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Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy

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Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Treatment of hypertension with ACE inhibitors in diabetic patients reduces proteinuria and slows progression of nephropathy compared with agents that do not maintain declines in proteinuria. Calcium channel blockers (CCBs) have variable effects on proteinuria; their long-term effects on progression of diabetic nephropathy are not known. The current study examines the hypothesis that CCBs that maintain reductions in proteinuria slow progression of nephropathy associated with non-insulin dependent diabetes mellitus (NIDDM) by a degree comparable to ACE inhibitors, given similar levels of blood pressure control. To test this hypothesis we randomized 52 patients with NIDDM associated nephropathy and hypertension, mean age of 63 ± 8 years, to either the ACE inhibitor, lisinopril ($N = 18$), nondihydropyridine CCBs (NDCCBs), verapamil SR ($N = 8$) or diltiazem SR ($N = 10$), or the β blocker, atenolol ($N = 16$). Goal blood pressure was ≤ 140/90 mm Hg. Patients were followed for a mean period of 63 ± 7 months. The primary end point was change in creatinine clearance (C_{Cr}) slope in each group. There was no significant difference in mean arterial pressure reduction among the groups over the study period ($P = 0.14$). The mean rate of decline in C_{Cr} was greatest in the atenolol group (−3.48 ml/min/year/1.73 m^2; $P < 0.0001$). There was no difference in the C_{Cr} slopes between lisinopril and NDCCBs groups ($P = 0.36$). Proteinuria was reduced to a similar extent in the lisinopril and NDCCBs groups ($P > 0.99$). Therefore, in persons with renal insufficiency secondary to NIDDM, similar levels of blood pressure control with either lisinopril or NDCCBs slowed progression of renal disease to a greater extent than atenolol. Moreover, this enhanced slowing of renal disease progression correlated with sustained and significant reductions in proteinuria, findings not observed in the atenolol group.

Diabetic renal disease is the leading cause of end-stage renal disease in the western world [1]. Early studies using β blockers and diuretics demonstrated that reduction of arterial pressure to levels of less than 140/90 mm Hg was one of the most effective ways to slow progression of diabetic renal disease [2]. Recently, however, several long-term clinical studies in patients with either insulin dependent diabetes mellitus (IDDM) or noninsulin dependent diabetes mellitus (NIDDM) demonstrate that angiotensin converting enzyme (ACE) inhibitors also slow progression of diabetic renal disease [3–10]. Moreover, reduction in disease progression by ACE inhibitors may be greater than that seen with β blockers and diuretics [5, 9, 10]. This may relate, in part, to the relatively greater reductions in proteinuria seen with ACE inhibitors, which have been shown to correlate with a slowed decline in renal function [6, 8–11].

Calcium channel blockers (CCBs) inhibit the vasoconstrictor as well as both the hypertrophic and hyperplastic effects of angiotensin II and other mitogens on mesangial and vascular smooth muscle cells through blockade of calcium dependent mechanisms [12–14]. Early studies, however, demonstrate marked differences between the antiproteinuric effects of dihydropyridine CCBs (nifedipine-like) and nondihydro-pyridine CCBs (NDCCBs) such as verapamil and diltiazem [15, 16]. Recent data support the concept that differences in antiproteinuric response between CCB subclasses relate to their differential effects on glomerular permeability, that is, dihydropyridine CCBs do not reduce permeability whereas nondihydropyridine CCBs attenuate permeability [17, 18]. In NIDDM patients this failure to reduce permeability increases exposure of glomerular cells to albumin which is glycated. Glycated albumin has been shown to have direct toxic effects on these cells as well as increase mesangial matrix production [11, 19–21]. No long term studies have examined the effects of CCBs on progression of NIDDM associated nephropathy in the context of proteinuria reduction.

The present six-year study evaluates the impact of three different classes of antihypertensive agents on progression of NIDDM associated nephropathy and changes in proteinuria in the context of similar levels of blood pressure control. CCBs that mimic the antiproteinuric effects of ACE inhibitors were selected for comparison, since, theoretically, they should provide similar benefit to the kidney.

Methods

This report represents a six-year follow-up of patients with NIDDM associated nephropathy who were prospectively randomized to one of three groups of antihypertensive treatments. The study protocol and consent forms were reviewed and approved by the Institutional Review Board of the Ochsner Clinic.

Study population

Both inclusion and exclusion criteria are listed in Table 1. The baseline demographic characteristics of the patients who completed the study are summarized in Table 2. Seventy-six patients were screened from both the nephrology and cardiology clinics of the Alton Ochsner Medical Institutions, New Orleans, Louisiana, 52 of whom met the criteria and were randomized to one of the

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Table 1. Inclusion and exclusion criteria for patient population studied

Inclusion criteria
- Non-insulin dependent diabetes for ≥ 8 years
- Diabetic retinopathy (by ophthalmologic examination)
- Proteinuria ≥ 2.0 g/day
- Renal insufficiency (creatinine clearance, < 1.16 ml/second [< 70 ml/min])
- Hypertension for ≥ 8 years
- Age ≥ 45 years

Exclusion criteria
- Heart failure (ejection fraction, ≤ 40%)
- History of poor diabetes control (blood glucose, 11 mmol/liter [198 mmol/liter] or glycosylated hemoglobin, > 13%)
- History of difficult blood pressure control (maximum dose of ≥ 3 medications or blood pressure > 105 mm Hg with medication)
- Blindness
- Documented coronary artery disease
- Severe claudication (peripheral arterial disease)
- Orthostatic hypotension (diabetic neuropathy)
- Required intake of antiarrhythmic medications, calcium channel blockers, or converting enzyme inhibitor
- Documented psychiatric disease
- Active urine sediment (casts, gross hematuria, eosinophils)
- Diastolic pressure > 125 mm Hg on three consecutive readings with no antihypertensive medications
- Blood glucose control by insulin therapy alone

