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PERSPECTIVES IN RENAL MEDICINE

Differential effects of calcium antagonist subclasses on markers of nephropathy progression

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Differential effects of calcium antagonist subclasses on markers of nephropathy progression.

Background. Numerous studies suggest that the dihydropyridine calcium antagonists (DCAs) and nondihydropyridine calcium antagonists (NDCAs) have differential antiproteinuric effects. Proteinuria reduction is a correlate of the progression of renal disease. In an earlier systematic review, calcium antagonists were shown as effective antihypertensive drugs, but there was uncertainty about their renal benefits in patients with proteinuria and renal insufficiency.

Methods. A systematic review was conducted to assess the differential effects of DCAs and NDCAs on proteinuria in hypertensive adults with proteinuria, with or without diabetes, and to determine whether these differential effects translate into altered progression of nephropathy. Studies included in the review had to be randomized clinical trials with at least 6 months of treatment, include a DCA or NDCA treatment arm, have one or more renal end points, and have been initiated after 1986. Summary data were extracted from 28 studies entered into two identical but separate databases, which were compared and evaluated by independent reviewers. The effects of each drug class on blood pressure ($N = 1338$) and proteinuria ($N = 510$) were assessed.

Results. After adjusting for sample size, study length, and baseline value, there were no statistically significant differences in the ability of either class of calcium antagonist to decrease blood pressure. The mean change in proteinuria was +2% for DCAs and −30% for NDCAs (95% CI, 10% to 54%, $P = 0.01$). Consistently greater reductions in proteinuria were associated with the use of NDCAs compared with DCAs, despite no significant differences in blood pressure reduction or presence of diabetes.

Conclusion. This analysis supports (*1*) similar efficacy between subclasses of calcium antagonists to lower blood pressure, and (*2*) greater reductions in proteinuria by NDCAs compared to DCAs in the presence or absence of diabetes. Based on these findings, NDCAs, alone or in combination with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), are suggested as preferred agents to lower blood pressure in hypertensive patients with nephropathy associated with proteinuria.

Key words: proteinuria, hypertension, diabetes, dialysis.

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Over the past 20 years, while deaths attributed to hypertensive vascular disease have declined in the United States, the incidence of end-stage renal disease (ESRD) associated with hypertension has increased [1]. Moreover, the presence of even early stage nephropathy is an independent risk factor for development of cardiovascular events [2]. Therefore, slowing progression of kidney disease is an important factor to consider when selecting antihypertensive medications for patients with kidney disease and proteinuria.

Proteinuria is a sensitive and independent predictor for the progression of nephropathy and cardiovascular disease [3–8]. Several clinical studies have shown that higher levels of proteinuria are associated with increased progression of renal and cardiovascular disease and that reductions in proteinuria are associated with a decrease in the rate of renal function deterioration and cardiovascular events [4–7, 9]. As a result of this relationship, proteinuria is frequently used as a surrogate end point in clinical research studies assessing the effects of antihypertensive agents on the progression of renal disease [5].

Reductions in blood pressure have been associated with decreases in both urine protein excretion and the progression of nephropathy in patients with chronic kidney disease [4, 8, 10–12]. Both the angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to have these effects [12–16]. However, the evidence for the renoprotective effects of calcium antagonists is more equivocal. This is exemplified by the results of prospective randomized trials where, in spite of similar levels of blood pressure, nephropathy progression was faster and proteinuria

higher in the group randomized to a dihydropyridine calcium antagonist (DCA) compared to a blocker of the renin-angiotensin system (RAS) [12, 14, 16].

A number of studies have suggested that the dihydropyridine and nondihydropyridine subclasses of calcium antagonists may have differential effects on proteinuria and the progression of renal disease [11, 12, 16–19]. In an earlier systematic review by Kloke et al, the authors concluded that calcium antagonists are effective antihypertensive drugs, but there was uncertainty about the renal benefits of these medications in patients with proteinuric renal disease and renal insufficiency [5]. In several studies, dihydropyridine calcium antagonists (DCAs) were not shown to reduce proteinuria or slow the progression of renal insufficiency [9, 11, 12, 18, 20–36]. In a limited number of studies, data suggested that nondihydropyridine calcium antagonists (NDCAs) may provide beneficial effects on kidney function [19, 37–41]. However, data from an adequately powered clinical trial are needed to reach a conclusion regarding the ability of NDCAs to reduce proteinuria and slow nephropathy progression.

The purpose of this systematic review was to evaluate data from recent clinical studies to determine the differential effects of calcium antagonists on renal outcomes as measured by changes in proteinuria. The primary objective was to assess whether DCAs and NDCAs have differential effects on proteinuria in hypertensive adults with or without diabetes.

METHODS

Data sources

Multiple sources were used to obtain published and unpublished data relevant to this systematic review. Computerized databases, including MEDLINE, PubMed, Internet Grateful Med, Library of the National Medical Society, Find Articles, and EMBASE, were searched using key words and index terms to identify relevant published articles (Table 1). The references from these articles were reviewed to identify additional clinical trials. In addition, governmental agencies, medical organizations, thought leaders, and pharmaceutical companies that manufacture a calcium antagonist were contacted to identify additional studies, with either negative or positive outcomes that should be considered for inclusion in the systematic review. It should be noted that no additional substantive data beyond that of the published literature was produced using these sources. All studies considered for this review were documented. From the 139 abstracts screened, 47 full-text articles were retrieved, and 20% (28/139) were included in the review [9, 11, 12, 17–41]. Criteria for study selection are described below.

Table 1. Key words and index terms used to identify articles for inclusion in the review

Albumin	Gallopamil
Albuminuria	Glomerular filtration rate (GFR)
Angiotensin-converting enzyme (ACE) inhibitor	Hemodialysis
Angiotensin receptor blocker (ARB) inhibitor	High blood pressure
Calcium antagonist	Microalbuminuria
Calcium-channel blocker	Nephropathy
Chronic renal failure	Nicardipine
Creatinine	Nifedipine
Creatinine clearance	Nimodipine
Diabetes	Nisoldipine
Diabetic	Nondihydropyridine (NDHP)
Dihydropyridine (DHP)	Protein
Diltiazem	Proteinuria
End-stage renal disease (ESRD)	Renal
Felodipine	Verapamil

Study selection

Summary data was obtained from 28 randomized, controlled trials assessing the effects of calcium antagonists on renal end points in hypertensive patients with and without diabetes. In order to be included in the review, studies had to be designed as a randomized clinical trial with a duration of at least 6 months of treatment; had to include a DCA or NDCA treatment arm; had to have 1 or more renal end points (e.g., proteinuria, glomerular filtration rate [GFR], creatinine level, ESRD, or dialysis); and had to have been initiated after 1986. This cut-off date was chosen for two reasons. Prior to 1986, proteinuria was not used as an end point in any controlled, randomized trials of the effects calcium antagonists on renal function, and after this date, a highly sensitive radioimmunoassay became the most commonly used technique for measuring urine protein [42]. Twenty-eight studies were included in this systematic review. Twenty-one studies included DCA treatment groups, six included NDCA treatment groups, and 1 included both (Table 2). Five studies included treatment arms with combination therapy of calcium antagonists and ACE inhibitors.

