Kidney International, Vol. 54 (1998), pp. 1771–1784

NEPHROLOGY FORUM

Calcium antagonists and renal disease

Principal discussant: MURRAY EPSTEIN

University of Miami School of Medicine, Miami, Florida, USA

CASE PRESENTATION

A 50-year-old white man was referred to the hypertension clinic at the Miami VA Medical Center for better control of hypertension. The patient had had hypertension for 8 years, during which time he had followed a number of different medical regimens. During the past year, he had taken hydrochlorothiazide, 25 mg daily; atenolol, 50 mg daily; and hydralazine, 50 mg three times daily. He was examined in the emergency room one week prior to being evaluated at the hypertension clinic. At that time, his chief complaints were left facial weakness, and numbness and decreased control of his left hand. The latter had lasted for about 20 minutes but had disappeared by the time he was seen. A CT scan of the brain was normal, and a transient ischemic attack (TIA) was diagnosed. His supine blood pressure was 170/114 mm Hg and 166/112 mm Hg on two occasions. The patient admitted having failed to take his hypertensive medications for the previous 10 days; these were reinstituted. An appointment was made for the neurology clinic the next day. While in the neurology clinic, a carotid Doppler study revealed bilateral carotid artery plaques, but no ulcerative lesions. His blood pressure was 168/94 mm Hg sitting. Therapy with one aspirin per day was begun and he was referred to the hypertension clinic.

When seen in the hypertension clinic, the patient gave no history of additional TIA episodes or other symptoms. The patient reported no other medical problems other than having been told by a physician at his workplace that his cholesterol was "a little elevated" and that his blood sugar was "somewhat high but did not need to be treated medically." He had a 40-pack-year smoking history. Ethanol intake was limited to 2 beers on weekends; coffee intake was 4 to 5 cups daily. The patient's diet was geared towards "meat and potatoes." He was involved in some physical activity at work (walking and lifting) but had exercised very little outside of work. His father had died at age 56 of a myocardial infarction and his mother at age 67 of a massive stroke. She also was known to have been hypertensive during her last 15 years. A maternal uncle and a sister, aged 49, had type-II diabetes mellitus; two of his grandparents had died of strokes.

Physical examination revealed a large man (height, 74 inches; weight, 252 pounds) with primarily android obesity. He was alert and oriented and had no neurologic residua. Blood pressure was 164/104 mm Hg supine and 160/100 mm Hg standing. Funduscopic examination revealed grade-II Keith-Wagener changes. Cardiac examination disclosed an S4 gallop. The point of maximal impulse was 2 cm to the left of the midclavicular line and sustained. His lungs were clear to auscultation and percussion. Abdominal examination disclosed obesity, without organomegaly or bruits. The extremities showed decreased popliteal and absent dorsalis pedis and posterior tibialis pulses bilaterally.

Laboratory evaluation disclosed an electrocardiogram with sinus rhythm and voltage criteria for left-ventricular hypertrophy; the heart rate was 68 beats/min. A chest radiograph was normal. Other relevant laboratory data included: serum creatinine, 1.4 mg/dl; serum potassium, 5.1 mEq/liter; fasting blood glucose, 204 mg/dl; glycosylated hemoglobin, 10%; total cholesterol, 267 mg/dl; HDL cholesterol, 27 mg/dl; and triglycerides, 192 mg/dl. Urine sediment examination was unremarkable, and the urine protein was 2+. Quantitation of urinary protein excretion disclosed 640 mg/24 hrs. Ultrasonographic examination disclosed slight renal asymmetry, and a nuclear scan revealed symmetric but modestly diminished renal perfusion.

A clinical diagnosis of diabetic nephropathy was made, and captopril was started at a dose of 12.5 mg orally every 12 hours. Subsequent laboratory tests revealed an increase of the serum potassium to 6.2 mEq/liter and of the serum creatinine to 1.8 mg/dl. The ACE inhibitor was discontinued with a subsequent return of serum creatinine and serum potassium to previous levels. The blood pressure then was controlled with amlodipine, 10 mg/day; the serum creatinine remained stable.