Table 2. Baseline Characteristics of Study Groups

	L (N = 18)	NDCCB (N = 18)	Atenolol (N = 16)	P valuc
Demographic				
Height *cm*	175 ± 15	178 ± 18	180 ± 16	0.42
Weight *kg*	101 ± 7	107 ± 6	104 ± 6	0.33
Age years	62 ± 7	64 ± 7	60 ± 8	0.27
Male sex %	61	50	38	0.51
Race N				
Black	50	50	63	0.69
White	50	50	37	
Duration of NIDDM *years*	14 ± 3	14 ± 5	13 ± 4	0.59
Duration of HTN *years*	16 ± 5	13 ± 4	16 ± 4	0.73
Metabolic				
FBG *mmol/liter*	10.5 ± 1.3	9.7 ± 1.0	9.9 ± 1.0	0.26
HbA_{1C} %	11.1 ± 1.1	10.7 ± 1.1	10.3 ± 1.3	0.03[a]
Hemodynamics				
Systemic				
SBP *mm Hg*	155 ± 11	156 ± 11	161 ± 13	0.26
DBP *mm Hg*	97 ± 6	97 ± 6	99 ± 7	0.62
Renal				
Serum creatinine *mmol/liter*	141 ± 44	168 ± 62	159 ± 71	0.16
C_{Cr} *ml/s/1.73 m²*	1.11 ± 0.3	1.01 ± 0.38	1.02 ± 0.38	0.53
$U_{protein}$ V *g/day*	2.7 ± 2.2	4.5 ± 3.4	4.2 ± 3.7	0.22
U_{sodium} V *mmol/day*	123 ± 28	113 ± 31	127 ± 27	0.39

Data represent mean ± standard deviation.
[a] ANOVA performed for within and between group differences
Abbreviation is FBG, fasting blood glucose.

three groups. Each subject gave informed consent to participate in the study after a thorough explanation of the protocol.

Study design and treatment plan

All antihypertensive medications were discontinued in each patient two weeks prior to any baseline measurements. Patients were monitored during this period with daily blood pressure checks in both the supine and standing positions by means of a blood pressure monitoring device (Dinemapp, Critikon, Inc., Tampa, FL, USA). If any individual had an average of three sitting diastolic pressures of greater than or equal to 125 mm Hg, they were excluded from the study.

After this two-week period, a complete physical examination and laboratory screening tests, including a complete ophthalmologic examination using fluoresceine angiography, were performed in each subject. Laboratory evaluation included: a 24-hour urine collection for protein, albumin, creatinine clearance, and sodium; urinalysis; complete blood cell count; renal electrolyte profile, which consisted of serum urea nitrogen, creatinine, sodium, potassium, chloride, and bicarbonate; fasting blood glucose and hemoglobin A_{1c}. An electrocardiogram was performed annually unless otherwise indicated. A renal dietitian also instructed patients to ingest a 90 mEq/day sodium, 0.8 g/kg/day protein, and 6300-kJ American Diabetes Association diet.

After baseline laboratory measurements were obtained and instructions given, patients were randomized to receive one of three antihypertensive treatments: lisinopril, atenolol or one of two NDCCBs, verapamil SR or diltiazem SR. The dosage of each drug was initially titrated over a two-week period and then periodically throughout the study to ensure similar arterial pressure control among groups.

After the drug titration phase, blood pressure and pulse rates were monitored weekly for the first month and quarterly, thereafter. All patients had blood pressure measured by the same person, using an appropriate sized blood pressure cuff. All readings were obtained in the morning between 9 a.m. and noon and at least one hour after eating and two hours after medication ingestion. All readings were performed in triplicate in both sitting and standing positions after a 10-minute rest period. Values were then averaged. The data presented in the **Results** section represent sitting blood pressure values, since there was no clinically significant difference between sitting and standing values.

Renal function studies including proteinuria measurements were performed every three months during the first year of the study and every six months thereafter. All urinary determinations of albumin were corrected for daily creatinine production. Urinary protein was measured by means of a dye-binding colorimetric method (Biotrol USA, West Chester, PA, USA), which required a pyrogallol red-molybdate complex formation. The interassay variability was 2.4%. The intra-assay variability was 3.7%. Urinary albumin excretion was measured by means of a double-antibody radioimmune assay (Diagnostic Products Corp., Los Angeles, CA, USA). The intra-assay variability was 3.5%. The interassay variability was 4.8%.

Fasting blood glucose levels were monitored daily by the patients throughout the study by placing a drop of blood onto a plastic strip and inserting it into a blood glucose measuring device (AccuCheck II; Boehringer Mannheim, Indianapolis, IN, USA) device. At the initiation of the study, all patients were instructed on the proper use of the AccuCheck II device. Furthermore, all AccuCheck II blood glucose measurements were compared initially and every month thereafter with standard laboratory glucose measurements.

Side effects due to drugs were monitored at each visit for blood pressure determination. Patients were asked what new complaints or problems had arisen since their last clinic visit.

