Relative Effects of Angiotensin Converting Enzyme Inhibitors and Calcium Antagonists in Advanced Diabetic Nephropathy

Errol D. Crook, MD; Dean C. Preddie, MD

Objective: We have previously observed that calcium antagonists (CA) were associated with poorer renal survival in African Americans (AA) with diabetic nephropathy (DN). Here, we investigate further the effects of CA alone, or in combination with angiotensin converting enzyme inhibitors (ACEI) in advanced DN.

Design: Retrospective study

Setting: Academic nephrology clinic

Patients: 1) Patients who entered the end-stage renal disease (ESRD) program in years 1993–1998 with a primary diagnosis of DN. 2) A cross-sectional analysis of pre-ESRD patients with DN, first seen in the clinic in 1996, then followed until 2000. Over 80% of patients were AA, and ~ 75% were female in both cohorts.

Interventions: Patients were categorized according to whether they were on either an ACEI or a CA, alone, or a combination of these, at presentation to the clinic, and during follow up.

Main Outcome Measures: Renal survival (time to ESRD) and effects on blood pressure

Results: In both data sets, patients presented with advanced renal disease. Those on CA tended to have lower blood pressure on presentation, and during follow up, and were more likely to experience a significant decrease in blood pressure over the course of follow up. Using a Cox proportional hazards model, ACEI–CA status was not found to be significantly associated with renal survival.

Conclusions: Calcium antagonists (CA) are effective at lowering blood pressure in advanced DN, and do not appear to negatively affect renal survival, especially when combined with an ACEI. (*Ethn Dis*. 2004;14:87–93)

Key Words: Diabetic Nephropathy, Calcium Channel Blocker, Angiotensin Converting Enzyme Inhibitor, Hypertension, Renal Survival, African American

From the Department of Medicine, Wayne State University School of Medicine and the John D. Dingell VA Medical Center, Detroit, Michigan.

Address correspondence and reprint requests to Errol D. Crook, MD; Harper University Hospital, 2 Hudson; 3990 John R.; Detroit, MI 48201; 313-745-8334; 313-745-0586 (fax); ecrook@dmc.org

Introduction

Diabetic nephropathy (DN) is currently the leading cause of end stage renal disease (ESRD) in the United States.[1] Studies among diabetics with DN have demonstrated that blood pressure control is the most important determinant in the rate of kidney disease progression in this population.[2–5] Among antihypertensive agents, clinical trials generally support a favorable effect of renin angiotensin system (RAS) blockade on proteinuria and progression of DN.[6–8] However, there has been some concern regarding the role of calcium channel antagonists (CA) in patients with DN, and in those with non-diabetic renal disease with proteinuria.[8,9] In addition, some debate has occurred regarding the relative effects of angiotensin converting enzyme inhibitors (ACEI) and CA on cardiovascular disease (CVD) in diabetic patients.[10,11]

To achieve recommended blood pressure goals, most patients with DN require treatment with several blood pressure-lowering agents, such as CA, the effects of which have been proven previously.[2,12] We have observed previously that African Americans (AA) with advanced DN who are taking a CA tended to have poorer rates of renal survival, compared to those who were not on CA.[13] In this analysis, we have investigated the relative effects of ACEI and CA, alone, or in combination, on renal survival in 2 cohorts of predominantly AA diabetics with severe renal disease. We hypothesized that any deleterious effects of CA on renal survival would be ameliorated by the presence of an ACEI, and that the combination of ACEI and CA would be equally efficacious as, if not better than, an ACEI or CA, alone.