DISCUSSION

DR. MURRAY EPSTEIN (*Professor of Medicine, University of Miami School of Medicine, Miami, Florida, USA*): The case before us today raises a number of important clinical issues regarding the management of patients with diabetes and hypertension. These include instituting rational once-daily dosing of antihypertensive agents to enhance compliance, attaining goal blood pressure in an attempt to attenuate progression of target organ disease, and selecting antihypertensive agents that maintain rather than worsen metabolic neutrality (for example, hypokalemia, hyperglycemia) and do not exacerbate dyslipidemia. Today, however, I will focus on one major issue—the role of calcium antagonists in the management of patients with diabetes mellitus and hypertension. I also will address a related important issue—whether calcium antagonists retard progression of renal disease. These issues are no longer theoretical considerations; we now know that reducing blood pressure to

Key words: renal protection, renal microcirculation, afferent arteriole, renal mesangium, growth factors, dihydropyridines, ACE inhibitors.

Presentation of this Forum is made possible by grants from Merck & Co, Incorporated; Astra Pharmaceuticals; Hoechst Marion Roussel, Incorporated; Dialysis Clinic, Incorporated; and R & D Laboratories, Incorporated.

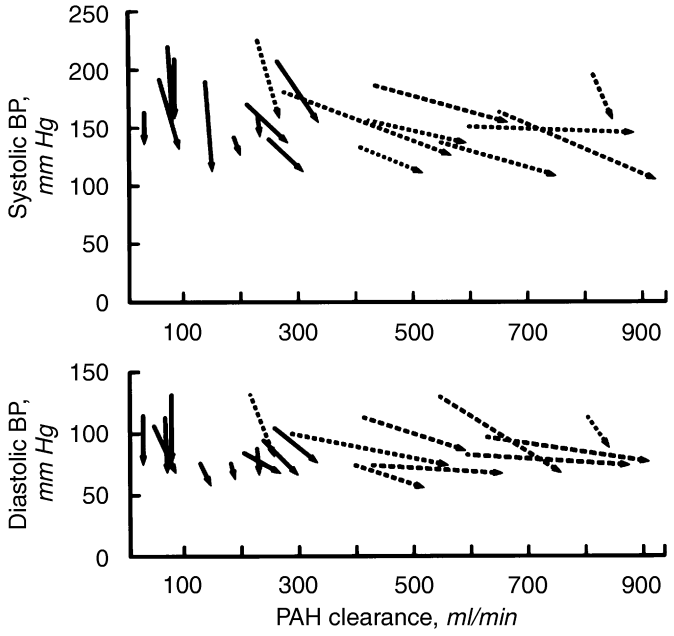

Fig. 1. Effects of intravenous nifedipine (1 mg) on systolic and diastolic blood pressure and para-aminohippurate (PAH) clearance in 9 patients with essential hypertension (---►) and 11 patients with hypertension and renal functional impairment (—►). Nifedipine significantly increased PAH clearance in patients with essential hypertension. In contrast, "renal" hypertensive patients failed to augment PAH clearance despite similar blood pressure reduction. (From Ref. 3 with permission.)

appropriate levels in diabetic patients with hypertension may require the concomitant use of several different antihypertensive agents [1, 2].

Before reviewing these points, however, I will discuss our current state of knowledge regarding the effects of calcium antagonists on renal function and hemodynamics. I then will review the available data regarding calcium antagonists' influence on the progression of renal failure in both nondiabetic renal disease and diabetic nephropathy.

In considering the effects of calcium antagonists, clinicians focus their attention primarily on the beneficial effects in the management of symptomatic coronary artery disease and on the ability to lower blood pressure. But calcium antagonists also have important effects on renal hemodynamics and renal function. More than 25 years ago, Klutsch et al reported that nifedipine increased renal perfusion and GFR in a group of patients with essential hypertension [3]. Further, they systematically investigated the effects of nifedipine in a large group of patients with hypertension accompanied by varying degrees of renal functional impairment. They observed that hypertensive patients with the highest basal inulin clearance manifested marked augmentation of renal hemodynamics, as assessed by increments in inulin and para-aminohippurate clearances. In contrast, hypertensive patients with impaired renal function failed to manifest a renal vasodilatory response to nifedipine (Fig. 1). Presumably the group (with normal renal function) that responded to the calcium antagonists exhibited a greater renal vasodilatory capacity than did the group with impaired renal function, in whom the decrement in renal perfusion might have been attributable to a "fixed" organic lesion.

Table 1. Methodology for assessing the renal microcirculation[a]

	Methods	Reference	Characteristics
Indirect	Micropuncture		
	Laser Doppler		
Direct	Isolated microvessels	7, 8	Without glomerulus
		7–10	With glomerulus
	Juxtamedullary nephron	11	Blood-perfused
	Needle CCD	12	Intravital
	Hydronephrotic kidney	13	In vivo
		14–18	In vitro

[a] Adapted with permission from Ref. 18.