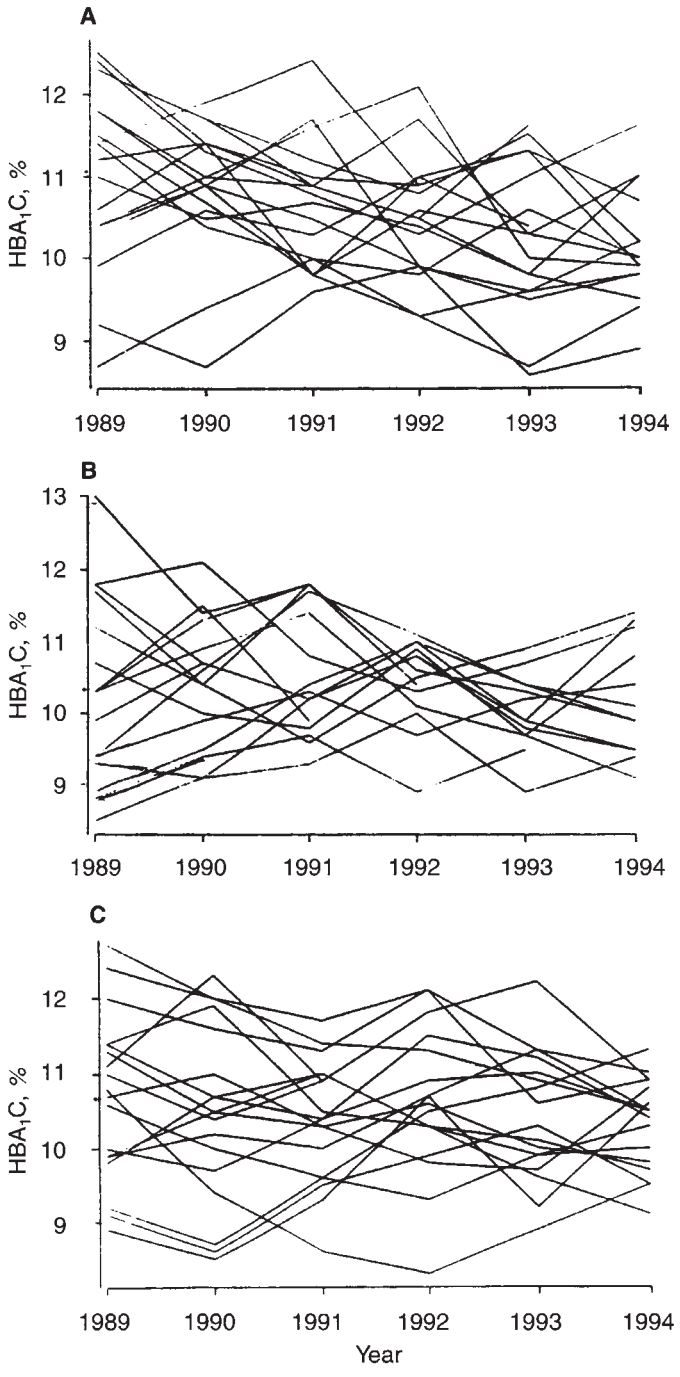

Fig. 1. *The annual values of HbA_1C for each patient in the ACE inhibitor group (A), β blocker group (B) and NDCCB groups (C).*

End points

The primary end-point of the study was defined as the rate of decline in renal function as assessed by the slope of creatinine clearance, corrected for body surface area. Secondary end-points included doubling of serum creatinine from baseline, reductions in urinary protein excretion rate from baseline as well as progression to death, dialysis, or transplantation.

Statistical analysis

The data were analyzed with SAS version 6.07 [21] and Splus version 3.2 [22]. Nominal characteristics are summarized by percentages; continuous variables are summarized by means and SDs or by medians when the distributions are skewed. Dichotomous baseline characteristics were compared with Fisher's exact test, and continuous baseline characteristics were compared primarily with Kruskal-Wallis nonparametric tests and secondarily with ANOVA. When all the groups differed significantly, Wilcoxon rank-sum tests were used for pairwise comparisons. A Wilcoxon matched-pair signed rank test was used to assess differences in side effect profiles among the groups. The time courses of blood-pressure and renal function were compared by reducing the data to slopes and intercepts of least-squares lines, and then using Kruskal-Wallis and ANOVA as described above. Lastly, a subgroup analysis was planned, prior to statistical evaluation, and performed to assess whether patients with serum creatinine values of > 133 mmol/liter had differences in their rate of progression. A P value of less than 0.05 was considered to indicate statistical significance for comparisons among the three groups. Bonferroni corrections were used for pairwise comparisons, so a nominal significance level of 0.05/6 = 0.00833 was used for the pairwise comparisons. Such analyses were performed to assess changes in the slope of creatinine clearance among the groups.

Results

Patients were randomized to one of three treatment groups between September 1988 and October 1989. Eighteen patients received lisinopril, eighteen received NDCCBs (8 to verapamil SR, 10 to diltiazem SR) and sixteen patients received atenolol. The baseline clinical and laboratory characteristics of these three groups were similar (Table 2). One difference, however, was that the atenolol group had a significantly lower baseline HbA_1C value (P = 0.03) compared to the other groups. No significant differences in HbA_1C, however, were noted among the three groups at any other time point throughout the study (Fig. 1). Moreover, there were no significant differences in baseline fasting blood glucose values among the groups (Table 2). This lack of difference in fasting blood glucose values among the three groups persisted throughout the study (P = 0.16). Lastly, there was no formal monitoring of urine urea nitrogen content throughout the study. Twenty-four hour urine values of sodium and creatinine were assessed. The distribution of urinary sodium excretion for each group over the entire study is shown in Figure 2.

A total of 43 patients completed the study (median follow-up, 64 months, range 36 to 73). Six patients did not complete the study either because they failed to return for follow-up visits or other non-medical problems unrelated to drug side effects. Three of these six, died after being terminated from the study for missing more than three follow-up visits. Additionally, three of the 52 patients died by the end of the study. Thus, six of 52 patients (11.6%) died by study end. Five of the six died within the last two years of the study. Five other patients (9.6%) started dialysis by study end. Two patients, included in the six deaths, died shortly after dialysis was initiated.

Clinical management

Blood pressures were under 140/90 mm Hg in all patients by eight weeks into the study. The mean systolic and diastolic blood