Materials and Methods

We performed additional analysis of 2 previously obtained data sets. The first was a retrospective chart review of patients entering the end-stage renal disease (ESRD) program through the nephrology clinic at the University of Mississippi Medical Center from 1993–1998.[13] Charts from 171 patients with DN as their primary ESRD diagnosis were reviewed, and data on basic demographics, blood pressure, renal function, and blood pressure medications were collected at the time of presentation to the renal clinic. For those with at least one blood pressure measurement at $\geq$3 months of follow up, the mean arterial blood pressure (MAP) over follow up was determined. For purposes of this analysis, patients were categorized according to whether they were on an ACEI and/or a CA on presentation to the renal clinic, and during the follow-up period. A small number of patients on angiotensin receptor blockers (ARBs) ($<$ 10) were included in the ACEI group. The categories were as follows: ACEI (ACEI, alone), CA (CA, alone), ACEI/CA (ACEI and CA combined), or neither (neither agent present). Blood pressure response is the difference between MAP on presentation and mean follow-up MAP. Blood pressure responders were defined as those who, over the course of follow up, had a decrease from initial MAP of 8 mm Hg (roughly 12–15 mm Hg systolic and 4–6 mm Hg diastolic). Blood pressure was

We have observed previously that African Americans (AA) with advanced DN who are taking a CA tended to have poorer rates of renal survival, compared to those who were not on CA.[13]

usually taken by a clinic nurse, with the patient sitting in a chair for 3–5 minutes with either an auscultatory or automated sphygmomanometer.

The second data set was from a cross-sectional analysis performed to address the bias inherent in an ESRD population.[14] The charts of 119 pre-ESRD diabetic nephropathy (DN) patients seen in the University of Mississippi Medical Center renal clinic in 1996 were reviewed in 2000. Data was extracted, and patients were grouped according to presenting and follow-up ACEI–CA status, as described above.

Statistical Analysis

Data was entered into STATVIEW (Abacus®) for analysis. Differences between groups were compared by *t* test and chi-square test. The effects of ACEI–CA status on blood pressure, likelihood of lowering MAP by 8 mm Hg (BP responder), and renal survival, were examined at presentation and follow up. Renal survival was defined as the time from the first clinic visit to the initiation of dialysis (time to ESRD [**TTE**]). In the cross-sectional study, the change in level of the inverse creatinine at each year of follow up was also used as a measure of renal survival. For effects on renal survival, univariate proportional hazards regression (Cox model) was performed. For this analysis, the 4 ACEI–CA groups were examined as individual variables, and as a group variable. In those cases where ACEI–CA status was significantly associated with renal survival, a multivariate analysis was performed. The multivariate analysis included factors previously found to be significantly associated with renal survival. For the ESRD data set this included creatinine levels, race, starting ACEI during follow up, and follow-up MAP $<$100 mm Hg.[13] For the cross-sectional analysis, this included age, levels of creatinine and proteinuria, and follow-up MAP $<$100 mm Hg.[14] A P value of $<.05$ was considered significant.

RESULTS

The ESRD data set comprised 171 patients who were predominantly female (75.4%), AA (83.0%), hypertensive, obese, and exhibited severe renal compromise at presentation. The characteristics of the patients by presenting ACEI–CA group are shown in Table 1. Slightly more than 40% of patients were on an ACEI, alone, and 43.2% were on a CA, alone, at presentation. Table 2 gives similar information by follow-up ACEI–CA status. Patients who were on neither agent at presentation, or during follow up, had the highest levels of creatinine at presentation, and the shortest TTE.

The number of those in the ACEI/CA group during follow up increased significantly when compared to the number at presentation ($P<.001$ by χ^2). Twenty-eight of the 49 presenting on CA, alone, had an ACEI added to their regimen. Those with higher levels of creatinine at presentation were least likely to be placed on an ACEI (Table 2). A noteworthy finding was that a lower percentage of Whites were likely to be on CA, alone, at presentation (4 of 28), or during follow up (0 of 28), as compared to AA ($P=.044$ by χ^2 for follow up). Patients with CA in their regimen had lower blood pressure levels at presentation, and tended to have lower MAPs over follow up. A patient's status as a BP responder was not predicted by follow-up ACEI–CA status, gender, or race. However, those presenting on a CA (with or without ACEI) were more likely to be BP responders (25 of 62 on CA at presentation were BP responders vs 12 of 70 not on CA at presentation, $P=.0037$ by χ^2). The effects of CA on blood pressure did not differ by subtype (dihydropyridine vs nondihydropyridine).