Several subsequent reports have confirmed that, in contrast to the lack of hemodynamic effect in normal subjects, hypertensive subjects exhibit an *exaggerated* renal hemodynamic response to calcium antagonists [4], with sustained increases in glomerular filtration rate (GFR) and renal plasma flow (RPF) [4].

A similar exaggerated vasodilatory response has been demonstrated in normotensive offspring of hypertensive parents [5, 6]. Blackshear et al reported that at least 50% of normotensive subjects with a family history of hypertension exhibited an exaggerated renal vasodilatory response to diltiazem, a response suggesting an inherited abnormality of the renal vascular bed associated with hypertension. Montanari and coworkers subsequently have confirmed and extended these observations [6].

Aside from their effects on overall renal hemodynamics, calcium antagonists induce substantive changes in the renal microcirculation. Over the past decade several laboratories have succeeded in characterizing the renal microcirculatory profile of calcium antagonists. These studies have utilized several innovative techniques and experimental models including isolated microvessels, blood-perfused juxtamedullary nephrons, in-vivo hydronephrotic kidneys, and isolated perfused hydronephrotic kidneys (Table 1) [7–18]. Collectively, these direct in-vivo and in-vitro observations in diverse experimental models indicate that calcium antagonists antagonize preglomerular vasoconstriction, resulting in afferent arteriolar vasodilation. In contrast, most studies suggest that the efferent arteriole is refractory to the vasodilatory effect of these agents [17–20]. This same renal microcirculatory profile is found regardless of whether vasoconstriction had been produced by endothelin, norepinephrine, angiotensin II, KCl depolarization, or thromboxane mimetics such as U44069. Most dihydropyridines and the benzothiazepine diltiazem also have manifested a similar renal microcirculatory profile [18, 19]. By contrast, recent studies have suggested that several of the

