Kidney International, Vol. 54 (1998), pp. 889–896

Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy

AMY C. SMITH, ROBERT TOTO, and GEORGE L. BAKRIS

Rush University Hypertension Center, Department of Preventive Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, and University of Texas Southwestern Medical Center, Dallas, Texas, USA

Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy.

Background. Calcium channel blockers (CCBs) are known to have differential effects on both changes in proteinuria as well as progression of diabetic nephropathy. No clinical study, however, has evaluated whether the differential antiproteinuric effects of CCBs may be explained by their effect on glomerular membrane permeability. We, therefore, tested the hypothesis that certain subclasses of CCBs reduce proteinuria by changing size selectivity of the glomerular membrane, hence changing its permeability.

Methods. Twenty-one patients with type 2 diabetes and the presence of nephropathy with hypertension were randomized to receive either diltiazem CD or nifedipine GITS after baseline data for mean systolic and diastolic pressure, urinary protein excretion, glomerular filtration rate, renal plasma flow, neutral dextran and IgG clearances were obtained. Glomerular filtration rate, renal plasma flow, neutral dextran and IgG clearance were measured every three months, arterial pressure and heart rate every month. Patients were followed for 21 months.

Results. At 21 months, both patient groups had similar levels of blood pressure control, however, only the diltiazem group had a change in proteinuria ($4 \pm 10\%\Delta$, nifedipine vs. $-57 \pm 18\%\Delta$, diltiazem; $P < 0.001$) with improvement in glomerular size selectivity and change in IgG clearance.

Conclusions. These data support the hypothesis that CCBs that provide sustained reductions in proteinuria do so, in part, by improving glomerular size permselectivity.

At comparable levels of blood pressure control, reductions in proteinuria and/or blunted increases in microalbuminuria correlate strongly with both a reduced progression of diabetic nephropathy as well as a reduction in cardiovascular mortality [1–3]. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists consistently reduce urinary protein excretion in the presence of moderate to low sodium diets [4–7]. Conversely, the data from long-term clinical trials with calcium channel blockers (CCBs) demonstrates that their antiproteinuric effects are variable.

Recent data support the concept that nondihydropyridine (nonDHP) CCBs consistently reduce or blunt the rise in proteinuria in patients with type II diabetes who ingest a low to moderate sodium intake [8, 9]. Conversely, dihydropyridine (DHP) CCBs, regardless of their duration of action, tend to have neutral effects on proteinuria [6, 10–12]. This latter observation is supported by most literature with the exception of one small, single center study [13]. In this study, the glomerular filtration rate (GFR) declined with administration of amlodipine to the same degree as the ACE inhibitor. This is contrary to reported studies of greater than one-year duration [11, 14].

The present study examines the hypothesis that the nonDHP CCB, diltiazem CD reduces glomerular membrane permeability to high molecular weight species compared to the DHP CCB, nifedipine. Hence, the nonDHP CCB will reduce proteinuria. This change in membrane permeability is assessed by changes in glomerular size and charge selectivity. The data from this study form the basis of this report.

METHODS

The Institutional Review Boards of both Holy Family Hospital and Rush-Presbyterian-St. Luke's Medical Center approved the study protocol, where the study was conducted. All participants signed informed consents prior to entry into the study.

Study design

The inclusion and exclusion criteria for study participation are summarized in Table 1. Sixty-seven subjects were screened from both medical centers, 28 of whom were found eligible and consented to participate in the study. The baseline characteristics of the study participants are shown in Table 2. Of these, 21 completed the entire study and 15 of 21 participants completed all dextran clearance measurements. The baseline characteristics of both the

Key words: glomerular filtration rate, albuminuria, proteinuria, dextran clearance, diabetes, hypertension, and nephropathy.

Received for publication January 8, 1998
and in revised form April 6, 1998
Accepted for publication April 6, 1998

Table 1. Inclusion and exclusion criteria

Inclusion criteria
- >4 year history of type II diabetes
- >4 year history of hypertension (≥140/90 mmHg)
- >300 mg/day proteinuria
- Age ≥ 45 years

Exclusion criteria

Presence of:
- Secondary cause of hypertension
- Serum creatinine ≥2.5 mg/dl
- Clinically apparent congestive heart failure or ejection fraction <40%
- Stroke or myocardial infarction within the past year
- History of allergic reaction to study drugs
- Terminal diseases including cancer or AIDS
- Collagen vascular diseases
- Serum creatinine increase >20% over baseline within one month of study entry
- Required ingestion of ACE inhibitor, CCBs or anti-arrhythmic medications
- Psychiatric illness or mental retardation

Table 2. Baseline characteristics of all recruited participants

Variable	Nifedipine ($N = 14$)	Diltiazem ($N = 14$)
M/F	11/3	13/1
Age *years*	57 ± 4	59 ± 8
Caucasian *%*	100	93
Diabetes Hx. *years*	12 ± 5	10 ± 4
Hypertension Hx. *years*	14 ± 6	13 ± 5
Body Weight[a] *kg*	91 ± 6	88 ± 7
Family Hx. CVD *%*	85	100
Smoking Hx. *%*	36	50
ACEI naïve *%*	86	79

[a] Based on height, 89% of the participants were greater than 20% above ideal body weight

Table 3. Baseline characteristics of participants who did not complete the study including dextran clearance studies