The cross-sectional data set (Tables 3 and 4) comprised 119 patients. The demographics at presentation to the clinic were similar to those in the ESRD data set, except that the initial levels of serum creatinine were lower. Again, those presenting on a CA tended to have lower presenting and follow-up blood pressure levels compared to those on ACEI, alone. Those in the group taking neither medication tended to have more advanced renal disease, with shorter TTE despite having the lowest blood pressure levels of any group. Neither race, gender, nor type of blood pressure-lowering agent, predicted whether a patient would be a BP responder.

We examined the effects of presenting and follow-up ACEI–CA status on renal survival. The presenting ACEI–CA status was not significantly associated with renal survival in either data set (not shown). Table 5 shows the associations of follow-up ACEI–CA status with renal survival, after univariate analysis. In general, taking an ACEI, alone, was most often significantly associated with improved renal survival, but this group also tended to have lower levels of creatinine. On multivariate analysis, follow-up ACEI–CA status was not significantly associated with renal survival. However, in contrast to previous analysis,[13,14] inclusion of follow-up ACEI–CA status in the multivariate model resulted in follow-up MAP $\leq$100 mm Hg continuing to be a significant negative predictor of TTE (ESRD data set: hazard ratio 2.23 [CI: 1.1–4.4, $P=.023$]; cross-sectional: hazard ratio 3.2 [CI: 1.4–6.9,

Table 1. Baseline characteristics of patients in ESRD dataset*

Characteristic	ACEI	CA	ACEI/CA	Neither	*P*<.05†
N	43	49	26	53	
Age (years)	52.1 (2.0)	53.7 (2.1)	56.1 (3.0)	54.7 (1.4)	
Gender (M/F)	14/29	7/42	6/20	15/38	
# AA	34	45	18	45	
SBP (mm Hg)	172.6 (4.5)	157.8 (3.3)	146.2 (7.1)	163.9 (4.2)	1, 2, 6
DBP (mm Hg)	92.5 (2.6)	85.2 (2.1)	82.6 (3.5)	87.2 (2.0)	1, 2
Creatinine (mg/dL)	5.2 (3.3)	5.9 (4.0)	5.8 (0.8)	6.5 (0.5)	
BMI	33.0 (1.4)	32.3 (1.3)	33.6 (2.2)	30.1 (1.0)	
Duration of DM (yr)	16.2 (1.1)	17.5 (1.2)	19.8 (2.2)	15.5 (1.1)	6
24 hr urine protein (gm)	7.3 (0.7)	6.6 (1.4)	7.1 (2.3)	4.3 (0.6)	3
TTE (weeks)	62.5 (10.5)	54.7 (8.0)	44.4 (7.6)	72.1 (11.4)	
# BP meds on presentation	1.63 (.12)	2.22 (.12)	2.96 (.18)	.740 (.13)	1, 2, 3, 4, 5, 6

* Values are means ± standard deviation (SD).
† Statistical comparisons: 1=ACEI vs CA; 2=ACE vs ACEI/CA; 3=ACEI vs neither 4=CA vs ACEI/CA; 5=CA vs neither; 6=ACEI/CA vs neither.
SBP=systolic blood pressure; DBP=diastolic blood pressure; BMI=body mass index (kg/m^2); TTE=time to ESRD.

P=.004]). As observed previously, initial levels of serum creatinine remained the strongest predictor of renal survival, on multivariate analysis of both data sets (not shown).

DISCUSSION

The importance of blood pressure control in decreasing the progression of DN, the leading cause of ESRD in the United States, is well established, and has been demonstrated using several different classes of blood pressure-lowering agents.[2,8] Inhibition of the RAS is important in preserving renal function in diabetic and non-diabetic patients with proteinuria, or reduced glomerular filtration rate.[2,6–9] While the beneficial effects of RAS inhibitors in DN are widely accepted, there have been concerns regarding the role of CA in patients with DN or proteinuria. Recently, 2 large trials have demonstrated that RAS inhibition is superior to CA in patients with diabetic and non-diabetic renal disease.[8,9] The results of these trials support the recommendation that RAS inhibitors should be first-line agents for the treatment of hypertension in patients with renal disease. However, these results have led many practitioners to question whether CA should be used at all in this population.