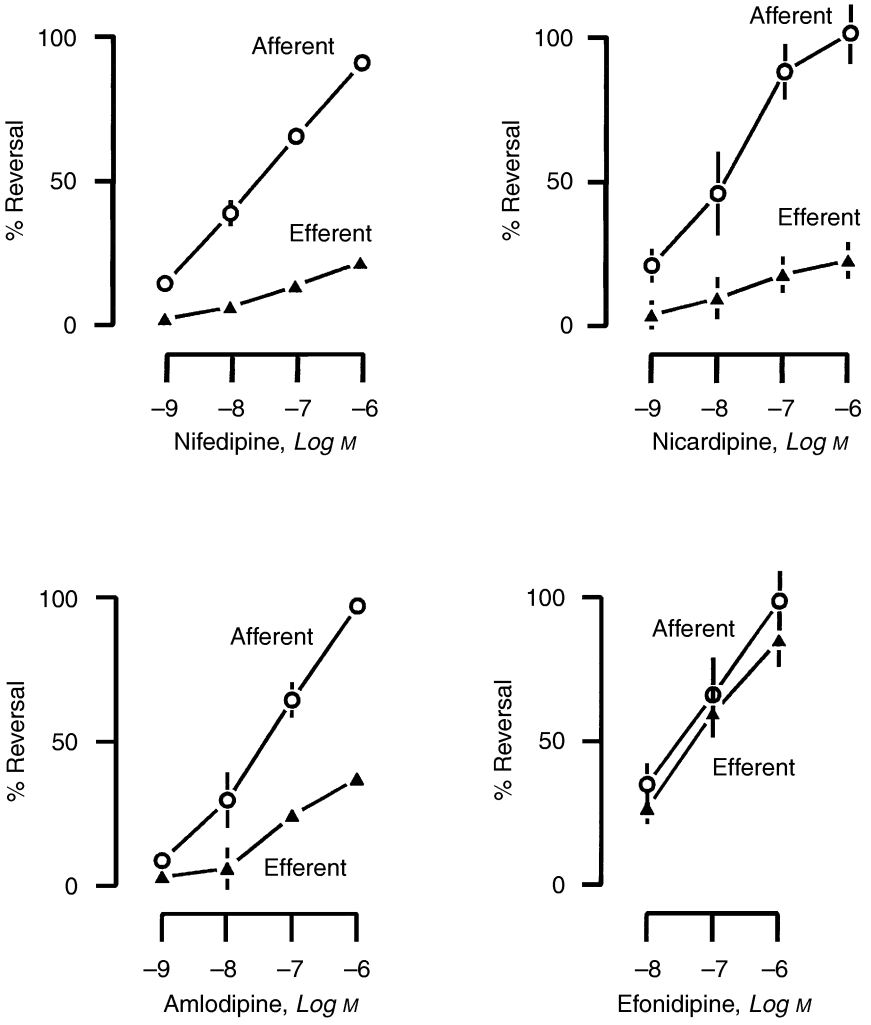

Fig. 2. The effects of various calcium antagonists on norepinephrine-induced constriction of renal microvessels. Nifedipine, nicardipine, and amlodipine elicited predominantly afferent arteriolar vasodilation. In contrast, efonidipine dilated both afferent and efferent arterioles in a dose-dependent manner. (Adapted with permission from Ref. 18.)

newer calcium antagonists differ in their renal microcirculatory profile and are more favorable to the kidney [18]. Thus, efonidipine dilated virtually equally the afferent and efferent arterioles (Fig. 2). Further, Tojo et al characterized the effects of manidipine hydrochloride on the renal microcirculation in SHR rats using classic micropuncture techniques [21]. Studies conducted after two months of manidipine administration did not change single-nephron GFR but increased single-nephron glomerular plasma flow. Glomerular transcapillary hydraulic pressure difference (ΔP), assumed to be the parameter most related to development of glomerulosclerosis, fell significantly; both afferent and efferent arteriolar resistances (R_A and R_E) declined. Consequently, drugs such as manidipine and efonidipine might be desirable antihypertensive agents for patients with renal diseases because their renal microcirculatory profile theoretically would favor retarding progression of renal disease.

A large body of evidence indicates that, in addition to their renal hemodynamic effects, calcium antagonists are natriuretic in specific clinical settings [22–24]. Following initiation of calcium antagonist therapy, sodium excretion increases significantly on the first and second day, inducing a negative sodium balance that averages 80 mEq over the first 5 days [22, 23]. The natriuresis is highly variable and occurs independently of the hypotensive response. After the first or second day of treatment, a number of compensatory adjustments are activated, so that daily sodium balance thereafter returns to zero. Nevertheless, the negative sodium balance established initially appears to be sustained over the long term [23, 24].

Therapeutic strategies for preventing progressive renal failure by treating hypertension

The consensus of most experts in the field, including the Working Group on Hypertension and Chronic Renal Failure of the National High Blood Pressure Education Program, is that the most important strategy for protecting the kidney from hypertensive damage is effective control of blood pressure [25, 26]. In addition to the compelling importance of blood pressure reduction per se, increasing evidence indicates that some classes of antihypertensive

Table 2. Effects of calcium antagonists on renal microcirculation in various types of renal injury models

		AP[a] (*mm Hg*)	R_A ($dyne/sec/cm^{-5} \times 10^{10}$)	R_E ($dyne/sec/cm^{-5} \times 10^{10}$)	P_{GC} (*mm Hg*)	ΔP (*mm Hg*)	Ref.
5/6 Nx	Control	154 ± 6	1.20 ± 0.20	0.80 ± 0.10	68 ± 3	51 ± 3	43
	Diltiazem	102 ± 2*	1.10 ± 0.20	0.70 ± 0.20	50 ± 2*	35 ± 3*	
SHR-UniNx	Control	172 ± 4	1.97 ± 0.26	1.10 ± 0.12	67 ± 2	55 ± 2	45
	Nifedipine	126 ± 3*	1.00 ± 0.11*	0.73 ± 0.06	60 ± 1	45 ± 1*	
DOCA-UniNx	Control	139 ± 4	1.41 ± 0.19	0.94 ± 0.14	60 ± 1	49 ± 2	46
	Nifedipine	106 ± 2*	0.83 ± 0.08*	0.97 ± 0.08	62 ± 2	49 ± 1	
DM-UniNx	Control	118 ± 5	0.80 ± 0.10	0.70 ± 0.10	60 ± 1	47 ± 1	44
	Nifedipine	106 ± 2*	0.60 ± 0.10	0.60 ± 0.10	60 ± 2	45 ± 2	

[a] AP = arterial pressure, SHR = spontaneously hypertensive rat, Nx = nephrectomized, UniNx = uninephrectomized, DOCA = deoxycorticosterone acetate, R_A = afferent resistance, R_E = efferent resistance, P_{GC} = glomerular capillary pressure, $\Delta P = P_{GC} - P_{BS}$, where P_{BS} is hydraulic pressure in Bowman's space. * indicates $P < 0.05$ vs. control. Reproduced with permission from Ref. 18.

medications confer a greater effect than others in slowing progression of renal disease despite similar reductions in systemic blood pressure. A substantive body of experimental studies has provided a theoretic framework suggesting that ACE inhibition retards the progression of renal disease [27–32].