Variable	Nifedipine ($N = 7$)	Diltiazem ($N = 6$)
Demographic		
M/F	3/4	5/1
Age *years*	60 ± 5	62 ± 4
Caucasian *%*	86	83
Diabetes Hx. *years*	14 ± 6	12 ± 7
Hypertension Hx. *years*	12 ± 5	15 ± 6
Body weight[a] *kg*	85 ± 9	83 ± 8
Family Hx. CVD *%*	86	100
Smoking Hx. *%*	43	33
ACEI naïve *%*	57	50
Hemodynamic		
Systolic pressure *mm Hg*	179 ± 8	185 ± 7
Diastolic pressure *mm Hg*	99 ± 5	102 ± 5
GFR *ml/min/1.73 m²*	88 ± 11	91 ± 8
$U_{protein}$ V *mg/day*	636 ± 194	784 ± 206

[a] Based on height, 62% of the participants were greater than 20% above ideal body weight

Table 4. Adverse events and reasons for study withdrawal

	Nifedipine ($N = 14$)	Diltiazem ($N = 14$)
Number not completing study	4 (29)	3 (21)
Adverse events		
Pedal edema	3 (21)	1 (7)
Headache	1 (7)	0
Gingival hyperplasia	1 (7)	0
Worsening DM	2 (14)	0
Nausea	1 (7)	1 (7)
Stroke	1 (7)	0
Rash	0	1 (7)

Number in parenthesis indicates the percent of a particular adverse event.

dropouts and those that did not complete the dextran measurements are summarized in Table 3. The primary reasons for dropouts during the study were related to drug side effects and summarized in Table 4. Moreover, the primary reason for only 76% participant completion of all dextran measurements related primarily to either a history of specific allergies to sulfa or penicillin type drugs or development of allergic reactions during a dextran study. Two of the six patients who did not complete the dextran studies developed an anaphalactoid type reaction during the study. The four remaining participants had previously mentioned drug allergies and refused to undergo the dextran clearance procedures.

The study design is illustrated in Figure 1. After a two-week washout period off their current antihypertensive medications, baseline measurements of arterial pressure, fasting blood glucose, serum IgG levels and hemoglobin A_1c were assessed. Additionally, glomerular filtration rate (GFR) as measured by inulin clearance, renal plasma flow (RPF) as assessed by para-aminohippurate clearance, dextran clearance along with 24-hour urinary protein, albumin and IgG excretion were measured. Participants were then randomized to receive either nifedipine or diltiazem in a once daily preparation to achieve a goal blood pressure of < 140/90 mm Hg. These agents were titrated to achieve a blood pressure goal of < 140/90 mm Hg or until a maximum dose of 90 mg or 480 mg per day of nifedipine or diltiazem, respectively was attained. If blood pressure goal was not achieved, furosemide, 40 milligrams once daily, was added. If control was still inadequate, clonidine, at a starting dose of 0.1 mg twice daily, was added and titrated upwards. Furosemide was selected to help restore volume homeostasis, a well-known problem in with diabetes and renal insufficiency [15]. Clonidine was selected due to its neutral effects on proteinuria [16]. After blood pressure control was achieved, participants had monthly follow-up visits to insure appropriate blood pressure control and medication compliance. Additionally, they returned every three months for measurement of GFR, RPF, and 24-hour urinary determinations of total protein, albumin and sodium excretion rates. Additionally, every six months IgG and dextran clearances were assessed.

Following baseline measurements of all variables, all

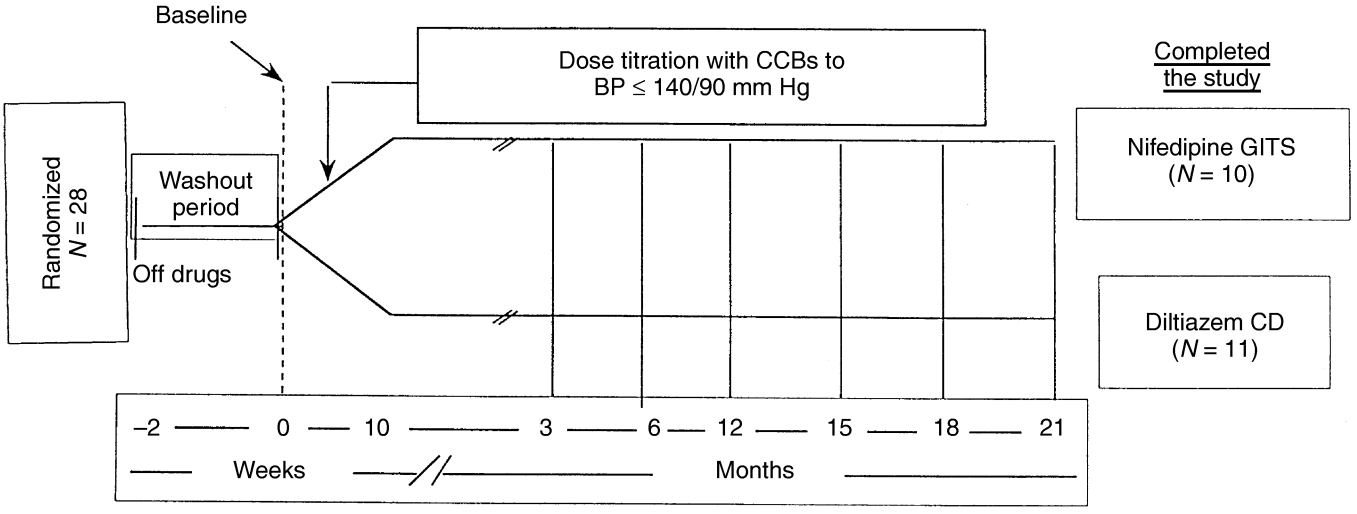

Fig. 1. Illustrated protocol. Abbreviations are: CCBs, calcium channel blockers; BP, blood pressure.

participants were counseled to follow moderately low sodium, that is, <120 mEq per day sodium diet. To improve compliance with the diet, it was reviewed at each visit. Moreover, participants were informed that we would assess sodium intake through urinary determinations.

