and smoking.

Education is key, to identify and communicate the risk attributable to health beliefs and behaviors, particularly in patients with known cardiovascular disease, and to encourage the

patient to be proactive in risk-reduction strategies (TABLE 1). However, effective communication depends on compassion and concern by the health care provider to engender a sense of trust.²⁷ Other health care professionals such as dietitians, pharmacists, and social workers as well as family members can reinforce messages and improve communication with the patient to optimize outcomes.

The International Society on Hypertension in Blacks recommends a blood pressure target of less than 130/80 mm Hg in blacks with elevated blood pressure and target-organ damage. The authors suggest monotherapy with a diuretic or calcium channel blocker if the blood pressure is 10 mm Hg or less above target levels. When blood pressure is more than 15/10 mm Hg above target, two-drug therapy is recommended, either with a calcium channel blocker plus a renin-angiotensin system blocker or, alternatively, in edematous or volume-overload states, with a thiazide diuretic plus a renin-angiotensin system blocker.^{28,29}

The Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative recommend starting anti-hypertensive therapy with an ACE inhibitor or an angiotensin receptor blocker for most patients with CKD, regardless of ethnicity, recognizing that many will require combination therapy.³⁰ Evaluation of the response to therapy should include not only checking that the blood pressure is at or below the recommended target of 130/80 mm Hg, but also assessing for complications and monitoring the change in the level of proteinuria, which is a powerful predictor of progression of hypertensive kidney disease in all patients at any given GFR.³¹

OUR RECOMMENDATIONS

African Americans with hypertension and kidney disease require an aggressive and comprehensive approach to slow the progression of kidney disease and its complications, often necessitating aggressive care of the primary cause and the use of two or more antihypertensive agents to control blood pressure, proteinuria, or both (FIGURE 1).³²

We recommend that the initial evaluation of patients with hypertension include a screening for albuminuria and that the initial therapy for hypertension or proteinuria in all patients with CKD include renin-angiotensin system inhibition with a diuretic, because this combination appears most effective to achieve blood pressure control and to confer additional cardiorenal protection beyond that offered by blood-pressure control alone. Although some studies have reported that African Americans have lower blood-pressure response rates than whites to renin-angiotensin system inhibition,¹⁸ it is nevertheless beneficial for clinical outcomes in this group, especially in the presence of proteinuria, a hallmark of hypertension-related CKD in African Americans. Thus, until more data are available, ethnicity should not be the primary criterion for selecting a given class of antihypertensive therapy, especially in patients with hypertensive nephropathy.

The overall treatment decision should be guided by individual response, coexisting risk factors, and potential cultural and socioeconomic considerations such as cost of medications and insurance coverage, which affect adherence to both pharmacologic and non-pharmacologic interventions.³³

Future studies should strive for adequate representation of racial and ethnic minority populations in order to enhance the evidence base for CKD treatment as we move toward using personalized medicine approaches in an increasingly diverse society.³⁴

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KEY POINTS

- To provide optimal care for African Americans, we need to be sensitive to factors that may pose barriers to care, such as poverty, unemployment, lack of insurance, low education level, lack of family support, inaccurate health beliefs, and unhealthy behaviors.
- If we detect CKD earlier, we can better implement strategies to prevent its progression, refer the patient to specialists, and possibly arrange for preemptive kidney transplantation if needed.
- Progression of CKD can be prevented or slowed by controlling blood pressure, proteinuria, and blood glucose. However, CKD progresses in a subset of patients despite evidence-based therapy to target goals.
- African Americans with hypertensive CKD and proteinuria should receive a diuretic, a renin-angiotensin system inhibitor, or both as initial therapy, with a target blood pressure of less than 130/80 mm Hg.

Algorithm for hypertension treatment in African Americans with chronic kidney disease

Systolic pressure 130–150 mm Hg or diastolic pressure 80–95 mm Hg

Initiate lifestyle intervention
Consider diuretic, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (beta-blocker or calcium channel blocker as second line)
Confirm primary diagnosis
Recognize and honor cultural values
Initiate support systems
Consider environment, eg, toxins, psychosocial stresses, subclinical inflammation

Systolic pressure > 150 mm Hg or diastolic pressure > 95 mm Hg

Initiate two drugs for most patients, diuretic and ACE inhibitor or angiotensin receptor blocker (beta-blocker or calcium channel blocker as second line)
Initiate lifestyle intervention
Continue education, communication, building trust
Assess and treat for other risk factors for chronic kidney disease and cardiovascular disease (eg, normalize hemoglobin A_{1c}, possibly start a statin, aspirin)

Not at goal blood pressure

Assess adherence to sodium restriction and medication
Consider 24-hour urine sodium collection
Loop diuretic if estimated glomerular filtration rate < 30 mL/min (may need two or three doses per day)
Exclude barriers to care (eg, side effects, costs, sociocultural conflicts with recommendations)
Add antihypertensive drugs based on cardiovascular risk factors (eg, proteinuria) and coexisting medical conditions (anemia, erythropoietin therapy, secondary hyperparathyroidism)

Still not at goal blood pressure

Optimize dosages or add additional drugs until goal blood pressure is achieved
Consider consultation with a hypertension specialist

Figure 1.