Studies over the past 15 years have demonstrated that the sustained increase in glomerular capillary pressure evoked in response to loss of renal mass produces a destructive sclerosing reaction [27–30]. Administration of ACE inhibitors countervails the effects of angiotensin II on the renal microvasculature, decreasing glomerular capillary pressure and reducing glomerular sclerosis. These findings indicate that ACE-inhibitor therapy protects the injured kidney from hemodynamically mediated glomerular damage [31, 32]. The ACE inhibitors also might confer their beneficial effects by modulating events independent of their ability to ameliorate glomerular hypertension [33, 34]. These effects are summarized in several recent reviews [35–37] and have been considered in a recent Nephrology Forum [38].

Subsequently a number of clinical trials have investigated the renal protective effects of ACE inhibitors in patients with diabetes, and more recently in those with nondiabetic renal disease [39–42]. The largest and most compelling of these trials was conducted by the Diabetes Collaborative Study Group [39]. Collectively, these studies have validated the predictions from the earlier experimental models.

Calcium antagonists: Can they retard progression of renal insufficiency?

As noted previously, calcium antagonists preferentially block preglomerular vasoconstriction. However, inferences from micropuncture studies on the effects of calcium antagonists on preglomerular resistance in experimental renal disease conflict. Table 2 summarizes the results from studies in diverse renal injury models [43–46]. These divergent observations in remnant kidney models, heminephrectomized SHR, and heminephrectomized DOCA-treated rats suggest that calcium antagonists have variable effects on afferent and efferent arteriolar resistance and glomerular hypertension in different experimental models.

Table 3. Known and postulated mechanisms mediating the renal protective actions of calcium antagonists[a]

Reduction in systemic blood pressure
Reduction in renal hypertrophy
Modulation of mesangial traffic of macromolecules
Reduction in metabolic activity of remnant kidneys
Amelioration of uremic nephrocalcinosis
Attenuation of mitogenic effects of growth factors
Blockade of pressure-induced calcium entry
Decreased free radical formation

[a] Modified with permission from Ref. 47.

Theoretically, preferential afferent vasodilation should not reduce intraglomerular hypertension. However, calcium antagonists have additional properties that may contribute to their ability to protect the kidney under diverse experimental conditions and perhaps in clinical disorders [47–49]. Some of the more prominent mechanisms postulated to mediate the renal protective actions of calcium antagonists are listed in Table 3. These include the ability of calcium antagonists to lessen injury by retarding renal growth [50–52], to attenuate mesangial entrapment of macromolecules [53, 54], to countervail or attenuate the mitogenic effect of diverse cytokines and growth factors, including platelet-derived growth factor and platelet-activating factor [53], and possibly to act as free-radical scavengers [49, 53].

Several studies suggest that calcium antagonists can protect the kidney after reduction of renal mass. Dworkin and Benstein have postulated that, in great part, glomerular injury depends not solely on the pressure developed within the glomerular capillary, but also on the tension in the vessel wall [55]. Tension appears to be influenced equally by glomerular pressure (P_{GC}) and vessel radius (R_{GC}). Thus, if the glomerular capillary radius increases when kidneys hypertrophy, wall tension rises on both a hemodynamic and a structural basis. Conversely, therapies

that prevent hypertrophy could decrease tension by reducing R_{GC}. Extending this hypothesis, Dworkin and colleagues have demonstrated that both enalapril and nifedipine reduce blood pressure, lessen proteinuria, and preserve glomerular architecture in a renal ablation model [56]. They reported that R_{GC} was significantly increased in rats 8 weeks after 5/6 nephrectomy. Chronic administration of the dihydropyridine nifedipine in doses chosen to normalize systemic blood pressure reduced hypertrophy as measured by kidney weight, glomerular capillary radius, and glomerular volume. Because nifedipine reduced glomerular injury without lowering glomerular pressure, the investigators postulated that the reduction in R_{GC} was sufficient to cause a decline in tension similar in magnitude to that produced by agents such as ACE inhibitors, which prevent injury by reducing P_{GC}.