Most patients with significant renal risk factors, such as proteinuria, hypertension, diabetes, and reduced GFR, require multiple medications for control of blood pressure.[2] Calcium antagonists (CA) are effective blood pressure-lowering agents in this high-risk group of patients and are, therefore, often necessary to achieve recommended blood pressure goals. In this study, we investigated the effects of ACEI and CA, alone, or in combination, in 2 predominantly African-American data sets with DN and advanced renal insufficiency.

Calcium antagonists (CA) and ACEI were used in <50% of patients at the time of their presentation to the nephrology clinic, despite the presence of significantly elevated blood pressure. The infrequent use of ACEI is probably secondary to the advanced disease seen in these patients. In addition, at the

Table 2. Characteristics of patients in ESRD dataset by follow-up ACEI-CA status*

	ACEI	CA	ACEI/CA	Neither	*P*<.05†
N	48	26	68	29	
Age (years)	51.6 (1.8)	57.0 (2.8)	53.4 (1.8)	56.6 (2.1)	
# AA	40	26	53	23	
Initial creatinine (mg/dL)	4.9 (0.5)	7.9 (0.9)	5.0 (0.4)	7.89 (0.6)	1, 3, 4, 6
TTE (weeks)	78.1 (12.0)	41.6 (11.3)	63.9 (7.1)	36.2 (9.9)	3, 6
# with ≥3 months follow-up	38	18	62	15	
MAP on follow-up (mm Hg) (*N* = 133)	114.8 (2.3)	110.0 (3.3)	112.0 (1.6)	109.3 (2.8)	
BP response (mm Hg)	1.2 (2.4)	−2.1 (4.3)	−2.3 (2.3)	4.9 (3.3)	
BP responder (*N*)‡	8	6	21	3	

* Values are means ± SD.
† Comparisons between groups are as per Table 1.
‡ BP responders achieved a decrease in MAP of 8 mm Hg when comparing mean follow-up MAP to initial MAP.
MAP=mean arterial pressure, other abbreviations are as per text and Table 1.

Table 3. Characteristics of patients in cross-sectional dataset by presenting ACEI-CA status*

	ACEI	CA	ACEI/CA	Neither	$P<.05$†
Age (years)	31	30	21	37	
Male/female	54.4 ± 2.4	55.8 ± 2.1	58.5 ± 2.4	55.0 ± 1.8	
# AA	25	25	18	30	
SBP mm Hg	163.0 ± 5.2	160.6 ± 4.4	158.9 ± 6.5	147.3 ± 4.8	3, 5
DBP mm Hg	89.3 ± 1.3	85.1 ± 2.5	86.0 ± 3	85.6 ± 2.7	
Creatinine (mg/dL)	3.5 ± 0.4	3.4 ± 0.4	3.3 ± 0.4	5.2 ± 0.6	3, 5, 6
BMI	33.0 ± 1.5	33.4 ± 1.6	34.1 ± 2.6	32.5 ± 1.6	
Duration of DM (years)	16.7 ± 1.6	16.3 ± 1.3	18.5 ± 2.7	16.2 ± 1.8	
24 hr urine protein	5.1 ± 0.9	5.8 ± 1.0	4.6 ± 1.1	2.9 ± 0.6	3, 5
# progressed to ESRD	18	20	13	19	
TTE (weeks)	62.4 ± 14.1	81.3 ± 13.2	79.6 ± 10.0	87.2 ± 22.4	
# BP meds on presentation	1.84 (.69)	2.07 (.74)	3.24 (1.0)	1.38 (1.1)	2, 3, 4, 5, 6

* Values are means ± SD.
† Between group comparisons as per Table 1.
Abbreviations per text and Table 1.

time that many of these patients presented, the benefits of ACEI in DN were not as widely publicized. During the course of follow up, there was a significant increase in the number of patients treated with both agents in combination. Those with a CA in the regimen tended to have lower blood pressure levels over the course of follow up, when compared to those not on a CA. Furthermore, presenting on a CA was associated with a significant (8 mm Hg) decrease in MAP over the course of follow up. In contrast to some other studies, renal survival was not significantly associated with the type of antihypertensive agent used. However, there was a tendency for regimens including an ACEI to have better renal survival, which is explained by the lower levels of creatinine seen in those groups at presentation.