In the systematic review process, the validity or quality of each study included in the review must be measured. However, the authors recognized that this approach is inherently subjective and has been the subject of some controversy [43–45]. As a result, an assessment of the methodologic quality of each study in this review was completed by instituting strict selection criteria that were specific to the design of the study. Because the selection criteria were objective, a single individual assessed the quality of each study. This individual was blinded to the outcome of the study in order to minimize selection bias. These criteria were employed to ensure inclusion only of studies with high methodological quality with respect to the study design. Studies that were relevant to the clinical

Table 2. Summary of treatment groups contributed by each study[a]

Author	Number	DCA *number*	NDCA *number*	Study length *months*	Medication	Mean dose (SD)/regimen	Primary end points
Abbott, Smith, and Bakris [18]	28	28	0	6	Nifedipine XL	71 (7) mg QD	Proteinuria
					Nifedipine XL	78 (9) mg QD	
					Isradipine	15 (6) mg TDD	
					Isradipine	19 (4) mg TDD	
Agodoa et al [11]	653	217	0	36	Ramipril	2.5–10 mg QD	Change in GFR (GFR slope)
					Amlodipine	5–10 mg QD	
Bakris, Barnhill, and Sadler [37]	30	0	16	12	Lisinopril	29 (2) mg [10–40 mg] ND[a]	Albuminuria, change in GFR
					Verapamil SR	362 (21) mg [240–480 mg] ND	
					Lisinopril + verapamil SR	16 (2) mg [10–25 mg] + 187 (8) mg [180–240 mg] ND	
					Hydrochlorothiazide + guanfacine	19 (3) mg [12.5–25 mg] + 2 (1) mg [1–3] mg ND	
Bakris et al [19]	52	0	18	63	Lisinopril	15 (9) mg QD	Change in creatinine clearance (creatinine clearance slope), proteinuria
					Verapamil SL or diltiazem	205 (16) mg or 212 (19) mg BID	
					Atenolol	86 (9) mg QD	
Bakris et al [38]	37	0	25	12	Verapamil	180–360 mg QD	Proteinuria
					Trandolapril	2–8 mg QD	
					Verapamil + trandolapril	180–24 mg + 2–4 mg QD	
Bianchi et al [20]	16	8	0	12	Enalapril	20 mg QD	Proteinuria, change in creatinine clearance
					Nicardipine	40 mg QD	
Bigazzi et al [21]	40	20	0	24	Enalapril	10–20 mg QD	Proteinuria
					Nicardipine SR	40–80 mg QD	
Chan et al [22]	102	52	0	102	Nifedipine SR	20–40 mg BID	Renal function: proteinuria, creatinine clearances, regression coefficient of yearly plasma creatinine reciprocal; clinical end points: death, cardiovascular events, renal events (transplantation or doubling of plasma creatinine)
					Enalapril	10–40 mg QD	
Estacio et al [23]	470	235	0	470	Nisoldipine	60 mg QD	Correlation between change in blood pressure and change in creatinine clearance
					Nisoldipine	10–40 mg QD	
					Enalapril	5–20 mg QD	
					Enalapril	40 mg QD	
Ferder et al [9]	30	12	0	30	Enalapril	20 mg BID	Proteinuria, creatinine clearance
					Nifedipine	10 mg QD	
Fogari et al [24]	38	19	0	38	Ramipril	5 mg QD	Albuminuria
					Nitrendipine	20 mg QD	
Herlitz et al [25]	158	105	0	0	Ramipril + felodipine	5 mg + 5 mg QD	Serum creatinine, iohexol clearance, albuminuria
					Ramipril	10 mg QD	
					Felodipine	9 mg QD	
Kumagai et al [26]	28	16	0	0	Amlodipine	2.5–5.0 mg QD	Progression of renal impairment (change in creatinine clearance, change in GFR, change in proteinuria)
					Enalapril or captopril	5–10 mg or 37.5 mg QD	
Lewis et al [12]	1715	567	0	1715	Irbesartan	75–300 mg QD	Time to doubling of the baseline serum creatinine concentration, and the development of end-stage renal disease, or death from any cause.
					Amlodipine	2.5–10 mg QD	
					Placebo	NA	
Marin et al [27]	67	40	0	0	Fosinopril	10–30 mg QD	Progression of renal function (time to doubling of serum creatinine, entering in a dialysis program)
					Nifedipine GITS	30–60 mg QD	
Norgaard et al [28]	15	8	0	15	Spirapril	6 mg QD	Change in fractional albumin clearance
					Isradipine	5 mg QD	

Table 2. (Continued)