Renal hemodynamic measurements

In each case urine was voided spontaneously after diuresis had been established with oral water loading. A priming infusion containing 10% inulin (30 mg/kg), neutral dextrans (140 mg/kg) and 20% sodium para-aminohippuric acid (PAH, 8 mg/kg) was then administered over 30 minutes. Thereafter, inulin, PAH and neutral dextrans were continuously infused to maintain plasma levels constant at 20 and 1.5 mg/dl of inulin and PAH, respectively. Four carefully timed urine collections were then made, each of which was bracketed by blood samples drawn from a peripheral vein. The average inulin clearance for the timed collection periods was taken to represent the GFR.

Plasma and urine concentration of PAH and inulin for determination of RPF and GFR, respectively, were measured as previously described [17]. Plasma and urine samples for dextran sieving were analyzed by previously published methods [18]. Briefly, urine and plasma samples were deproteinized with $ZnSO_4$ and 0.75 N NaOH. The samples were centrifuged at 4°C for 10 minutes and the supernatant was decanted, recentrifuged then dehydrated by Speed-vac overnight, reconstituted and prefiltered. Separation of dextrans into narrow fractions was performed by HPLC (Beckman Instruments, Fullerton, CA, USA) using Ultragel 500 and 250 columns in series (Millipore, Milford, MA, USA). The columns were calibrated with four narrowly dispersed dextrans of known molecular weight (10, 20, 40, 70). Dextran concentration was measured using an on-line UV detector (Model 156; Beckman Instruments Inc.). Chromatograms were translated into a PRN file and the area under the curve for the region of interest corresponding to 32 to 70 angstroms (Å) was analyzed by SigmaPlot for Windows version 2.0 (Jandel Scientific Software, San Rafael, CA, USA). Sieving curves were constructed from slices taken at 2.0 Å increments and the area for each slice equated with the dextran concentration at the corresponding retention time. Fractional dextran clearance at each radius (θm) was computed from the first timed collection using the equation

$$\theta m = U_{dextran} \cdot P_{inulin}/U_{inulin} \cdot P_{dextran}$$

where the urine-to-midpoint plasma concentration ratio of sized dextran was assessed. Additionally, the clearances of other macromolecules that is, albumin and IgG, were also assessed in the same way.

IgG concentrations were measured by nephrolometry (Behring Diagnostics, San Jose, CA, USA). Samples underwent electrophoresis, using lazer analysis, to determine total IgG concentrations.

Statistical analysis

The study was designed with 80% power to detect a 30% difference in proteinuria reduction from baseline levels between CCB groups. We assumed a five percent reduction in the nifedipine group. Proteinuria, however, increased in the nifedipine group by 4.6%. Therefore, the power to detect a 30% reduction was adequate.

All data are expressed as mean ± SD from the mean. Comparisons between groups with regard to proteinuria and demographic characteristics were assessed by an analysis of variance. Even with adequate power, we used a Bonferonni correction in our analyses to reduce the probability of committing a Type I error. Differences between groups with regard to dextran and IgG clearances were assessed by a Student's *t*-test comparing baseline to 21-month values. Differences between groups were evaluated

Table 5. Baseline and 21 month systemic and renal hemodynamic, metabolic profiles of 21 patients with NIDDM nephropathy

	Nifedipine XL ($N = 10$)		Diltiazem CD ($N = 11$)	
	Baseline	21 Months	Baseline	21 Months
Arterial pressure				
Systolic mm Hg	172 ± 11	136 ± 9[a]	182 ± 12	138 ± 9[a]
Diastolic *mm Hg*	106 ± 6	84 ± 5[a]	104 ± 6	86 ± 7[a]
Renal				
GFR *ml/min/1.73 m²*	94 ± 8	91 ± 9	98 ± 7	101 ± 9
RPF *ml/min/1.73 m²*	397 ± 31	434 ± 32	448 ± 34	472 ± 36
$U_{protein}$ V *mg/day*	873 ± 167	905 ± 208	908 ± 234	389 ± 127[a]
U_{sodium} V *mmol/day*	171 ± 32	136 ± 37	158 ± 28	129 ± 32
U_{IgG} V *mg/dl*	0.72 ± 0.27	0.98 ± 0.36	0.65 ± 0.22	0.29 ± 0.17[a]
Metabolic				
FBS *mg/dl*	178 ± 16	165 ± 18	192 ± 13	171 ± 15
HbA_1c[b] %	8.9 ± 0.7	8.2 ± 0.8	9.4 ± 0.8	8.5 ± 0.7

Abbreviations are: FBS, fasting blood sugar; GFR, glomerular filtration rate; RPF, renal plasma flow.
[a] $P < 0.05$ compared to baseline values. [b] Normal range for HbA_1c are 3.8–6.2%

for clearances of dextran molecules of various sizes ranging from 30 to 60 Å. Differences were regarded as significant when $P < 0.05$.