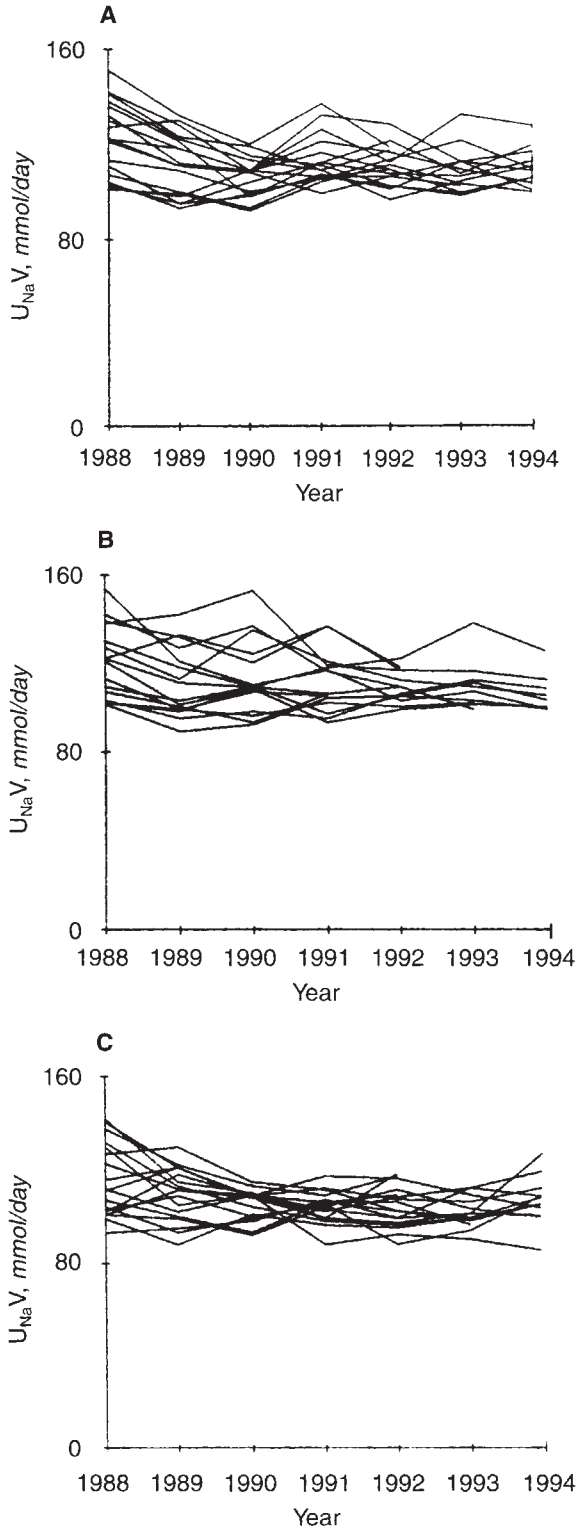

Fig. 2. *The annual values of urinary sodium excretion for each patient in the ACE inhibitor (A) group, β blocker group (B) and NDCCB groups (C).*

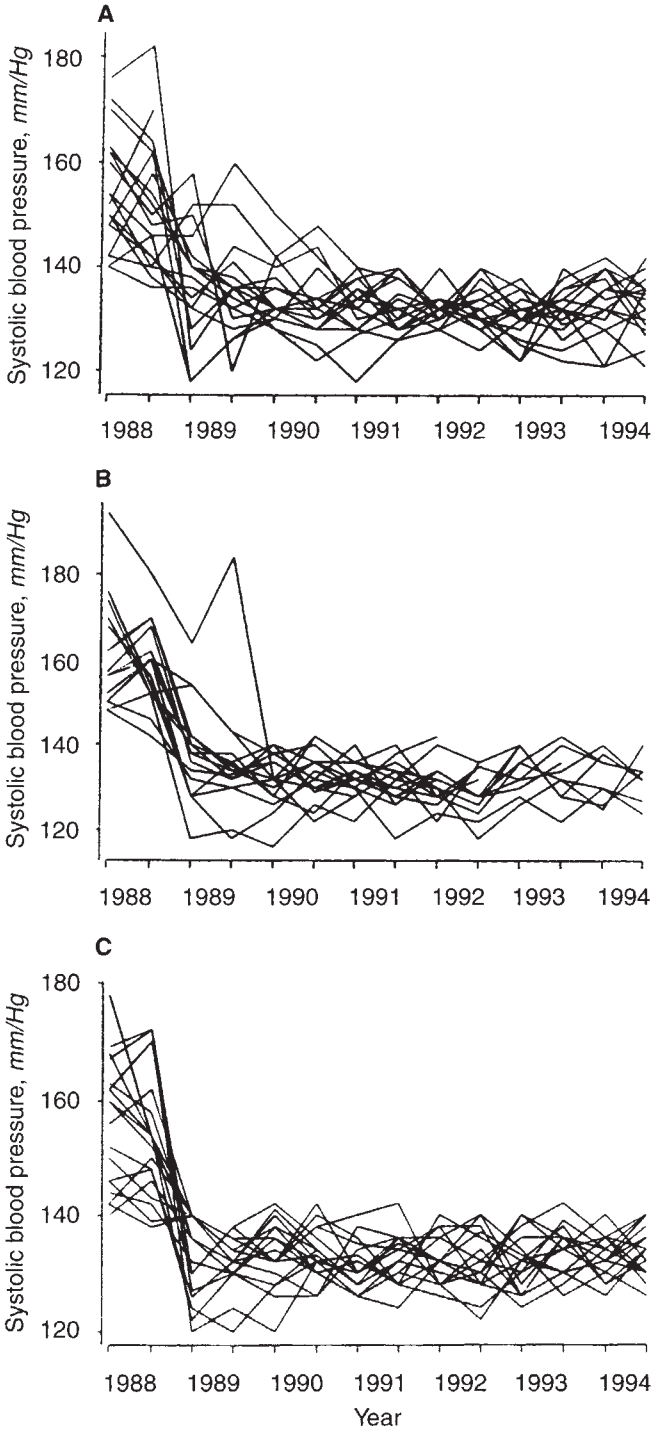

Fig. 3. *The annual values of systolic blood pressure for each patient in the ACE inhibitor group (A), β blocker group (B) and NDCCB groups (C).*

pressure distributions in all patients throughout the study are shown in Figures 3 and 4. The median systolic pressure at baseline was 154 mm Hg in the lisinopril group, 159 mm Hg in the NDCCB group and 155 mm Hg in the atenolol group. The median diastolic pressure was 96 mm Hg in the lisinopril group and 98 mm Hg in both the NDCCB and atenolol groups. During the study, median systolic pressure ranged from 132 to 138 mm Hg. The median diastolic pressure varied from 82 to 86 mm Hg. The mean arterial pressure (± SD), averaged over all follow-up visits, was 99 ± 4 mm