Author	Number	DCA *number*	NDCA *number*	Study length *months*	Medication	Mean dose (SD)/ regimen	Primary end points
Okamura et al [29]	20	9	0	0	Nifedipine or nicardipine Captopril or enalapril	ND ND	Progression of renal function (hypertensive patients with chronic renal failure of IgA nephropathy), blood urea nitrogen, serum creatinine, creatinine clearance, proteinuria
Petersen et al [30]	60	40	0	12	Spirapril Isradipine Spirapril + isradipine	6 mg QD 5 mg QD 3 mg + 2.5 mg QD	Progression of renal failure [decline in GFR, time to end-stage renal failure (e.g., need of dialysis, doubling of serum creatinine, change in creatinine clearance, proteinuria)]
Preston et al [39]	206	0	61	0	Hydrochlorothiazide Atenolol Captopril Diltiazem	12.5–50 mg QD 25–100 mg QD 25–100 mg QD 120–360 mg QD	Proteinuria
PROCOPA Study Group [41]	101	0	51	0	Atenolol Trandolapril Verapamil Trandolapril + verapamil	50 mg QD 2 mg QD 240 mg QD 2 mg + 180 mg QD	Changes in blood pressure, proteinuria
Romero et al [31]	20	10	0	20	Nifedipine Captopril	20 mg BID 60 (17.5) mg QD	Change in proteinuria, GFR, renal plasma flow, filtration fraction
Ruilope et al [32]	34	22	0	0	Nitrendipine Nitrendipine Atenolol	20–40 mg QD 20–40 mg QD 50–100 mg QD	Progression of renal function (GFR, proteinuria, renal plasma flow, insulin clearance)
Sawicki [33]	39	9	0	39	Metoprolol Ramipril Felodipine	117 (41) mg QD 2.9 (1.8) mg QD 9 (5) mg QD	Progression of renal failure (GFR, insulin clearance)
Schnack et al [34]	15	8	0	15	Nifedipine Placebo	30 mg QD NA	Progression of renal function (albuminuria, GFR, renal plasma flow)
Slataper et al [40]	30	0	10	30	Lisinopril Diltiazem Furosemide + atenolol	ND ND ND	Progression of renal failure (decline in GFR, albuminuria)
Smith, Toto, and Bakris[17]	21	10	11	21	Nifedipine XL Diltiazem CD	78 (12) mg QD 436 (43) mg QD	Change in proteinuria, fractional dextran clearance, blood pressure
Velussi et al [35]	44	22	0	44	Cilazapril Amlodipine Cilazapril Amlodipine	2.5 mg QD 5 mg QD 2.5 mg QD 5 mg QD	Progression of diabetic nephropathy for normoalbuminuric and microalbuminuric patients (decrease in GFR, albuminuria, blood pressure)
Zucchelli, Zuccala, and Gaggi [36]	121	61	0	0	Nifedipine Captopril	10–20 mg BID 12.5–50 mg BID	Need for dialysis, progression of established nondiabetic chronic renal disease (proteinuria, serum creatinine, creatinine clearance)

Abbreviations are: DCA, dihydropyridine calcium antagonist; NDCA, nondihydropyridine calcium antagonist.
[a]ND indicates not documented.

goals of the review but did not meet the selection criteria were excluded from further consideration.

Data extraction

Several individuals received training on the process of abstracting data for the systematic review in order to minimize interextractor variability. Each individual received training on how to use the electronic data collection form and an equivalent term dictionary. These individuals were divided into two teams that independently reviewed all of the articles included in the systematic review. Each team entered information into identical but separate electronic databases. In situations where data was not available from published sources, the corresponding author was contacted whenever possible to obtain the missing data. After the data were abstracted from the articles, the data in the two databases were compared to identify discrepancies.

A third team of independent reviewers evaluated each discrepancy. The reviewers compared the disparate data to the original article and made a final determination concerning which data to accept. An audit log was maintained of all changes to the database. The two original independent databases were locked and archived for analysis of interextractor variability. Interextractor agreement was 97%, whereas tertiary verification led to error-free rates of 100% for primary data fields and 99% for the secondary data fields.

Study outcomes

The primary end point of this review was the percentage change in proteinuria from baseline in patients treated with DCAs or NDCAs. Proteinuria is a widely accepted surrogate end point for the progression of renal disease in studies of antihypertensive agents. In addition, proteinuria was expected to occur more frequently than ESRD or other renal outcomes, providing higher statistical power for analysis using this measure. Secondary end points included effect of DCAs and NDCAs on ending proteinuria values, systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP). Progression of nephropathy was defined as an increase in proteinuria in spite of blood pressure reduction or worsening of renal function relative to the comparator defined as either an increase of greater than 50% in serum creatinine or a 25% reduction in GFR, if measured.

Study characteristics

Summary-level data were extracted from published articles for 28 randomized trials that assessed the effects of calcium antagonists and other antihypertensive agents on the progression of renal disease. The characteristics of the patients evaluated in these studies were considered to be sufficiently similar to justify pooling the data for an aggregate analysis. With the exception of 15 patients included in the study by Schnack et al [34], all patients were hypertensive (blood pressure greater than 140/90 mm Hg), and all patients had decreased renal function.

Statistical analysis

The studies included in the review followed different protocols, requiring standardization of variable definitions for the purpose of analysis. Measures of urine protein (excluding albumin) were recorded in mg/day. Based on the accepted estimation that 40% of total urine protein is albumin, urine albumin measurements were converted to urine protein values by dividing by 0.4 [46]. MAP was calculated by adding the systolic blood pressure reading plus two times the diastolic blood pressure reading, divided by three.

The SAS® (SAS Institute, Inc., Cary, NC, USA) software program was used for all statistical analyses. Clinical and demographic characteristics of each treatment group were summarized with means and standard deviations (SD) or percentages and were presented for groups treated with DCA or NDCA and with and without diabetes. In order to evaluate the treatment effects of the calcium antagonists, studies that included combination treatment arms were not used for the primary analysis.

Treatment groups were compared in terms of the percentage change from baseline values while adjusting for sample size. The effect of treatment duration on proteinuria could not be assessed without individual patient data, and comparisons of end values were also adjusted for duration of treatment. Both end points were evaluated with analysis of covariance (ANCOVA) using each study as an experimental unit. The assumptions of ANCOVA were confirmed, and no interactions between the covariates were found. In addition, ANCOVA techniques were used to compare diabetic groups on proteinuria end points and to compare the treatment groups on the blood pressure end points. All P values were based on two-sided tests, and significance was set at $P < 0.05$.

Summary tables were compiled from study data reported for the 28 trials included in the review. As a result, the statistical methods used to analyze summary data from these articles treated each study as an independent observation unit in the analysis.