Algorithm for hypertension treatment in African Americans with chronic kidney disease

TABLE 1

Frequently asked questions about hypertension and chronic kidney disease in African Americans

What are the main risk factors for chronic kidney disease?

Diabetes accounts for nearly half and hypertension for nearly a third of the new cases of kidney failure among African Americans. High rates of low socioeconomic status, low health literacy, being underinsured or uninsured, and lack of awareness of risk factors also contribute to the increased risk. A unique genetic variation, originally linked to the *MYH9* gene and now attributed to the *APOL1* gene, is highly associated with the rapid progression of nondiabetic end-stage renal disease in African Americans.

What are some of the key lifestyle changes to optimize blood pressure and blood sugar control and preserve renal function?

- Eat a healthy diet
- Increase physical activity as part of the daily routine by undertaking an enjoyable physical activity for 30–45 minutes per day, 3–5 days per week
- Maintain weight by making permanent changes in the daily diet
- Develop coping skills for specific stressors in work and home environments with meditation, relaxation, yoga, biofeedback
- Ensure a smoke-free environment.

What are some of the key approaches to achieve healthy dietary changes?

Consider culturally appropriate nutritional substitutions:

- Eat fewer processed foods, fast foods, and fried foods
- Limit seasoning of foods with smoked meats, such as bacon and ham hocks
- If lactose intolerant, try lactose-free milk or yogurt, or drink calcium-fortified juices or soy milk
- Limit alcohol consumption to less than 2 beers, 1 glass of wine, or 1 shot of hard liquor per day
- Limit the intake of sugar-sweetened beverages and juices.

When should antihypertensive drug therapy be initiated?

With persistent blood pressure > 130/80 mm Hg in spite of therapeutic lifestyle changes. The duration of therapeutic lifestyle changes before starting pharmacotherapy depends on the level of blood pressure and the comorbidities. Most patients will require two or more medications to achieve this treatment goal.

Which drugs are effective for controlling blood pressure?

- Diuretics (loop diuretics if the estimated glomerular filtration rate is < 30 mL/min)
- Renin-angiotensin system inhibitors
- Calcium channel blockers
- Centrally acting sympatholytic agents
- Direct vasodilators.

What is a practical approach for treating high blood pressure?

- The target blood pressure should be < 130/80 mm Hg; expect to use two or more agents to achieve this goal
- Therapy should include an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and a diuretic
- If hypertension is refractory to therapy, evaluate potential sociocultural barriers, consider secondary causes, and assess adherence to medication and sodium restriction (consider 24-hour urine sodium collection)
- Diuretics should be a thiazide-type if the estimated glomerular filtration rate is greater than 30 mL/min, and a loop diuretic (usually given two or three times a day) if the estimated filtration rate is less than 30 mL/min.

Is blood-pressure response to antihypertensive therapy different in African Americans?

African Americans exhibit lesser blood pressure reductions on monotherapy with renin-angiotensin system inhibition compared with whites, but there are no differences in the cardiorenal benefits of renin-angiotensin system inhibition across racial or ethnic categories.

Is there evidence of ethnic differences in clinical outcomes based on antihypertensive treatment regimens in people with renal disease?

No clinically relevant ethnic differences in outcomes have been noted in patients with hypertension and chronic kidney disease following most randomized, controlled, evidence-based pharmacologic interventions for blood-pressure control. However, the paucity of data with adequate numbers of African American study participants reinforces the need to achieve greater ethnic diversity in clinical trials.

TABLE 2**Results of clinical trials of treating chronic kidney disease in African Americans****African American Study of Kidney Disease and Hypertension (AASK)^{22,23}**

An angiotensin-converting enzyme (ACE) inhibitor as initial therapy led to better clinical outcomes (lower rates of end-stage renal disease, doubling of serum creatinine, or death) than beta-blocker or calcium channel blocker therapy

Blood pressure can be controlled in African Americans with chronic kidney disease, usually with two or three drugs, including a diuretic

Intensive blood pressure control (<120/80 vs standard: ~135–140/85–90 mm Hg) led to no change in clinical outcomes but did lead to a reduction in urinary protein excretion

AASK Cohort²⁴

A blood pressure target of less than 130/80 mm Hg was beneficial in patients with a urinary protein-to-creatinine ratio of more than 0.22 (protein > 300 mg/day; estimated to be present in > 95% of African Americans)

Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL)²⁵

No racial or ethnic differences were noted in the renoprotective effect of an angiotensin receptor blocker, as assessed by albuminuria and development of end-stage renal disease in patients with diabetes and elevated blood pressure

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)²⁶

Secondary analysis of patients with reduced glomerular filtration rates found amlodipine (Norvasc), lisinopril (Zestril), and chlorthalidone as initial monotherapy were equivalent in preventing progression of kidney disease (mean achieved blood pressure < 135/75 mm Hg)