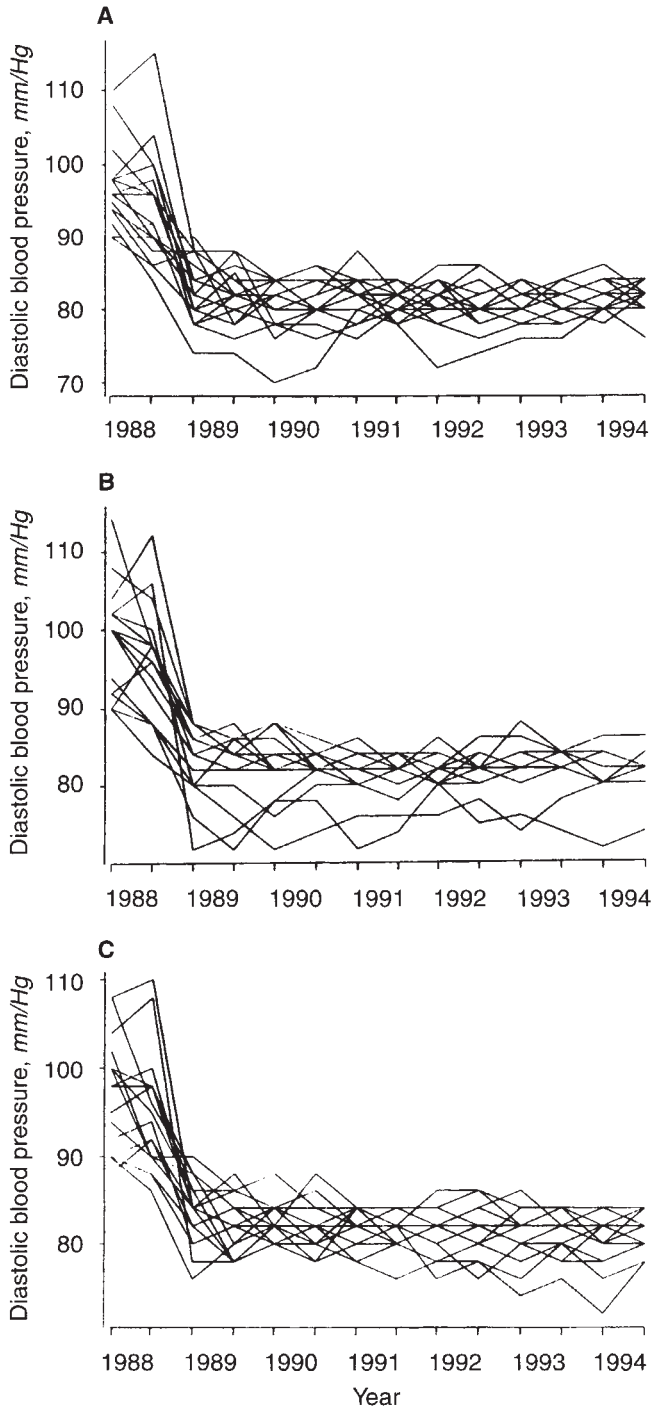

Fig. 4. *The annual values of diastolic blood pressure for each patient in the ACE inhibitor group (A), β blocker group (B) and NDCCB groups (C).*

Hg in the lisinopril group, 100 ± 4 mm Hg in the NDCCB group and 99 ± 3 mm Hg in the atenolol group. During the study there were no significant differences in the slopes of diastolic blood pressure among the different groups ($P = 0.44$). Conversely, an analysis of systolic blood pressure slopes over the six year period demonstrated a significantly higher mean systolic pressure in the atenolol group relative to the lisinopril ($P = 0.015$) and the NDCCBs ($P = 0.007$) groups. The decrease in baseline mean arterial pressure in each group averaged 16 ± 6 mm Hg in the lisinopril group, 18 ± 6 in the NDCCB group and 15 ± 5 mm Hg in the atenolol group.

Table 3. Number of patients who received more than two antihypertensive medications by the end of the study[c]

	L ($N = 18$)	NDCCB Verapamil SR ($N = 8$)	NDCCB Diltiazem SR ($N = 10$)	Atenolol ($N = 16$)
Central alpha agonists	2 (11)	0	1 (10)	0
Alpha blockers[b]	9 (50)	3 (38)	5 (50)	0
Hydralazine	0	0	0	4 (25)
Minoxidil	0	0	0	1 (6)

The % of patients in that group is in parentheses.
[a] Methyldopa or clonidine
[b] Prazosin or doxazosin
[c] All patients were receiving study drug plus a loop diuretic

Drug administration

The mean dose of lisinopril over the course of the study was 51 ± 9 milligrams per day, for diltiazem SR, 212 ± 19 milligrams twice daily and 205 ± 16 milligrams twice daily for verapamil SR. The atenolol group received a mean dose of 86 ± 9 milligrams per day of atenolol. If additional blood pressure reduction was required, furosemide was added. If further blood pressure reduction was needed, other antihypertensive agents were added. By the end of the second year, 40 of the 52 (77%) patients were receiving furosemide for either blood pressure control or management of peripheral edema. By year four, all patients received furosemide. Additionally, by the end of the study 25 of 52 (48%) patients also received additional blood pressure medications other than those used for initial randomization. These included alpha blockers and/or vasodilators such as hydralazine (Table 3).

Changes in creatinine clearance slopes

Each of 52 patients had a minimum of four determinations (maximum 14) of creatinine clearance during the study. The mean rate of decline in creatinine clearance was −0.98 ± 0.44 ml/min/year/1.73 m^2 in the lisinopril group, −1.44 ± 0.63 ml/min/year/1.73 m^2 in the NDCCBs group, and −3.48 ± 1.1 ml/min/year/1.73 m^2 in the atenolol group. The slope of creatinine clearance decline for each group is shown in Figure 5. The rate of decline in creatinine clearance was most pronounced in the group of 41 patients with a baseline serum creatinine of > 133 mmol per liter. Among this group the decline in creatinine clearance was −1.06 ± 0.51 ml/min/year/1.73 m^2 for the lisinopril group; −1.56 ± 0.84 ml/min/year/1.73 m^2 for the NDCCBs group and −3.54 ± 1.39 ml/min/year/1.73 m^2 for the atenolol group. A comparison of the atenolol group with either the lisinopril ($P = 0.0001$) or NDCCBs groups ($P = 0.004$) demonstrated a significant difference in the renal function decline rates. No significant difference, however, was noted between the lisinopril and NDCCB groups ($P = 0.11$).

Changes in serum creatinine

Among the 52 patients who had four or more determinations of serum creatinine (median 16 determinations, maximum 33) during an average follow-up of 63 months per patient (maximum 73