RESULTS

Blood pressure parameters were analyzed for 1338 patients from 22 studies. The baseline characteristics were not significantly different between the 1338 patients included in the analysis and the 235 patients excluded because of missing values. Both classes of calcium antagonists decreased mean systolic and diastolic blood

Table 3. Effects of dihydropyridine calcium antagonists (DCAs) and nondihydropyridine calcium antagonists (NDCAs) (monotherapy) on blood pressure parameters

Mean (95% CI)	Baseline systolic blood pressure value *Mm Hg*	End-of-study systolic blood pressure value *mm Hg*[a]	Change in systolic blood pressure %[a]	Baseline diastolic blood pressure value *mm Hg*	End-of-study diastolic blood pressure value *mm Hg*[a]	Change in diastolic blood pressure %[a]	Baseline MAP Value *mm Hg*	End-of-study MAP value *mm Hg*[a]	Change in MAP %
DCA	160 (153 to 167)	139 (136 to 142)	−13 (−17 to −9)	95 (91 to 99)	82 (80 to 84)	−13 (−16 to −10)	116 (112 to 120)	101 (98 to 104)	−13 (−16 to −10)
NDCA	164 (138 to 190)	133 (126 TO 140)	−18.5 (−28 to −9)	99 (88 to 110)	81 (76 to 86)	−17 (−26 to −8)	120 (113 to 127)	99 (94 to 104)	−17 (−23 to −11)
Difference	−4 (−31 to 23)	6 (−2 TO 14)	5.5 (−5 to 16)	−4 (−16 to 8)	1 (−5 to 7)	4 (−5 to 13)	−4 (−14 to 4)	2 (−3 to 7)	4 (−3 to 11)
P value	NA	0.13	0.28	NA	0.75	0.4	NA	.5	.35

MAP is mean arterial pressure.
[a]Results were adjusted for sample size, study length, and baseline values.

pressure (Table 3). After adjusting for sample size, study length, and baseline value, there was no statistically significant difference in blood pressure reduction between the classes.

Twenty-three studies had both baseline and end-of-study proteinuria levels documented. As a result, 510 patients contributed data for this analysis. The baseline characteristics were not significantly different between the 510 patients included in the analysis and the 1081 patients excluded because of missing values. The baseline, end-of-study, and change in proteinuria values are shown in Table 4. A 32% difference in proteinuria values was observed between the two subclasses. There was +2% change in proteinuria for DCAs and −30% change for NDCAs (95% CI, 10% to 54%, $P < 0.01$) (Fig. 1). There were consistently greater reductions in proteinuria associated with the use of NDCAs than with the use of DCAs, despite no statistically significant differences in blood pressure between the groups.

In order to assess the effect of reductions in blood pressure on proteinuria levels with DCA or NDCA treatment, an analysis was completed that adjusted for sample size, study length, and change in systolic blood pressure. A 27% mean change in proteinuria was observed between the two calcium antagonist subclasses. There was +1% change in proteinuria for DCAs and −26% change for NDCAs (95% CI, −8% to 63%, $P = 0.16$) (Table 5). Although not statistically significant, these results suggested that the trend demonstrating greater reductions in proteinuria associated with the use of NDCAs compared with DCAs persisted after adjusting for changes in blood pressure. A possible explanation for the lack of statistical significance for this analysis is that there were fewer studies that documented both baseline and end-of-study blood pressure and proteinuria values, resulting in low statistical power.

A secondary analysis that included data for calcium antagonists as monotherapy and in combination with ACE inhibitors or ARBs showed the mean change in proteinuria was 2% for DCAs and −39% for NDCAs (95% CI for a 41% difference, 19% to 63%, $P = 0.002$) (Table 6). These findings suggest that NDCAs alone or in combination with an ACE inhibitor or ARB produced significant reductions in proteinuria, whereas DCAs did not demonstrate an antiproteinuric effect.

As a result of this differential effect of DCAs and NDCAs on proteinuria, NDCAs were expected to reduce the progression of renal disease whereas DCAs were not. However, an analysis of this end point was inconclusive because of the limited number of studies involving NDCAs included in this review. In addition, this review was performed using summary data rather than individual patient data, and the relationship between calcium antagonists and renal disease progression could not be fully assessed.

There were also no statistically significant differences in proteinuria or blood pressure parameters in patients with or without diabetes in any of the studies. As a result, no further analysis of diabetic patients by treatment was undertaken.

The sensitivity of the aggregate results was evaluated by assessing the impact of each individual study on the pooled results in order to determine whether the observed effects of the DCAs and NDCAs were affected by inclusion of any of the clinical trials. The analysis was schematically repeated, excluding each study in turn, to identify which studies were most influential on the results. Because only seven studies included a NDCA, it was expected that the results would be somewhat sensitive. However, the direction of the results and the magnitude of the effects were expected to remain stable.

The sensitivity analysis revealed that the study by Smith, Toto, and Bakris [17], when removed from the analysis, was most influential in reducing the magnitude of the treatment effect (+2% for DCAs and −26% for NDCAs, $P = 0.038$) [17]. The study by Preston et al [39] was the most influential in increasing the magnitude of the treatment effect when removed from the analysis (+1%

Table 4. Effects of dihydropyridine calcium antagonists (DCAs) and dihydropyridine calcium antagonists (NDCAs) (monotherapy) on proteinuria in patients with renal disease, by study[a]

Study	Number (entire population under study)	Number (sample of the population under study)	Study length *months*	Baseline proteinuria value *mg/day*	End-of-study proteinuria value *mg/day*	Change %
DCAs						
Abbott, Smith, and Bakris [18]	28	28	6	10313	10188	−1
Agodoa et al [11]	653	217	36	500	ND	NA
Bianchi et al [20]	16	8	12	1688	ND	NA
Bigazzi et ak [21]	40	20	24	163	132	−19
Chan et al [22]	102	52	66	190	224	18
Estacio et al [23]	470	235	60	ND	ND	NA
Ferder et al [9]	30	12	12	2840	2660	−6
Fogari et al [24]	38	19	6	1939	1743	−10
Herlitz et al [25]	158	54	22	913	ND	NA
Kumagai et al [26]	28	16	12	1700	1500	−12
Lewis et al [12]	1715	567	30	ND	ND	NA
Marin et al [27]	67	40	36	2400	2900	21
Norgaard et al [28]	15	8	6	1995	2340	17
Okamura et al [29]	20	9	12	2000	2000	0
Petersen et al [30]	60	20	21	4325	5300	18
Romero et al [31]	20	10	6	3300	3800	15
Ruilope et al [32]	34	22	12	753	658	−13
Sawicki [33]	39	9	24	2500	4000	60
Schnack et al [34]	15	8	12	210	98	−54
Smith, Toto, and Bakris [17]	21	10	21	873	905	4
Velussi et al [35]	44	22	36	10705	10852	1
Zucchelli, Saccala, and Gaggi. [36]	121	61	36	1900	1500	−21
Total	3734	1447				
Mean	170	66	23	2830	2988	2
NDCAs						
Bakris, Barnhill, and Sadler [37]	30	8	12	5700	2900	−49
Bakris et al [19]	52	18	63	4500	2700	−40
Bakris et al [38]	37	11	12	1510	1053	−30
Preston et ak [39]	206	61	24	143	172	20
PROCOPA Study Group [41]	101	25	6	4730	4870	3
Slataper et ak [40]	30	10	18	7250	4000	−45
Smith, Toto, and Bakris [17]	21	11	21	908	389	−57
Total	477	144				
Mean	68	21	22	3534	2298	−30

[a]Mean adjusted for sample size and study length.