RESULTS

General

The baseline systemic and renal hemodynamic as well as metabolic profile of the participants who completed the study is listed in Table 5. There were no significant differences between any baseline values between groups. Moreover, a comparison of the demographic features between those who completed the study versus dropouts failed to reveal any significant difference between groups. However, the dropout group tended to be slightly older with a female preponderance in the nifedipine group.

The trends in arterial pressure, proteinuria and HbA_1c are summarized in Figures 2 to 4. No significant differences were noted between groups with regard to either of these variables at any time points measured throughout the study. Moreover, to achieve adequate blood pressure control each person ingested an average of 2.6 and 2.8 different antihypertensive agents in the nifedipine and diltiazem groups, respectively. The breakdown of doses and types of agents used are summarized in Table 6. Compliance with sodium intake is found in Table 5. No significant differences in sodium intake were noted between groups.

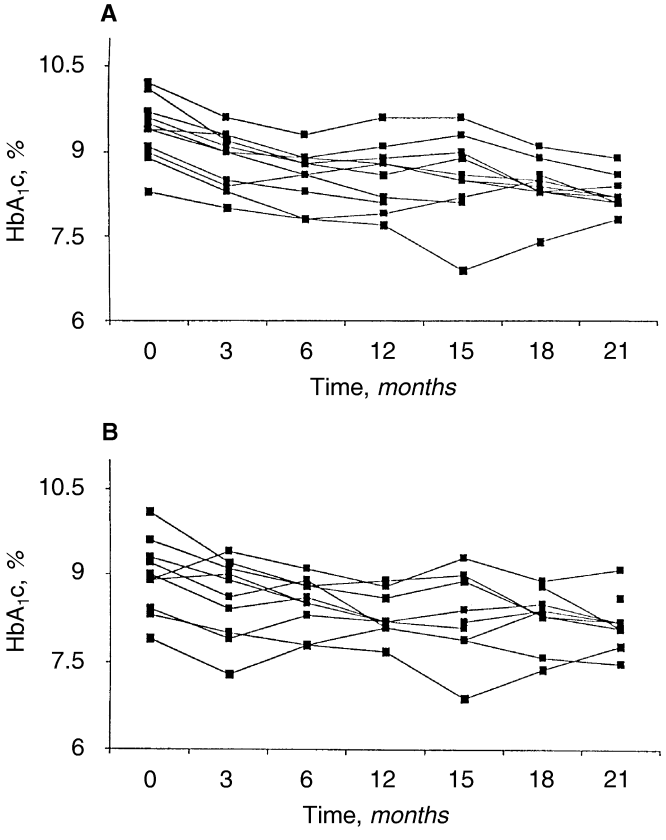

Fig. 2. Effects of nifedipine (*A*) or diltiazem (*B*) in a once daily dosage formulation on HbA_1c throughout the study period in each patient.

Renal hemodynamics

GFR and RPF were not significantly altered over the 21-month period of study in either group (Table 5). The changes in proteinuria at baseline and study-end are also noted in Table 5. Trends in proteinuria changes in each patient that completed the study are illustrated in Figure 4. Clear differences at 21 months were noted between groups in the amount of proteinuria change from baseline (4 ± 10%Δ, nifedipine vs. −57 ± 18%Δ, diltiazem, $P < 0.001$). Furthermore, only the group randomized to diltiazem manifested a reduced clearance with too large sized dextrans (≥ 50 Å) at 21 months (Fig. 5).

Reduction in dextran clearance was paralleled by a reduction in IgG clearance in the diltiazem group (5.9 ± 2.3, baseline vs. 2.6 ± 1.7 × 10^{-5}, 21 months; $P < 0.05$). IgG clearance was not reduced in the nifedipine group (7.6 ± 3.1, baseline vs. 11.2 ± 4.3 × 10^{-5}, 21 months; $P = 1.8$). The change in clearance of large sized dextrans was

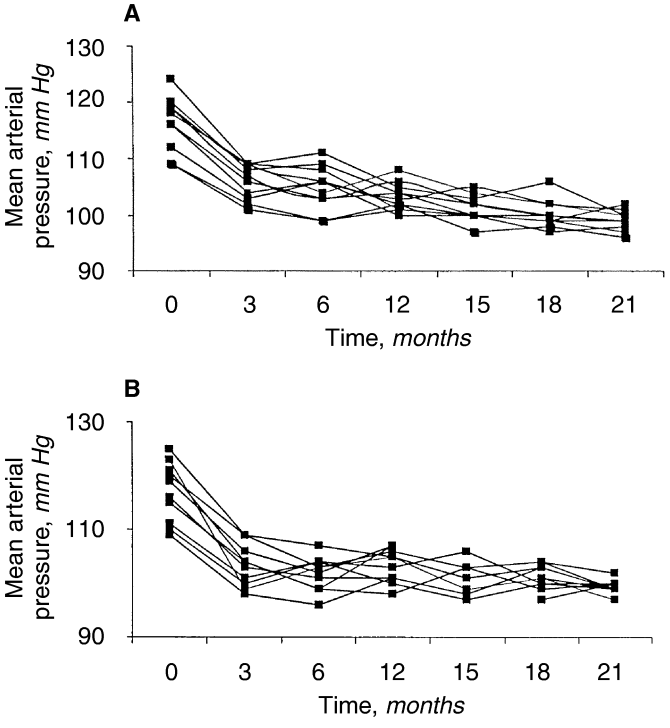

Fig. 3. Effects of nifedipine (*A*) or diltiazem (*B*) in a once daily dosage formulation on mean arterial pressure throughout the study period in each patient.

not significant, however, until one year after the study started (Fig. 5). Moreover, the trends in size selectivity change continued until study end, although they were not significantly different from those at one year the the larger sized dextrans (Fig. 5). This reduction in clearance of large sized dextrans correlated with reductions in proteinuria at 21 months ($r = 0.62$; $P < 0.03$). This correlation was not present at six months but was detectable at one year ($r = 0.49$; $P < 0.05$). Additionally, the change in proteinuria from baseline did not become significant in the diltiazem group until six months after the study started (Fig. 4). Therefore, changes in membrane permeability account for only part of the benefit in proteinuria change.