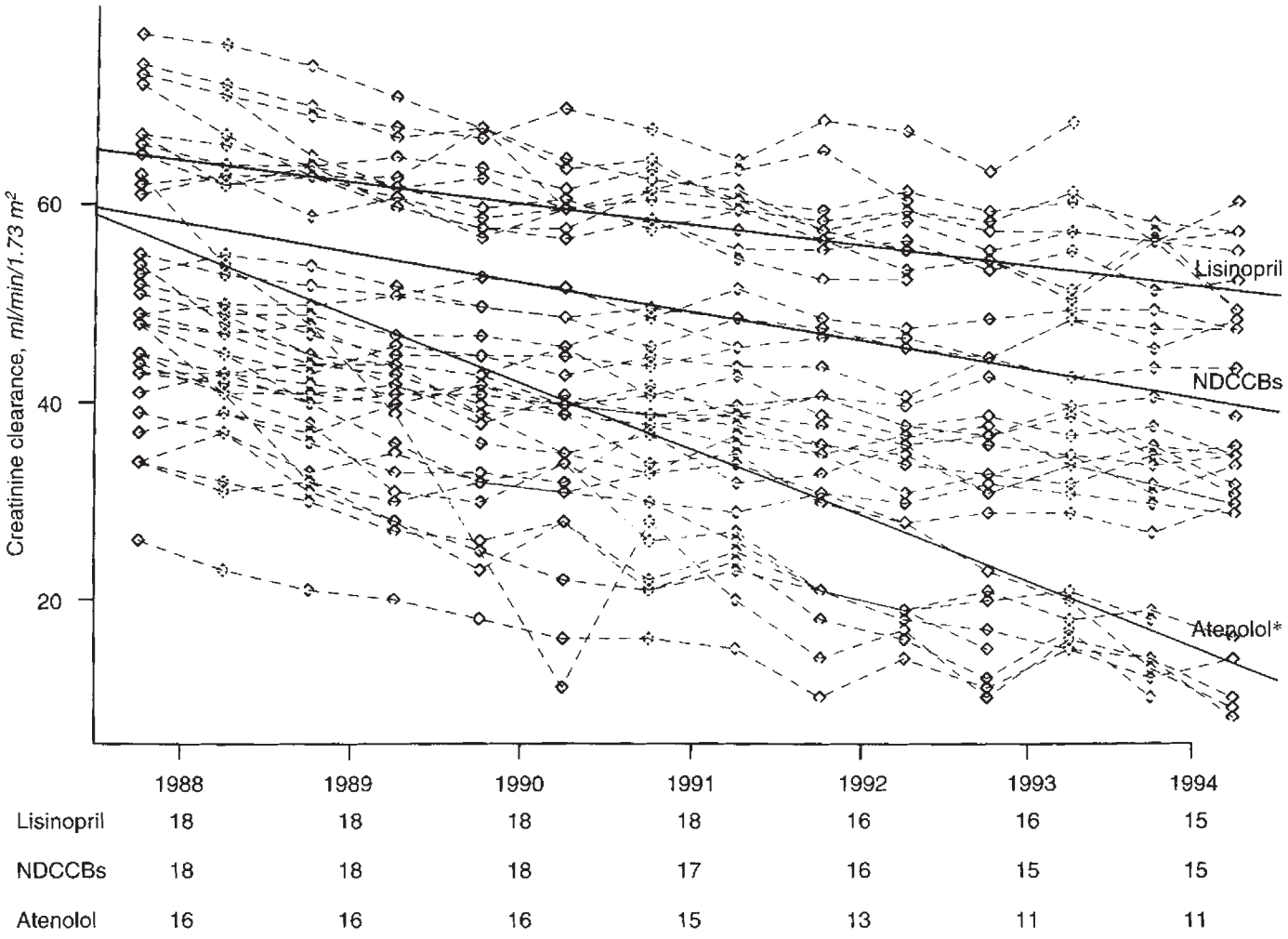

Fig. 5. *The annual rate of decline in creatinine clearance in 52 patients with NIDDM associated nephropathy.* *$P < 0.01$ compared to other two slopes.

months), the mean annual rate of increase in serum creatinine was 85.7 ± 20.3 micromoles per liter.

Eight of the 52 patients (15.4%) who completed the study doubled their serum creatinine by study end ($P = 0.09$). Five of these eight (63%) were in the atenolol group; four of these five had to start dialysis by study end. Of the three remaining patients one was in the lisinopril group and two were in the NDCCB group. The mean (± SD) baseline serum creatinine among this group of eight patients was 194.5 ± 9.7 mmol/liter; the value in the five patients who received atenolol was 186.1 ± 7.1 mmol/liter. While an insignificant number of patients doubled their serum creatinine from baseline, a significant number increased it by more than 50% in the atenolol group compared to the other groups (69% atenolol vs. 17% lisinopril, 22% NDCCBs; $P < 0.001$).

Changes in urinary protein excretion rate

The mean change from baseline in urinary albumin excretion at the first three month visit was −0.713 ± 0.628 grams per day in the lisinopril group, −0.818 ± 0.663 grams per day in the NDCCB group and 0.168 ± 0.291 grams per day in the atenolol group. The mean change from baseline proteinuria in each group at 63

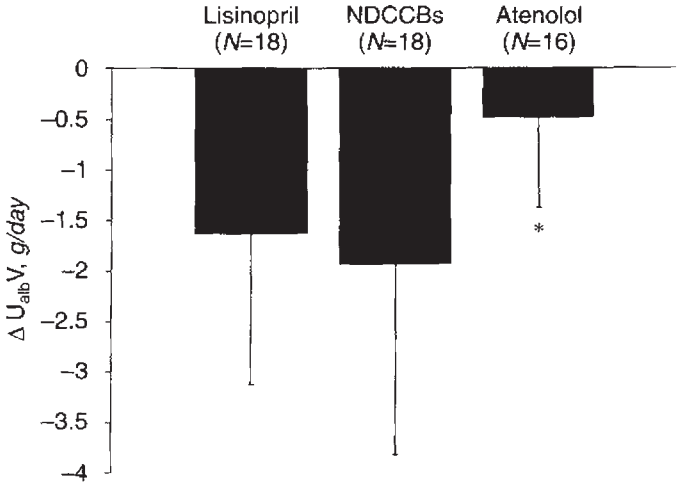

Fig. 6. *The mean reduction in albuminuria at 63 months in each of three groups of participants receiving different antihypertensive medications.* ACEI-angiotensin converting enzyme inhibitor, lisinopril; NDCCBs nondihydropyridine calcium channel blockers, atenolol; atenolol. *$P < 0.01$ compared to other groups.