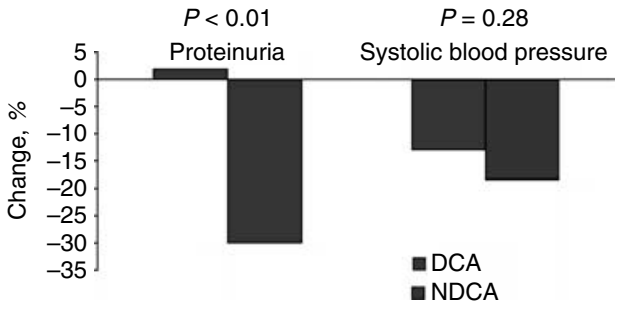

Fig. 1. The change in proteinuria and systolic blood pressure. The percentage change in proteinuria, after adjustment for sample size and study length, for dihydropyridine calcium antagonists (DCAs) and nondihydropyridine calcium antagonists (NDCAs) was 2% and −30%, respectively ($P < 0.01$). The percentage change in systolic blood pressure, after adjustment for sample size and study length, for DCAs and NDCAs was −13% and −18.5%, respectively ($P = 0.28$).

for DCAs and −36% for NDCAs, $P = 0.004$). All steps in the sensitivity analysis showed a significant differential effect on proteinuria between the DCAs and NDCAs. In addition, the magnitude of the effect remained stable. Therefore, the aggregate results of this review were not sensitive to the inclusion or exclusion of any individual study.

DISCUSSION

It has been established that calcium antagonists are effective for reducing blood pressure in patients with renal failure who are considered to be relatively resistant to antihypertensive treatment [5]. This benefit is consistent with the results from this review. According to this analysis, both DCAs and NDCAs equally reduced blood pressure. There were no significant differences in any of the blood pressure parameters after treatment. This is further supported by outcomes data from large trials such as the Irbesartan Diabetic Nephropathy Trial (IDNT) and the African American Study of Kidney Disease and Hypertension (AASK) trials as well as other studies, which show a strong association between reductions in proteinuria and slower declines in kidney function [11, 12, 15, 16]. In the trials, a DCA (amlodipine) failed to

Table 5. Estimated changes in proteinuria among patients treated with dihydropyridine calcium antagonists (DCAs) or nondihydropyridine calcium antagonists (NDCAs) (monotherapy) adjusted for sample size, study length, and blood pressure parameters

Mean (SE)	Change in proteinuria adjusted for baseline systolic blood pressure %	Change in proteinuria adjusted for baseline diastolic blood pressure %	Change in proteinuria adjusted for baseline mean arterial pressure %	Change in roteinuria adjusted for change systolic blood pressure %	Change in proteinuria adjusted for change diastolic blood pressure %	Change in proteinuria adjusted for change mean arterial pressure %
DCA	2	2	1.4	1.4	1.5	1.3
	(6.9)	(6.9)	(6.3)	(7.0)	(7.0)	(6.3)
NDCA	−32	−31	−37	−26	−26	−36
	(14.2)	(14.4)	(10.9)	(16.9)	(16.7)	(10.9)
Difference	34	33	38.4	27.4	27.5	37.3
P value	0.05	0.06	0.009	0.16	0.15	0.009

Table 6. Effects of dihydropyridine calcium antagonists (DCAs) and nondihydropyridine calcium antagonists (NDCAs) [monotherapy or with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) on proteinuria in patients with renal disease, by study*a*

Study	Number (entire population under study)	Number (sample of the population under study)	Study length *months*	Baseline proteinuria value *mg/day*	End-of-study proteinuria value *mg/day*	Change %
DCAs						
Abbott, Smith, and Bakris [18]	28	28	6	10313	10188	−1
Agodoa et al [11]	653	217	36	500	ND	NA
Bianchi et al [20]	16	8	12	1688	ND	NA
Bigazzi et al [21]	40	20	24	163	132	−19
Chan et al [22]	102	52	66	190	224	18
Estacio et al [23]	470	235	60	ND	ND	NA
Ferder et al [9]	30	12	12	2840	2660	−6
Fogari et al [24]	38	19	6	1939	1743	−10
Herlitz et al [25]	158	105	22	1113	ND	NA
Kumagai et al [26]	28	16	12	1700	1500	−12
Lewis et al [12]	1715	567	30	ND	ND	NA
Marin et al [27]	67	40	36	2400	2900	21
Norgaard et al [28]	15	8	6	1995	2340	17
Okamura et al [29]	20	9	12	2000	2000	0
Petersen et al [30]	60	40	21	3763	4413	17
Romero et al [31]	20	10	6	3300	3800	15
Ruilope et al [32]	34	22	12	753	658	−13
Sawicki [33]	39	9	24	2500	4000	60
Schnack et al [34]	15	8	12	210	98	−54
Smith, Toto, and Bakris [17]	21	10	21	873	905	4
Velussi et al [35]	44	22	36	10705	10852	1
Zucchelli, Succala, and Gaggi [36]	121	61	36	1900	1500	−21
Total	3734	1518				
Mean[a]	170	69	23	2797	2936	2
NDCAs						
Bakris, Barnhill, and Sadler [37]	30	16	12	6250	2300	−63
Bakris et al [19]	52	18	63	4500	2700	−40
Bakris et al [38]	37	25	12	1605	791	−51
Preston et al [39]	206	61	24	143	172	20
PROCOPA Study Group [41]	101	51	6	4439	3381	−24
Slataper [40]	30	10	18	7250	4000	−45
Smith, Toto, and Bakris [17]	21	11	21	908	389	−57
Total	477	192				
Mean[a]	68	27	22	3585	1962	−39

[a]Mean adjusted for sample size and study length.

reduce proteinuria, an effect that correlated with a faster decline in kidney function, despite substantial reductions in blood pressure.