DISCUSSION

This study provides the first evidence to explain differences in antiproteinuric effects between subclasses of CCBs in participants with nephropathy from type 2 diabetes. While some of the early changes in proteinuria in the diltiazem group may be ascribed to hemodynamic changes, that is, blood pressure reduction, this does not explain the entire effect, since proteinuria was not reduced with nifedipine. It is clear that changes in membrane size selectivity also contribute significantly to this antiproteinuric effect.

The changes in size selectivity especilly to large sized dextrans begin to occur as early as six months after diltiazem is initiated but do not become significant until one year. Moreover, these reductions in dextran clearance to large sized dextrans continue for at least another nine months. These changes in membrane size selectivity correlate with changes in proteinuria in participants treated with diltiazem but not nifedipine. This contrast in proteinuria reduction could not be explained by differences in blood pressure at any time point or other baseline demographic data. Moreover, our data on size selectivity and proteinuria extend the findings of Hartmann et al, who failed to demonstrate a reduction in proteinuria or size permselectivity among participants with hypertension and non-diabetic renal disease that received nifedipine [19]. Thus, our data, taken together with other human and animal studies, strongly supports the notion that DHP CCBs do not affect glomerular permeability and hence, proteinuria [2, 20, 21].

Previous studies have clearly established the utility of dextran clearance as a method of determining size selective properties of the glomerular capillary wall (GCW) [22, 23]. These studies demonstrate that those with proteinuria have an increased transglomerular passage of dextrans with a radius of > 50 Å [24]. Our data support this observation. Moreover, it is the reduction in transglomerular passage of these larger sized dextrans that primarily account for the attenuated increase in proteinuria that is observed with diltiazem. Additionally, a reduction in IgG clearance further supports the concept of altered permeability of the GCW. According to pore theory, this reduction in permeability is presumably due to an expansion of the minor region of the GCW that behaves as a non-restrictive shunt pathway [22].

Reductions in proteinuria are important in diabetes since they have been associated with a slowed progression of renal disease [2]. Evidence from a *post hoc* analysis of The Captopril trial by Hebert et al demonstrate that individuals with reductions in nephrotic range proteinuria manifested a remission in renal disease [1]. Moreover, we and others have demonstrated that among patients with diabetic nephropathy those who manifest reductions in proteinuria also manifest a slowing in nephropathy progression [8, 9, 25]. Additionally, both animal and human studies reveal that blood pressure control without proteinuria reduction does not slow progression of nephropathy [11, 26, 27]. Thus, while blood pressure reduction is clearly important in patients with diabetic nephropathy, reduction in proteinuria must also be a consideration to optimally preserve renal function.

Another possible explanation for the differences in proteinuria reduction between these two CCBs might be differences in intrarenal hemodynamic effects. *In vitro* studies reveal that while diltiazem dilates both the afferent and efferent arterioles, nifedipine does not [28, 29]. However, in animal models of diabetes these CCBs [27, 30] do not reduce increases in intraglomerular pressure that result from both afferent dilation and efferent arteriole constriction. Thus, differences in intrarenal hemodynamics do not