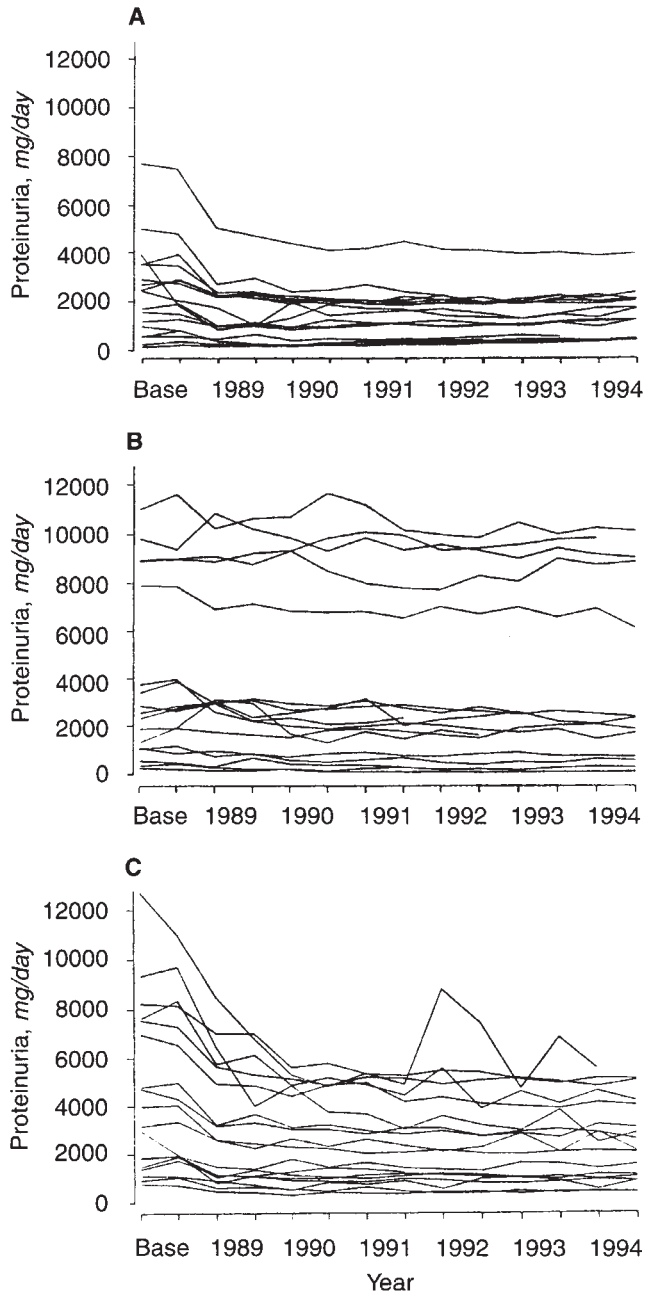

Fig. 7. *The annual values of urinary protein excretion for each patient in the ACE inhibitor group (A), β blocker group (B) and NDCCB groups (C).*

months is shown in Figure 6. The changes in proteinuria over the course of the study for each patient are shown in Figure 7. The mean reductions in blood pressure during this same three month period were comparable (−23 + 5 mm Hg lisinopril group; −22 + 4 mm Hg NDCCB group and −24 + 5 mm Hg, atenolol group). A statistical analysis of the changes in proteinuria, using a Bonferroni correction, demonstrated a statistical difference between the atenolol group and the lisinopril ($P = 0.016$) and NDCCBs groups ($P = 0.012$), respectively. Moreover, changes in proteinuria over the mean follow-up period of 63 months were independent of systolic ($P = 0.29$) or diastolic ($P = 0.79$) blood pressure reduction as well as changes from baseline creatinine clearance ($P = 0.48$).

Table 4. Adverse events in patients with NIDDM associated nephropathy in one of three treatment groups

Adverse event	Lisinopril	NDCCBs: Verapamil SR ($N = 8$)	NDCCBs: Diltiazem SR ($N = 10$)	Atendolol ($N = 16$)
Cough[a]	4 (22)	0	0	0
Dizziness	4 (22)	2 (25)	0	3 (19)
Constipation	2 (11)	6 (75)	4 (40)	7 (44)
Headache	2 (11)	0	2 (11)	1 (6)
Impotence	0	1 (13)	2 (20)	9 (56)
Lethargy/fatigue	0	0	0	13 (81)
Exercise Intolerance	0	0	0	7 (43)
Hyperkalemia[b]	2 (11)	0	0	1 (13)
No return to F/U visits	1 (6)	1 (13)	1 (10)	3 (19)
Pedal edema	1 (6)	1 (13)	1 (10)	2 (13)
Insomnia	0	1 (13)	0	6 (38)
Dry mouth	0	0	1 (10)	13 (81)

Treatment withdrawn for one week and each patient given dietary counseling. Responsible drug reinitiated and plasma [K^+] remained at ≤ 5.5 mmol/liter in each case

[a] Cough was not intractable and did not require change of medication

[b] Defined ≥ 6 mEq/liter on any occasion.

Adverse effects of treatment

All adverse events related to drug therapy are summarized in Table 4. The most common side effect was cough in the lisinopril group. However, it was tolerable and no one had to discontinue treatment. During the study there were six deaths and five patients that needed to start dialysis. Five of the six deaths were due to cardiovascular causes (1 stroke and 4 myocardial infarctions) and one from sepsis. Four of the six deaths were in the atenolol group one in the NDCCB group, diltiazem, and one in the lisinopril group. Overall the highest side effect profile was noted in the atenolol group (Table 4). No medication discontinuance was required due to side effects.

Discussion

It is well known that reduction of blood pressure with a β blocker and/or diuretic will slow progression of diabetic nephropathy and reduce proteinuria to a modest degree in diabetic patients [2, 9, 23]. This study, however, was originally designed to test the hypothesis that CCBs that maintain reductions in proteinuria will slow progression of nephropathy associated with NIDDM to a degree comparable to ACE inhibitors, given similar levels of blood pressure control. Our data provide the first long-term evidence that NDCCBs have similar effects to an ACE inhibitor on both slowing the progression of nephropathy and maintaining sustained reductions in proteinuria. In contrast, blood pressure reduction with atenolol was less effective than either lisinopril or NDCCBs in slowing nephropathy progression. Lastly, this study demonstrates a strong correlation between proteinuria reduction and better renal outcomes among patients with NIDDM associated nephropathy, a finding already appreciated in patients with IDDM [6, 15, 16].

While the data from this study are compelling for a renoprotective effect of long acting verapamil or diltiazem, a number of

factors may account for this observation. These include: differences between groups in systolic blood pressure control, compliance with antihypertensive medication, number of patients enrolled in the study and limitations of creatinine clearance as a marker of renal function. Lastly, while the statisticians in this study were blinded to the study groups and all the analyses predetermined, the study, by virtue of its open label design, has inherent biases when compared to a double-blind placebo-controlled trial. These and related issues are discussed.