In our original analysis of the ESRD data set, we observed that use of CA was associated with poorer rates of renal survival in AAs.[13] This effect was not independent of serum creatinine, and probably represents physician preference for use of CA (and avoidance of ACEI) in patients with significantly elevated levels of serum creatinine (Table 1). In this analysis, we observed that the tendency for CA to be negatively associated with renal survival in this population was ameliorated by the addition of an ACEI. This is consistent with data demonstrating that the combination of ACEI and CA decrease proteinuria and glomerulosclerosis.[15,16] Most of the concerns regarding CA in patients with DN and/or proteinuria focus on the dihydropyridine subtype. These agents are less likely to lower urine protein excretion,[17] and have been shown to be inferior to ACEI in lowering risk for myocardial infarction in diabetics, and for slowing renal disease progression in diabetics and non-diabetics.[8,9,10,18] However, in placebo-controlled trials, dihydropyridine CA have beneficial effects on CVD in diabetic patients.[11,19] In contrast, rate-lowering CA (nondihydropyridines) lower urine protein excretion, and are hypothesized to be better for use in diabetic patients with proteinuria.[15,20] However, the use of rate-lowering CA is sometimes complicated by the need for β blockers for coronary heart disease treatment and protection, the high rates of congestive heart failure,

Table 4. Characteristics of cross-sectional dataset by follow-up ACEI-CA status*

	ACEI	CA	ACEI/CA	Neither	$P<.05$†
N	33	12	55	19	
# AA	28	10	44	16	
Creatinine (mg/dL)	3.2 (0.4)	4.6 (1.1)	3.3 (0.3)	6.7 (0.7)	3, 6
# progressed to ESRD	18	5	34	13	
TTE (weeks)	80.5 (20.3)	93.8 (32)	87.2 (10.2)	42.9 (15.2)	6
MAP on follow-up (mm Hg)	108.1 (1.9)	113.5 (3.8)	110.3 (1.3)	104.1 (3.9)	
BP response (mm Hg)	2.1 (2.4)	−6.3 (5.5)	0.4 (1.7)	6.4 (4.7)	
# of BP responders	6	2	13	2	

* Values are means ± (SD).
† Between group comparisons per Table 1.

Table 5. Relationship of follow-up ACEI-CA status to renal survival (univariate analysis)

ACEI-CA Group	Hazard Ratio	Confidence Interval		*P*
		Lower	Upper	
ESRD dataset				
ACEI-CA as individual variable				
ACEI (yes)	0.692	0.49	0.976	.036
CA (yes)	1.447	.949	2.207	.086
ACEI/CA (yes)	0.901	.661	1.228	.51
Neither (yes)	1.685	1.12	2.54	.013
ACEI-CA as group variable				
Neither (reference)	1			
ACEI	0.488	.302	.788	.003
CA	.878	.513	1.5	.633
ACEI/CA	.595	.381	.928	.221
Cross-sectional dataset*				
ACEI-CA as group variable for TTE				
Neither (reference)	1			
ACEI	.595	.285	1.24	.167
CA	.404	.142	1.148	.089
ACEI/CA	.517	.27	.991	.047
ACE-CA as group variable for delta 1/Cr at one year of follow-up relative to Neither				
ACEI	.19	.04	.902	.037
CA	.304	.061	1.521	.147
ACEI/CA	.293	.067	1.274	.102

* In cross-sectional dataset ACEI-CA status as independent variable was not significant.

and the presence of autonomic neuropathies in patients with diabetes. Despite these type-specific differences in the renal effects of CA, the effects of CA in the previous and current analysis did not differ by subtype.