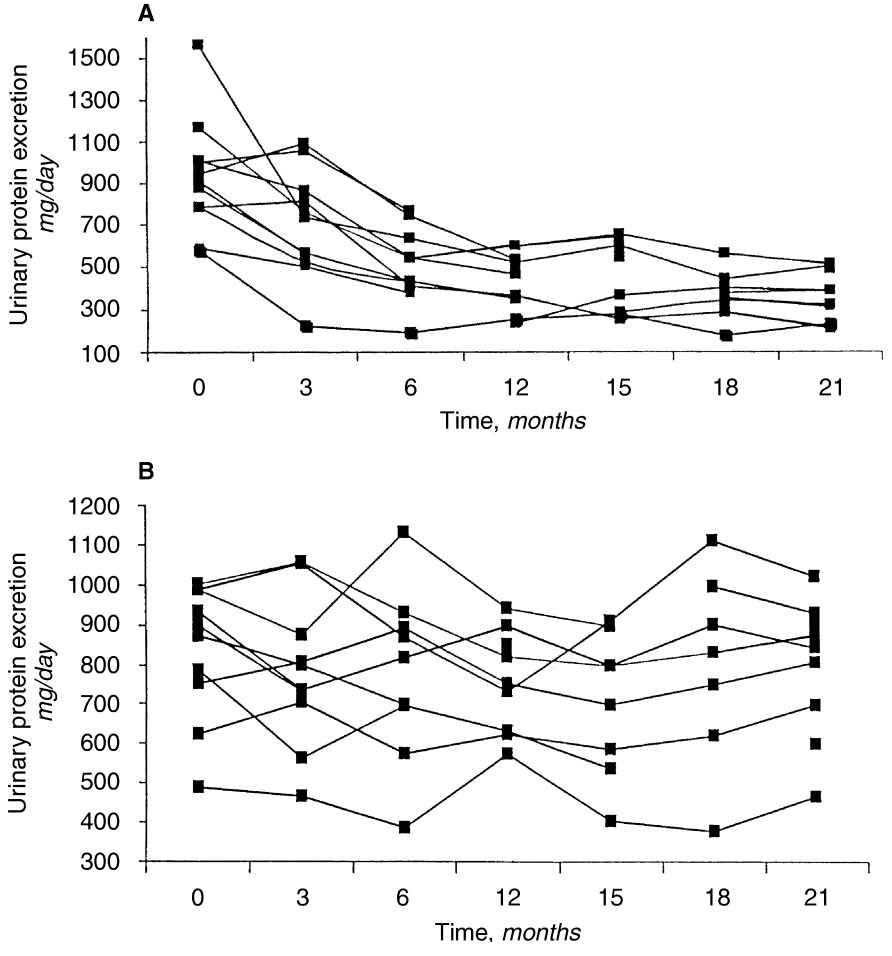

Fig. 4. Effects of diltiazem (*A*) or nifedipine (*B*) in a once daily dosage formulation on urinary protein excretion throughout the study period in each patient.

Table 6. Distribution of all antihypertensive agents used in study including the mean dose of each

	Nifedipine ($N = 10$)	Diltiazem ($N = 11$)
Mean dose of randomized drug *mg*	78 ± 12	436 ± 43
Mean dose of furosemide *mg*	40 (9)	40 (11)
Mean daily dose of clonidine[a] *mg*	0.29 ± 0.07 (4)	0.25 ± 0.04 (3)

Numbers in parentheses indicate number of people in group receiving this medication. Randomized drug was titrated to maximum prior to addition of other agents.

[a] Half the dose given twice daily

explain the variance in antiproteinuric effect between these two different CCBs.

The level of blood pressure achieved may also create differences in intrarenal hemodynamics. One animal study has demonstrated that nonDHP CCBs reduce efferent arteriolar tone and intraglomerular pressure [31]. However, blood pressure in these animals was profoundly reduced. Conversely, this has not been shown with either nifedipine or amlodipine [27, 32]. In clinical studies of patients with nephropathy, the level of blood pressure reduction also seems to affect progression of nephropathy [33, 34]. We did not randomize to different levels of blood pressure control, however, nor was there a difference in blood pressure control throughout our study. Moreover, based on animal data this would not have had an impact on outcome since nifedipine did not appear to protect the kidney even at lower blood pressures.

Other possible explanations for the differential effects of CCBs on proteinuria include (*a*) a differential distribution of calcium channels on the GCW, and (*b*) differential effects of CCBs on various structural proteins such as heparan sulfate of glucosaminoglycan or differences in autoregulatory responses of the kidney [35–37]. Animal experiments in diabetic animals clearly demonstrate an attenuated decrease in both glucosaminoglycan and heparan sulfate by diltiazem [38]. Moreover, nonDHP CCBs have been shown to blunt the increase in mesangial matrix expansion and proteinuria in animal model of diabetes [39]. Thus, diltiazem appears to have properties that affect