Previous studies in patients with IDDM nephropathy document that arterial pressure reduction with β adrenoreceptor antagonists reduce the rate of glomerular filtration rate loss when compared to those whose blood pressure was not controlled [2]. However, the relative effect of a β adrenoreceptor antagonist on slowing progression of diabetic nephropathy are dwarfed in comparison to an ACE inhibitor [4, 5, 9, 10, 12, 15, 16, 24]. Moreover, this latter association has also been described in patients with NIDDM nephropathy [9, 25]. Our data not only support these observations with ACE inhibitors, but extend the findings to patients with marked renal impairment from NIDDM. Moreover, we demonstrate for the first time that NDCCBs have similar renoprotective efficacy to the ACE inhibitor, lisinopril, in this group of patients.

The relatively higher level of systolic blood pressure in the atenolol group, noted at study end, may have contributed to differences in renal outcome among the groups. Two large scale clinical studies demonstrate that elevation in systolic pressure alone is a significant risk factor for progression to end-stage renal disease [26, 27]. The reasons for the higher level of systolic blood pressure in the atenolol group are unclear. Two plausible explanations, however, include a potentially greater degree of either vascular disease or medication non-compliance in this group.

From among the three groups, the atenolol group had the highest side-effect profile. This may have led to medication non-compliance in some patients and hence, higher levels of blood pressure. However, we did not observe similar trends in diastolic blood pressure. Assuming medication non-compliance was a factor, one could postulate that this trend in systolic pressure in the atenolol group might be related to a higher degree of underlying vascular disease, hence, this group may have poorer arterial compliance relative to the other groups. Unfortunately, no formal studies to test this hypothesis were not undertaken. This combined with the size of the groups precludes any definitive answer to this query. Moreover, we did not do a formal pill count to assess medication compliance, other than to monitor time to medication refill. Therefore, we cannot explain why this group had high systolic pressures.

A related factor that may explain differences in renal outcome among the groups is level to which blood pressure was reduced. A retrospective analysis of the Modification of Dietary Protein in Renal Disease (MDRD) trial demonstrates that African-Americans would not have achieved maximal benefit with regard to progression of renal disease at the level of blood pressure reduction set in our study [28]. This trial demonstrated that mean blood pressure needed to be reduced to less than 92 mm Hg for progression of renal disease to be slowed to levels comparable with Caucasians. Whether this was a factor in our study is unclear. Very few patients actually achieved and maintained blood pressures in this range throughout the study, so we do not have the statistical power to assess whether this factor contributed to the differences observed in progression of renal disease.

Reductions in proteinuria are associated with a slowed decline in renal function in persons with either insulin dependent or noninsulin dependent diabetes mellitus [2–12, 15, 16, 18]. We observed similar trends in our NIDDM patients. Furthermore, the MDRD trial demonstrated that those with higher baseline levels of proteinuria derived a greater benefit with regard to preservation of renal function from blood pressure lowering [28]. Our data support both these observations. Proteinuria reduction was independent of both systolic and diastolic pressure reduction as well as decline in creatinine clearance in our patient groups. Moreover, we used the most conservative statistical evaluation to assess the relationship between reductions in arterial pressure and changes in proteinuria. This suggests that both lisinopril and the NDCCBs may reduce proteinuria by mechanisms not directly related to blood pressure lowering. This concept is supported by recent studies demonstrating direct effects on glomerular membrane permeability by certain antihypertensive agents [17–18, 29].

Tight glucose control slows progression of early insulin dependent diabetic renal disease, as recently demonstrated by Barbosa et al [30]. Therefore, good overall glucose control would be anticipated to slow progression of diabetic nephropathy. In our study, however, the lowest baseline hemoglobin A_{1c} level was present in the atenolol group, the group with the fastest decline in renal function. Moreover, there were no significant differences in $HbA1_C$ levels between the different groups throughout the study. Therefore, it is unlikely that poor glucose control contributed to the excessive decline in renal function in the atenolol group.

Another factor that may have contributed to the differences among the groups is the presence of renal diseases other than diabetic nephropathy in the patients studied. Some studies report up tp to 25% of patients with NIDDM have renal diseases other than diabetic nephropathy to account for their renal mortality [31, 32]. However, a recent analysis of the incidence and prevalence of noninsulin dependent diabetes, especially among the elderly, suggests that diabetic nephropathy, as a cause of renal failure is seriously underestimated [33]. We are aware of this observation and designed the entry criteria to take this fact into account. While there is uncertainty about the diagnosis of NIDDM nephropathy without a renal biospy, we feel our entry criteria have eliminated most patients with other diagnoses that lead to renal failure. Moreover, five of the 52 patients studied had renal biopsies performed prior to entry into the study for other reasons, and all were consistent with a diagnosis of NIDDM associated nephropathy.

The contribution to differences in progressive renal disease among the groups may also be related to the use of a less than ideal marker of renal function, that is, creatinine clearance. While not an optimal marker of precise renal function, if used consistently to record trends in renal function, it is reproducible and accurate when compared to itself [34, 35]. Moreover, if adequate collection is ensured and correction for body mass index applied, as was done in our study, its reliability is enhanced [34, 35].

Another related factor that must also be taken into account when reviewing these data are the recent observation that secretion of creatinine is reduced by CCBs, specifically, diltiazem [36]. While this fact would lead to consistent changes in our NDCCB group, it may have affected differences between this and the other groups. However, given that CCBs reduce creatinine secretion, differences between this and the ACE inhibitor group would be

lessened not increased. Hence, we do not believe that use of this marker significantly contributed to the trends seen in our data.

A higher incidence of adverse effects is reported with the use of atenolol or diuretics compared to ACE inhibitors and CCBs [37, 38]. Our data confirm this observation. Moreover, since all patients received loop diuretics for most of the follow-up period, it is clear that the excess in adverse events was related to atenolol. This increased incidence of adverse effects may have affected medication compliance, however, as mentioned earlier we did not collect data on this variable.

Lastly, this study was designed to examine the change in creatinine clearance slopes and their relationship to changes in blood pressure and proteinuria. While there were no differences between the lisinopril and NDCCB creatinine clearance slopes, this may be the result of an underpowered study. In spite of this, the mean duration of follow-up, 5.3 years, was adequate to detect differences. Moreover, slopes were compared using a Bonferroni correction, which would partially compensate for any sample size insufficiency. Given this information clinicians should strongly consider addition of either long acting verapamil or diltiazem to either an ACE inhibitor or diuretic to achieve sufficient blood pressure control. Moreover, if patients with renal insufficiency cannot tolerate an ACE inhibitor secondary to either hyperkalemia or cough, long acting NDCCBs should be considered as alternatives for blood pressure reduction. Please note, however, that further large scale clinical trials are required to confirm these findings.

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