While much of the concern regarding blood pressure-lowering agents in diabetics is focused on the role of CA, there continues to be some concern regarding the use of RAS inhibitors. At the time that the patients in these data sets were seen, it was common practice to limit the use of ACEI in AA, based on the belief that AA did not respond to these agents. Indeed, we observed that AA were more likely than Caucasians to be treated with a regimen that did not include an ACEI. Despite this observation we found that AA race was independently associated with better renal survival in the ESRD data set.[13] Adding to the confusion are the results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) that showed that AA randomized to treatment with the ACEI lisinopril exhibited a systolic blood pressure 4 mm Hg higher than those randomized to chlorthalidone or amlodipine.[21] Another concern regarding the use of RAS inhibitors in patient populations like this is the potential deleterious effects on renal function and potassium.[22] In addition to being less likely to initiate an ACEI in patients with significant reductions in renal function, many physicians hesitate to increase ACEI dosage in this group. Failure to increase the dosage of ACEI may lessen their effect on blood pressure and protection of renal function. The question of how aggressively ACEI dosage should be increased in DN has not been settled, but it is generally agreed that reduced renal function is not an absolute contraindication to avoid RAS inhibitors. Since this analysis demonstrates that RAS inhibition tends to positively affect renal survival, we believe all diabetics should have a trial of RAS inhibition, regardless of level of renal function. The additional cardiovascular protection provided by ACEI in diabetics supports this idea, and the use of these agents in AA.[17,18,23,24]

While RAS inhibition is important in preserving renal function in diabetics, it appears to be relatively more important to lower blood pressure to currently recommended targets than to use any specific agent.[2,3] In support of this notion is our observation that those in the ESRD data set who presented on an ACEI had higher blood pressure and poorer rates of renal survival.[13] The higher blood pressure levels seen in those treated with an ACEI are probably due to practitioners' reticence in increasing the dosage in patients with reduced renal function. In addition to the efficacy of ACEI in lowering blood pressure in AA, the better blood pressure responses seen with regimens including a CA may be a result of practitioners' willingness to increase the dosage of a CA in patients with advanced renal insufficiency.[24] However, in these cohorts with advanced renal disease, the effect of substantially lowering blood pressure to recommended targets on renal survival is not entirely clear. With the inclusion of ACEI–CA status on follow up in the multivariate analysis, lower blood pressure (MAP $<$100 mm Hg) remained an independent predictor of shorter TTE. We are not sure why this is the case, but hypothesize that low MAP in these high-risk individuals suggest other comorbid conditions. This is illustrated, to some degree, in the cross-sectional data set, since 40% of those on neither agent at follow up, those with worst renal survival, had MAP $<$100 mm Hg (χ^2=.035, compared to those in other ACEI–CA groups). However, in diabetics with less advanced disease, blood pressure appears to be a continuous variable with regard to development of albuminuria or progression of nephropathy.[2,5,6,25]

. . . physicians need to be attentive to blood pressure in patients with DN, and should make every effort to achieve the recommended blood pressure targets.[2,23,24]

This study had limitations that restrict the strength of its conclusions. Both data sets were retrospective, and the ESRD data set had a selection bias, as it only included patients who had reached ESRD. However, the use of the cross-sectional data set addressed this selection bias, and the results from both data sets were similar. The patients in these data sets were treated by several nephrologists who did not follow a standard protocol. Therefore, several different ACEI and CA were used at various dosages. The effect of any medication on blood pressure is dependent on dosage and compliance, but we were not able to obtain consistent data on these factors. In addition, we may not have captured fully the effects of blood pressure-lowering agents on blood pressure, due to the lack of a specified protocol for measurement. Finally, we did not have adequate data on other factors that may influence progression of renal disease in diabetics, such as control of serum glucose and lipid levels. While these factors are important, they have not been definitively associated with progression of disease in patients with advanced renal insufficiency.[17,26]

In summary, physicians need to be attentive to blood pressure in patients with DN, and should make every effort to achieve the recommended blood pressure targets.[2,23,24] While CA may not be the initial antihypertensive agent to use in this patient group, they are often necessary to lower blood pressure to adequate levels. This is particularly true in those with significant albuminuria, or reduced GFR.[2,7,17,23,24] Therefore, antihypertensive regimens that contain a CA are more likely to achieve blood pressure goals in patients with moderate to severe DN. Moreover, any deleterious effects of CA on renal function and proteinuria will likely be ameliorated when used in combination with a RAS inhibitor. In conclusion, similar to findings with ACEI,[22] practitioners should not avoid using CA in hypertensive diabetics with nephropathy and reduced renal function.