However, an analysis of the studies included in this review suggested that a differential effect exists between DCAs and NDCAs on proteinuria, despite equal reductions in systemic blood pressure. This analysis showed that there were consistently greater reductions in proteinuria with the use of NDCAs, either alone or in combination with an ACE inhibitor or ARB, compared with DCAs. This trend persisted after adjusting for changes in blood pressure. This trend also remained unchanged for both diabetic and nondiabetic renal disease and differing levels of proteinuria.

The differential effect of DCAs and NDCAs on proteinuria has been studied in several animal models, and in one human study [17, 47–49]. This differential effect could be caused by a variety of factors, including differences in the ability of DCAs and NDCAs to affect renal autoregulation, glomerular permeability, and tubular protein reabsorption.

Results from animal studies suggested that DCAs, through their action on the afferent arteriole, markedly attenuate the autoregulatory ability of the kidney to alter GFR over a wide range of arterial pressures. This would result in linear transmission of the systemic blood pressure to the glomerular capillary [47–49], and hence, an increase in intraglomerular pressure, unless blood pressure was markedly reduced to levels well below 120 mm Hg [48]. Glomerular hypertension also results in increased protein filtration, albuminuria, and endothelial damage, leading to the release of soluble mediators that promote replacement of normal kidney tissue by fibrosis [47–49]. As a result, the beneficial effects of blood pressure reduction seen with DCAs are overcome by the increased transmission of pressure into the glomerulus due to sustained afferent vasodilatation [5]. In experimental studies, NDCAs also interfere with renal autoregulation, although they do not totally ablate this process [48]. This differential effect from DCAs may be related, in part, to the effects of NDCAs on efferent as well as afferent arteriolar tone [50–52]. Additionally, NDCAs, unlike DCAs, reduce glomerular permeability [9, 17, 25, 53]; this effect on permeability coupled with the partial preservation of renal autoregulation by NDCAs translate into decreases in albuminuria and preservation of renal morphology [47–49].

These differential effects on glomerular permeability are also described in clinical studies, with one study demonstrating a unique effect of DCAs to block tubular protein reabsorption [17, 49, 54]. However, this would only account for a small change in protein not albumin and would not be unique to the DCAs. In human studies of diabetic nephropathy, NDCAs were shown to reduce glomerular membrane permeability, especially to large molecules [17, 49]. This results in decreased albumin filtration, proteinuria, and endothelial damage, that is associated with reduced progression of nephrosclerosis [55, 56]. These differences in membrane permeability are not directly related to blood pressure lowering [17, 49].

Taken together, these mechanistic differences may explain the differential effect of DCAs and NDCAs on proteinuria observed in this review. Further data from large outcome trials is needed in humans to assess these hypothesized explanations.

It is well documented that antihypertensive agents that fail to reduce proteinuria in patients with nephropathy also fail to maximally alter progression of renal disease [8, 11, 16, 49, 57]. This suggests that reductions in both blood pressure and proteinuria are necessary to reduce nephropathy progression in patients with proteinuria [12, 58–61].

In two randomized, double-blind studies of patients with advanced nephropathy and proteinuria, IDNT and AASK, DCAs, in the absence of agents that block the RAS, failed to reduce proteinuria levels and to slow the progression of nephropathy, despite achieving reductions in blood pressure comparable to that achieved with an ACE inhibitor or ARB. In contrast, controlled clinical trials of NDCAs have consistently shown reductions in both blood pressure and proteinuria, and the use of NDCAs in participants with advanced diabetic nephropathy have been shown to slow the progression of renal disease in small studies with long-term follow-up [19, 37–41]. Based on the results of controlled clinical trials that demonstrated an association between a reduction in blood pressure and proteinuria and a slowing of the progression of renal disease, the results of this review support the suggestion that NDCAs may be superior to DCAs in reducing the progression of nephropathy.

Because DCAs have not demonstrated as beneficial as blockers of the RAS on the progression of kidney disease, they should not be considered a first-line treatment in patients with kidney disease who have proteinuria. Conversely, NDCAs, alone or in combination with an ACE inhibitor or an ARB, should be considered over DCAs alone for treating hypertensive patients with nephropathy and proteinuria. A recent post hoc analysis of the Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan (RENAAL) trial, however, shows that DCAs when used with an ARB do not abrogate the benefits of the ARB for slowing nephropathy progression [57]. Further, because ESRD and cardiovascular morbidity and mortality are clinically important outcomes of renal disease progression, an analysis of these outcomes should be incorporated into future comparative studies of the renoprotective effects of calcium antagonists. Such studies will provide valuable insight into the therapeutic advantages of using calcium antagonists in conjunction with antihypertensives in the treatment of renal disease.

The findings of this review have both clinical and economic implications for health care providers. In a recent cost analysis using United States Renal Data Service (USRDS) data, costs associated with the treatment of ESRD have been estimated at approximately $66,000 United States dollars per patient per year [62]. The worldwide cost is estimated to be between $70 and $75 billion United States dollars. The use of medications with renal protective properties can significantly reduce health care costs associated with renal disease. Herman et al recently performed a cost analysis of the RENAAL study and estimated that the ARB generated a net savings of $3555 United States dollars per patient over 3.5 years in

treatment costs for ESRD [63]. Therefore, antihypertensive agents with documented renal protective properties can improve clinical outcomes while reducing health care costs.

Limitations of the study

A meta-analysis was originally planned in order to more fully assess the differential effect of DCAs and NDCAs on blood pressure, and proteinuria. In order to assess these effects, all of the studies included in the meta-analysis had to have included treatment arms with both DCAs and NDCAs. However, only 1 study included in the review met this criterion. As a result, a differential effect between DCAs and NDCAs could not be assessed with meta-analytical techniques. Instead, a systematic review was conducted.

In addition, this review was performed using summary data rather than individual patient data. As a result, the unit of observation was the study and not the patient. Therefore, the statistical power of the analysis was lower than it would have been with an analysis of the individual patient data. The nonsignificant difference between groups in terms of systolic and diastolic blood pressure and MAP did not necessarily mean that groups were similar; a lack of data could also account for this lack of difference. However, even with the reduction in power caused by using the study as the unit of analysis, there was compelling evidence to support the findings that DCAs and NDCAs differentially affect proteinuria while having no significant difference in their effect on blood pressure.