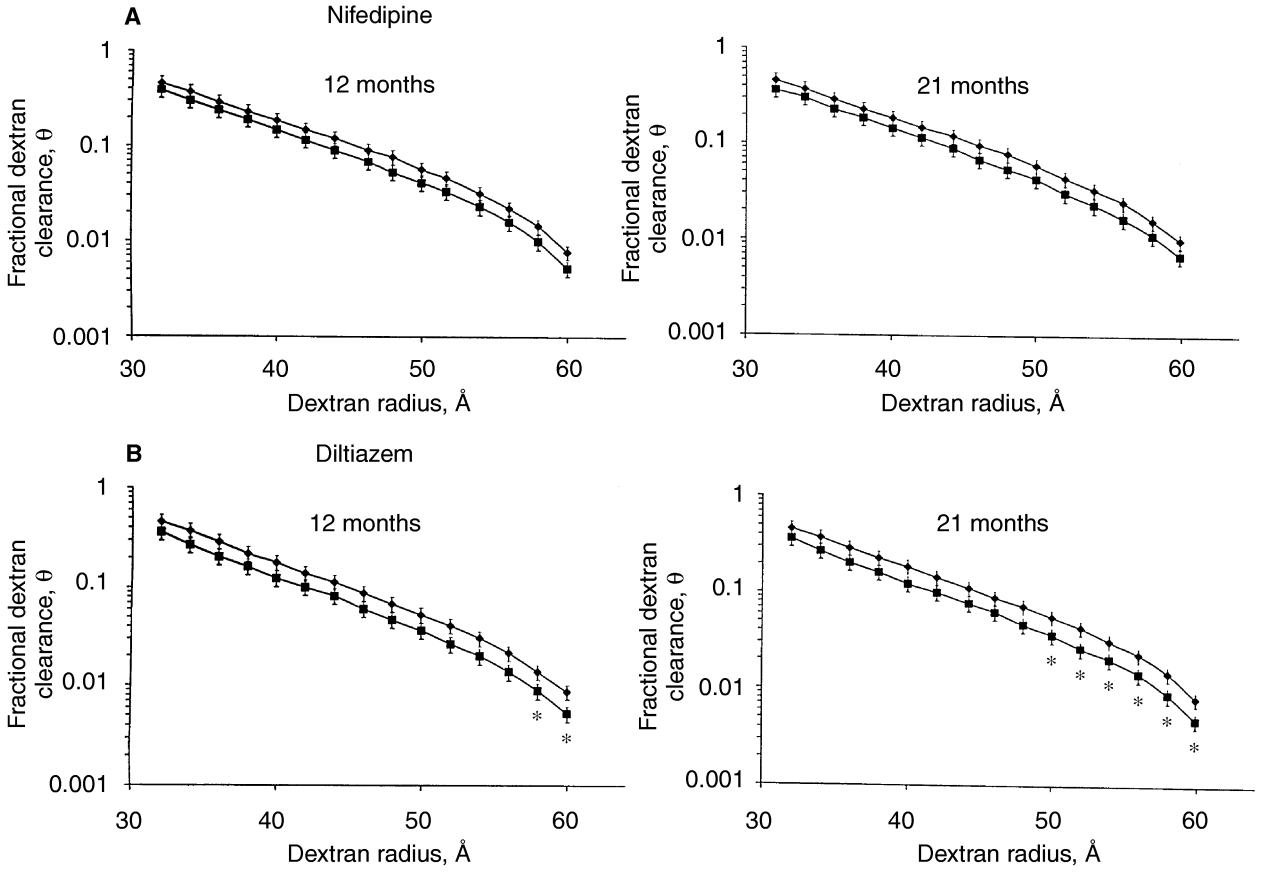

Fig. 5. Fractional dextran clearance profiles at baseline (off drug), at one year and 21 months in the presence of nifedipine (*A*) or diltiazem (*B*) in a once daily dosage.

glomerular permselectivity in different ways than nifedipine. This helps explain the differential effects of these two agents on proteinuria.

ACKNOWLEDGMENTS

This study was funded, in part, by an investigator-initiated grant from Hoechst Marion Roussell and Rush Presbyterian/St. Luke's Medical Center. We thank Ms. Kim Jones for her excellent technical support, Dinah White, RN and Mary Ann Gates, MSN for their administrative and recruiting assistance, and Ms. Juanita Buentello for her secretarial assistance. We are also grateful to Dr. Pete Meyer who assisted in the statistical analysis.

Reprint requests to George L. Bakris, M.D., Rush-Presbyterian-St. Luke's Medical Center, 1725 W. Harrison Street, Suite #119, Chicago, Illinois 60612, USA.
E-mail: gbakris@rpslmc.edu

APPENDIX

Abbreviations used in this article are: ACE, angiotensin converting enzyme; CCBs, calcium channel blockers; DHP, dihydropyridine; GCW, glomerular capillary wall; GFR, glomerular filtration rate; HPLC, high-pressure liquid chromatography; nonDHP, nondihydropyridine; PAH, para-aminohippuric acid; RPF, renal plasma flow.

REFERENCES

1. Hebert LA, Bain RP, Verme D, Cattran D, Whittier FC, Tolchin N, Rohde RD, Lewis EJ, for the Collaborative Study Group: Remission of nephrotic range proteinuria in type I diabetes. *Kidney Int* 46:1688–1693, 1994
2. Bakris GL: Microalbuminuria: Prognostic implications. *Curr Opin Nephrol Hypertens* 7:219–223, 1996
3. Parving HH, Smidt UM, Hommel E: Effective antihypertensive treatment postpones renal insufficiency in diabetic nephropathy. *Am J Kidney Dis* 22:188–195, 1993
4. Heeg JE, deJong PE, van der Hem GK, de Zeeuw D: Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int* 36:272–279, 1989
5. Gansevoort RT, de Zeeuw D, Shahinfar S, Redfield A, de Jong PE: Effects of the angiotensin II antagonist losartan in hypertensive patients with renal disease. *J Hypertens* 12 (Suppl 2):S37–S42, 1994
6. Bakris GL, Smith AC: Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 125:201–203, 1996
7. Bakris GL, Weir MR: Salt intake and reductions in arterial pressure and proteinuria: Is there a direct link? *Am J Hypertens* 9:200S–206S, 1996
8. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S: Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int* 50:1641–1650, 1996
9. Bakris GL, Mangrum A, Copley JB, Vicknair N, Sadler R: Calcium channel or beta blockade on progression of diabetic renal disease in African-Americans. *Hypertension* 29:743–750, 1997
10. Abbott K, Smith AC, Bakris GL: Effects of dihydropyridine calcium antagonists on albuminuria in diabetic subjects. *J Clin Pharmacol* 36:274–279, 1996
11. Remuzzi G, Ruggenenti P, Benigni A: Understanding the nature of renal disease progression. *Kidney Int* 51:2–15, 1997