REFERENCES

1. US Renal Data System. *USRDS 1999 Annual Data Report.* Bethesda, Md: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1999.
2. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis.* 2000;36:646–661.
3. Lewis EJ. Captopril in Type 1 Diabetic Nephropathy. In: Black HR, ed. *Clinical Trials in Hypertension.* New York, NY: Marcel Dekker, Inc; 2001:451–468.
4. Parving HH, Andersen AR, Smidt UM, et al. Early aggressive antihypertensive treatment reduces the rate of decline in kidney function in diabetic nephropathy. *Lancet.* 1983;1: 1175–1179.
5. Ravid M, Savin H, Lang R, Jutrin I, Shoshana L, Lishner M. Proteinuria, renal impairment, metabolic control, and blood pressure in type 2 diabetes mellitus: a 14-year follow-up report on 195 patients. *Arch Intern Med.* 1992;152:1225–1229.
6. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993; 329:1456–1462.
7. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001; 345(12):861–869.
8. Lewis EJ, Lawrence HG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851–860.
9. Wright JT Jr, Bakris G, Greene T, et al, for the African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease. *JAMA.* 2002;288:2421–2431.
10. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care.* 1998;21:597–603.
11. Hansson L, Zanchetti A, Carruthers SG, et al, for the HOT Study Group. Effects of intensive blood pressure lowering and low dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet.* 1998;351:1755–1762.
12. Hall WD, Reed JW, Flack JM, et al. Comparison of the efficacy of dihydropyridine calcium channel blockers in African-American patients with hypertension. International Society of Hypertension in Blacks Investigator Group. *Arch Intern Med.* 1998;158:2029–2034.
13. Crook ED, Harris J, Oliver B, Fleischman E, Crenshaw G, Taylor R. Endstage renal disease due to diabetic nephropathy in Mississippi: an examination of factors influencing renal survival in a population prone to late referral. *J Invest Med.* 2001;49:284–291.
14. Crook ED, Wofford P, Oliver B. Advanced diabetic nephropathy disproportionately affects African-American females: cross-sectional analysis and determinants of renal survival in an academic renal clinic. *Ethn Dis.* 2003; 13:28–33.
15. Bakris GL, Weir MR, Dequattro V, McMahon FG. Effects of ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int.* 1998;54: 1283–1289.
16. Bakris GL, Griffin KA, Picken MM, Bidani AK. Combined effects of angiotensin converting enzyme inhibitor and a calcium antagonist on renal injury. *J Hypertens.* 1997;15: 1181–1185.
17. Crook ED. Diabetic Renal Disease in African Americans. *Am J Med Sci.* 2002;323:78–84.
18. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med.* 1998;338:645–652.
19. Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med.* 1999;340: 677–684.
20. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S. Calcium channel blockers versus other antihypertensives therapies on progression of NIDDM associated nephropathy. *Kidney Int.* 1996;50:1641–1650.
21. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker

vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2002;288:2981–2997.
22. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med.* 2000;160:685–693.
23. Anonymous. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1997;157:2413–2446.
24. Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch Intern Med.* 2003;163:525–541.
25. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ.* 2000;321:412–419.
26. Crook ED, Thallapureddy A, Migdal S, et al. Lipid abnormalities and renal disease: is dyslipidemia a predictor of progression of renal disease. *Am J Med Sci.* 2003;325:340–348.

AUTHOR CONTRIBUTIONS

Design and concept of study: Crook
Acquisition of data: Crook
Data analysis and interpretation: Crook, Preddie
Manuscript draft: Crook, Preddie
Statistical expertise: Crook, Preddie
Administrative, technical, or material assistance: Crook
Supervision: Crook