CONCLUSION

This analysis supports the following conclusions: (*1*) there was no statistically significant difference between DCAs and NDCAs in their effect on blood pressure parameters; (*2*) NDCAs are superior to DCAs in reducing proteinuria, despite no statistically significant difference in the blood pressure–lowering effects of these two subclasses; and (*3*) the antiproteinuric superiority of NDCAs was evident in both diabetic and nondiabetic renal disease. Based on the findings of this systematic review and the fact that proteinuria levels correlate with higher risk of kidney failure and cardiovascular events [8, 64–66]. NDCAs, alone or in combination with an ACE inhibitor or an ARB, should be preferred over DCAs for treating hypertensive patients with proteinuric renal disease or renal insufficiency.

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REFERENCES

1. US Renal Data System: *USRDS 1999 Annual Data Report*, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, April 1999
2. Manjunath G, Tighiouart H, Ibrahim H, *et al*: Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 41:47–55, 2003
3. Garg JP, Bakris GL: Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc Med* 7:35–43, 2002
4. Jafar TH, Stark PC, Schmid CH, *et al*: Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 60:1131–1140, 2001
5. Kloke HJ, Branten AJ, Huysmans FT, *et al*: Antihypertensive treatment of patients with proteinuric renal diseases: Risks or benefits of calcium channel blockers? *Kidney Int* 53:1559–1573, 1998
6. Miettinen H, Haffner SM, Lehto S, *et al*: Proteinuria predicts stroke and other atherosclerotic vascular disease events in nondiabetic and non–insulin-dependent diabetic subjects. *Stroke* 27:2033–2039, 1996
7. Williams PS, Fass G, Bone JM: Renal pathology and proteinuria determine progression in untreated mild/moderate chronic renal failure. *Q J Med* 67:343–354, 1988
8. Jafar TH, Stark PC, Schmid CH, *et al*: Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 139:244–252, 2003
9. Ferder L, Daccordi H, Martello M, *et al*: Angiotensin converting enzyme inhibitors versus calcium antagonists in the treatment of diabetic hypertensive patients. *Hypertension* 19:237–242, 1992
10. Peterson JC, Adler S, Burkart JM, *et al*: Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 123:754–762, 1995
11. Agodoa LY, Appel L, Bakris GL, *et al*: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: A randomized controlled trial. *JAMA* 285:2719–2728, 2001
12. Lewis EJ, Hunsicker LG, 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* 345:851–860, 2001
13. Bakris GL, Weir M: ACE inhibitors and protection against kidney disease progression in patients with type 2 diabetes: What's the evidence. *J Clin Hypertens (Greenwich)* 4:420–423, 2002
14. Keane WF, Lyle PA: Reduction of end points in NIDDM with the angiotensin II receptor antagonist losartan study: Recent advances in management of type 2 diabetes and nephropathy: Lessons from the RENAAL study. *JAMA* 41(3 Suppl 2):S22–S25, 2003
15. Parving HH, Lehnert H, Brochner-Mortensen J, *et al*: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345:870–878, 2001
16. Wright JT, Jr., Bakris G, Greene T, *et al*: Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 288:2421–2431, 2002
17. Smith AC, Toto R, Bakris GL: Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy. *Kidney Int* 54:889–896, 1998
18. Abbott K, Smith A, Bakris GL: Effects of dihydropyridine calcium antagonists on albuminuria in patients with diabetes. *J Clin Pharmacol* 36:274–279, 1996
19. Bakris GL, Copley JB, Vicknair N, *et al*: Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int* 50:1641–1650, 1996