12. Rossing P, Tarnow L, Boelskifte S, Jensen BR, Nielsen FS, Parving HH: Differences between nisoldipine and lisinopril in GFRs and albuminuria in hypertensive IDDM patients with diabetic nephropathy during the first year of treatment. *Diabetes* 46:481–487, 1997
13. Velussi M, Brocco E, Frigato F, Zolli M, Muollo B, Maioli M, Carraro A, Tonolo G, Fresu Cernigoi A, Fioretto P, Nosadini R: Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. *Diabetes* 45:216–222, 1996
14. Tarif N, Bakris GL: Preservation of renal function: the spectrum of effects by calcium channel blockers. *Nephrol Dial Transplant* 12:2244–2250, 1997
15. Rocchini AP, Katch V, Kveselis D, Moorehead C, Maring MN, Lampamn R, Gregory M: Insulin and renal sodium retention in obese adolescents. *Hypertension* 14:367–374, 1989
16. Warren SE, O'Connor DT, Cohen IM, Mitas JA: Renal hemodynamic changes during long-term antihypertensive therapy. *Clin Pharmacol Ther* 29:310–317, 1981
17. Mitchell HC, Smith RD, Cutler PA, Sica D, Videon J, Thompson-Bell S, Jone K, Bradley-Guidry C, Toto RD: Racial differences in the renal response to blood pressure lowering during chronic angiotensin converting enzyme inhibition: A prospective, double-blind randomized comparison of fosinopril and lisinopril in older hypertensives with mild to moderate renal insufficiency. *Am J Kidney Dis* 29:897–907, 1997
18. Chan AYM, Cheng, MLL, Keil LC, Myers BD: Functional response of healthy and diseased glomeruli to a large, protein-rich meal. *J Clin Invest* 81:245–254, 1998
19. Hartmann A, Lund K, Holdasas H, Fauchald P, Reisaeter A, Berg KJ: Contrasting short term effects of nifedipine on glomerular and tubular functions in glomerulonephritic patients. *J Am Soc Nephrol* 5:1385–1390, 1994
20. August P, Lenz T, Laragh JH: Comparative renal hemodynamic effects of lisinopril, verapamil, and amlodipine in patients with chronic renal failure. *Am J Hypertens* 6:148S–154S, 1993
21. Abbott K, Smith AC, Bakris GL: Effects of dihydropyridine calcium antagonists on albuminuria in diabetic subjects. *J Clin Pharmacol* 36:274–279, 1996
22. Nakamura Y, Myers BD: Charge selectivity of proteinuria in diabetic glomerulopathy. *Diabetes* 37:1202–1211, 1989
23. Drumond MC, Kristal B, Myers BD, Deen WM: Structural basis for reduced glomerular filtration capacity in nephrotic humans. *J Clin Invest* 94:1187–1195,1994
24. Moscorie L, Remuzzi A, Ruggenenti P, Sangalli F, Gamara V, Remuzzi G: Glomerular size-selective dysfunction is not ameliorated by ACE inhibition and Ca channel blockade. (abstract) *J Am Soc Nephrol* 7:1362, 1996
25. Rossing P, Hommel E, Smidt UM, Parving HH: Reduction in albuminuria predicts a beneficial effect on diminishing the progression of human diabetic nephropathy during antihypertensive treatment. *Diabetologia* 37:511–516, 1994
26. Zucchelli P, Zuccala A, Borghi M, Fusaroli M, Sasdelli M, Stallone C, Sanna G, Gaggi R: Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int* 42:452–458, 1992
27. Anderson S, Rennke HG, Brenner BM: Nifedipine versus fosinopril in uninephrectomized diabetic rats. *Kidney Int* 41:891–897, 1992
28. Carmines PK, Navar LG: Disparate effects of Ca channel blockade on afferent and efferent arteriolar responses to ANG II. *Am J Physiol* 256(6 Pt 2):F1015–F1020, 1989
29. Carmines PK, Fowler BC, Bell PD: Segmentally distinct effects of depolarization on intracellular [Ca^{2+}] in renal arterioles. *Am J Physiol* 265(5 Pt 2):F677–F685, 1993
30. Brown SA, Walton CL, Crawford P, Bakris GL: Long-term effects of different antihypertensive regimens on renal hemodynamics and proteinuria. *Kidney Int* 43:1210–1218, 1993
31. Anderson S: Renal hemodynamics of calcium antagonists in rats with reduced renal mass. *Hypertension* 17:288–295, 1991
32. Dworkin LD, Benstein JA, Tolbert E, Feiner HD: Salt restriction inhibits renal growth and stabilizes injury in rats with established renal disease. *J Am Soc Nephrol* 7:437–442, 1996
33. Dillon JJ: The quantitative relationship between treated blood pressure and progression of diabetic renal disease. *Am J Kidney Dis* 22:798–802, 1993
34. Toto R, Mitchell HC, Smith RD, Lee HC, McIntire D, Pettinger WA: "Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis. *Kidney Int* 48:851–858, 1995
35. Makrilakis C, Bakris GL: Calcium Channel Blockers:Are they created equal with regard to slowing progression of diabetic nephropathy, in *Calcium Antagonists in Clinical Medicine* (2nd ed), edited by Epstein M, Philadelphia Hanley and Belfus Publishers (in press)
36. Griffin KA, Picken MM, Bidani AK: Deleterious effects of calcium channel blockade on pressure transmission and glomerular injury in rat remnant kidneys. *J Clin Invest* 96:793–800, 1995
37. Perez-Reyes E, Schneider T: Molecular biology of calcium channels. *Kidney Int* 48:1111–1124, 1995
38. Jyothirmayi GN, Reddi AS: Effect of diltiazem on glomerular heparan sulfate and albuminuria in diabetic rats. *Hypertension* 21(6 pt 1):795–802, 1993
39. Gaber L, Walton C, Brown S, Bakris, GL: Effects of different antihypertensive treatments on morphologic progression of diabetic nephropathy in uni-nephrectomized dogs. *Kidney Int* 46:161–169, 1994