20. Bianchi S, Bigazzi R, Baldari G, *et al*: Long-term effects of enalapril and nicardipine on urinary albumin excretion in patients with chronic renal insufficiency: A 1-year follow-up. *Am J Nephrol* 11:131–137, 1991
21. Bigazzi R, Bianchi S, Baldari D, *et al*: Long-term effects of a converting enzyme inhibitor and a calcium channel blocker on urinary albumin excretion in patients with essential hypertension. *Am J Hypertens* 6:108–113, 1993
22. Chan JC, Ko GT, Leung DH, *et al*: Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. *Kidney Int* 57:590–600, 2000
23. Estacio RO, Jeffers BW, Gifford N, *et al*: Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 23 (Suppl 2):B54–B64, 2000
24. Fogari R, Zoppi A, Pasotti C, *et al*: Comparative effects of ramipril and nitrendipine on albuminuria in hypertensive patients with non–insulin-dependent diabetes mellitus and impaired renal function. *J Hum Hypertens* 9:131–135, 1995
25. Herlitz H, Harris K, Risler T, *et al*: The effects of an ACE inhibitor and a calcium antagonist on the progression of renal disease: The Nephros Study. *Nephrol Dial Transplant* 16:2158–2165, 2001
26. Kumagai H, Hayashi K, Kumamaru H, *et al*: Amlodipine is comparable to angiotensin-converting enzyme inhibitor for long-term renoprotection in hypertensive patients with renal dysfunction: A one-year, prospective, randomized study. *Am J Hypertens* 13:980–985, 2000
27. Marin R, Ruilope LM, Aljama P, *et al*: A random comparison of fosinopril and nifedipine GITS in patients with primary renal disease. *J Hypertens* 19:1871–1876, 2001
28. Norgaard K, Jensen T, Christensen P, *et al*: A comparison of spirapril and isradipine in patients with diabetic nephropathy and hypertension. *Blood Press* 2:301–308, 1993
29. Okamura M, Kanayama Y, Negoro N, *et al*: Long-term effects of calcium antagonists and angiotensin-converting enzyme inhibitors in patients with chronic renal failure of IgA nephropathy. *Contrib Nephrol* 90:161–165, 1991
30. Petersen LJ, Petersen JR, Talleruphuus U, *et al*: A randomized and double-blind comparison of isradipine and spirapril as monotherapy and in combination on the decline in renal function in patients with chronic renal failure and hypertension. *Clin Nephrol* 55:375–383, 2001
31. Romero R, Salinas I, Lucas A, *et al*: Comparative effects of captopril versus nifedipine on proteinuria and renal function of type 2 diabetic patients. *Diabetes Res Clin Pract* 17:191–198, 1992
32. Ruilope LM, Araque A, Lahera V, *et al*: Antihypertensive effect of nitrendipine in the hypertensive patient with renal impairment. *Ren Fail* 15:359–363, 1993
33. Sawicki PT: Stabilization of glomerular filtration rate over 2 years in patients with diabetic nephropathy under intensified therapy regimens. Diabetes Treatment and Teaching Programmes Working Group. *Nephrol Dial Transplant* 12:1890–1899, 1997
34. Schnack C, Capek M, Banyai M, *et al*: Long-term treatment with nifedipine reduces urinary albumin excretion and glomerular filtration rate in normotensive type 1 diabetic patients with microalbuminuria. *Acta Diabetol* 31:14–18, 1994
35. Velussi M, Brocco E, Frigato F, *et al*: Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. *Diabetes* 45:216–222, 1996
36. Zucchelli P, Zuccala A, Gaggi R: Comparison of the effects of ACE inhibitors and calcium channel blockers on the progression of renal failure. *Nephrol Dial Transplant* 10 Suppl 9:46–51, 1995
37. Bakris GL, Barnhill BW, Sadler R: Treatment of arterial hypertension in diabetic humans: importance of therapeutic selection. *Kidney Int* 41:912–919, 1992
38. Bakris GL, Weir MR, DeQuattro V, *et al*: Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int* 54:1283–1289, 1998
39. Preston RA, Materson BJ, Reda DJ, *et al*: Proteinuria in mild to moderate hypertension: Results of the VA cooperative study of six antihypertensive agents and placebo. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Clin Nephrol* 47:310–315, 1997
40. Slataper R, Vicknair N, Sadler R, *et al*: Comparative effects of different antihypertensive treatments on progression of diabetic renal disease. *Arch Intern Med* 153:973–980, 1993
41. PROCOPA Study Group: Dissociation between blood pressure reduction and fall in proteinuria in primary renal disease: A randomized double-blind trial. *J Hypertens.* 20:729–737, 2002
42. Fioravanti M, Solerte SB, Patti AL, *et al*: Determination of albuminuria in type 1 and type 2 diabetic patients with microproteinuria and overt nephropathy. Comparative evaluation between a radial immunodiffusion procedure and a highly sensitive radioimmunoassay. *Ric Clin Lab* 17:171–179, 1987
43. Bailar JC, 3rd: Passive smoking, coronary heart disease, and meta-analysis. *N Engl J Med* 340:958–959, 1999
44. Juni P, Witschi A, Bloch R, *et al*: The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 282:1054–1060, 1999
45. Kemmeren JM, Algra A, Grobbee DE: Third generation oral contraceptives and risk of venous thrombosis: Meta-analysis. *Br Med J* 323:131–134, 2001
46. Pun KK, Ho P, Lau P, *et al*: Eight-month longitudinal study of urinary excretion of albumin and tubular proteins in diabetic subjects. *Am J Nephrol* 10:475–481, 1990
47. Bakris GL, Griffin KA, Picken MM, *et al*: Combined effects of an angiotensin converting enzyme inhibitor and a calcium antagonist on renal injury. *J Hypertens* 15:1181–1185, 1997
48. Griffin KA, Picken MM, Bakris GL, *et al*: Class differences in the effects of calcium channel blockers in the rat remnant kidney model. *Kidney Int* 55:1849–1860, 1999
49. Tarif N, Bakris GL: Preservation of renal function: the spectrum of effects by calcium-channel blockers. *Nephrol Dial Transplant* 12:2244–2250, 1997
50. Brown SA, Walton CL, Crawford P, *et al*: Long-term effects of antihypertensive regimens on renal hemodynamics and proteinuria. *Kidney Int* 43:1210–1218, 1993
51. Carmines PK, Navar LG: Disparate effects of Ca channel blockade on afferent and efferent arteriolar responses to ANG II. *Am J Physiol* 256:F1015–F1020, 1989
52. Hayashi K, Ozawa Y, Fujiwara K, *et al*: Role of actions of calcium antagonists on efferent arterioles–with special references to glomerular hypertension. *Am J Nephrol* 23:229–244, 2003
53. Gaber L, Walton C, Brown S, *et al*: Effects of different antihypertensive treatments on morphologic progression of diabetic nephropathy in uninephrectomized dogs. *Kidney Int* 46:161–169, 1994
54. Hartmann A, Lund K, Holdaas H, *et al*: Contrasting short-term effects of nifedipine on glomerular and tubular functions in glomerulonephritic patients. *J Am Soc Nephrol* 5:1385–1390, 1994
55. Russo LM, Bakris GL, Comper WD: Renal handling of albumin: A critical review of basic concepts and perspective. *Am J Kidney Dis* 39:899–919, 2002
56. Abbate M, Zoja C, Rottoli D, *et al*: Antiproteinuric therapy while preventing the abnormal protein traffic in proximal tubule abrogates protein- and complement-dependent interstitial inflammation in experimental renal disease. *J Am Soc Nephrol* 10:804–813, 1999
57. Bakris GL, Weir MR, Shanifar S, *et al*: Effects of blood pressure level on progression of diabetic nephropathy: Results from the RENAAL study. *Arch Intern Med* 163:1555–1565, 2003
58. Dahlof B: Cardiovascular morbidity and mortality in the losartan intervention for end point reduction in hypertension study (LIFE). *Lancet* 359:995–1003, 2002
59. Klahr S, Levey AS, Beck GJ, *et al*: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 330:877–884, 1994
60. Ruggenenti P, Perna A, Mosconi L, *et al*: Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 349:1857–1863, 1997
61. Yusuf S, Sleight P, Pogue J, *et al*: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 342:145–153, 2000

62. Lysaght MJ: Maintenance dialysis population dynamics: Current trends and long-term implications. *J Am Soc Nephrol* 13 (Suppl 1):S37–S40, 2002
63. Herman WH, Shahinfar S, Carides GW, *et al*: Losartan reduces the costs associated with diabetic end-stage renal disease: The RENAAL study economic evaluation. *Diabetes Care* 26:683–687, 2003
64. Culleton BF, Larson MG, Parfrey PS, *et al*: Proteinuria as a risk factor for cardiovascular disease and mortality in older people: A prospective study. *Am J Med* 109:1–8, 2000
65. Gerstein HC, Mann JF, Yi Q, *et al*: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286:421–426, 2001
66. Stephenson JM, Kenny S, Stevens LK, *et al*: Proteinuria and mortality in diabetes: The WHO multinational study of vascular disease in diabetes. *Diabet Med* 12:149–155, 1995