Subsequent studies attempting to test this hypothesis with a different calcium antagonist using similar experimental models have yielded inconsistent results. Dworkin et al investigated the effects of amlodipine on glomerular injury in two models of progressive renal failure—the DOCA-salt-treated hypertensive rat and the uninephrectomized SHR [57]. In contrast to the beneficial effects observed previously with nifedipine administration [56], amlodipine therapy failed to prevent glomerular injury. Although systemic blood pressure was significantly reduced in both models, amlodipine failed to reduce glomerular tuft volume and did not lessen glomerular injury. The reasons for these disparate results are not yet known.

An additional renal protective mechanism might relate to the possibility that calcium antagonists attenuate mesangial entrapment of macromolecules. Thus, angiotensin II has been demonstrated to influence the transport of blood-borne macromolecules into the mesangium [58]. More than a decade ago, Raij and Keane demonstrated that angiotensin II, when given to rats in subpressor doses, can both increase the uptake and decrease the disappearance rate of macromolecules such as radiolabeled IgG in the mesangium [54]. Entrapment of macromolecules in the mesangium can produce mesangial injury due to stimulation of local inflammation and ultimately to expansion of mesangial cell and/or matrix with subsequent progression to glomerular sclerosis [54, 58]. The proposal that calcium antagonists can counteract these mesangial effects of angiotensin II suggests an additional mechanism whereby they might attenuate or retard the development of glomerulosclerosis [49]. Calcium antagonists also might act by modulating the mitogenic effects of diverse cytokines and growth factors, including platelet activating factor (PAF) and platelet-derived growth factor (PDGF) [59]. Nifedipine, verapamil, and diltiazem have each been shown to inhibit the mitogenic effect of PDGF and thrombin on mesangial cells [60]. Subsequent studies have shown that the calcium antagonist amlodipine inhibits proliferation of human mesangial cells as well as protein synthesis and therefore hypertrophy [61]. Calcium antagonists also inhibit thrombin-induced stimulation of PAF production by endothelial cells; as a result, they can limit PAF-induced glomerular injury [62].

Yet another mechanism by which calcium antagonists might exert their protective effects includes amelioration of mitochondrial calcium overload, which leads to mitochondrial malfunction and eventually cell death [63, 64]. Indeed, calcium antagonists increase survival of ischemic tubular cells in culture [65].

The available data on the ability of calcium antagonists to retard progressive renal failure in experimental animals conflict. Several studies suggest that calcium antagonists are protective [66, 67]; others have failed to find such an effect. Goligorsky et al investigated the effect of chronic verapamil administration in experimental chronic renal failure and concluded that chronic verapamil administration ameliorates uremic nephrocalcinosis [67]. Subsequently, Harris and coworkers investigated the effects of long-term administration of verapamil on the progression of experimental chronic renal failure in the rat [66]. The indices studied included the degree of renal functional deterioration, the extent of histologic damage and nephrocalcinosis, and cumulative survival. These investigators concluded that verapamil protects against renal dysfunction, histologic damage, nephrocalcinosis, and myocardial calcification, and that it improves survival in the remnant model.

Münter et al compared the renoprotective effects of three interventions, the ACE inhibitor trandolapril, the calcium antagonist verapamil, and the combination of the two, on progression to glomerular sclerosis in adult, stroke-prone, spontaneously hypertensive rats (SHRSP) [68]. Because blood pressure reduction alone might attenuate renal damage, the doses of the antihypertensive drugs used were selected deliberately to not lower blood pressure. Monotherapy with either verapamil (20 mg/kg/day) or trandolapril (0.03 mg/kg/day) reduced proteinuria but did not change renal morphology. In contrast, treatment with the combination of these two agents favorably affected renal morphology. Despite persistence of the hypertension over the entire 11-week period of observation, combined treatment with trandolapril and verapamil retarded the progression to glomerular sclerosis and blunted the anticipated rise in proteinuria. Only minimal histologic alterations were observed, and the mean severity score of glomerular findings was significantly lower than that of the control animals. Furthermore, creatinine clearance was improved. The authors concluded that the combination of low doses of an ACE inhibitor and a calcium antagonist affords renal protection independent of blood pressure lowering. Additional studies are required to further substantiate and extend these promising results.

Another experimental model used to assess the renoprotective effects of calcium antagonists is passive Heymann

nephritis (PHN), a model of in-situ immune-complex disease. Arai and colleagues investigated the effects of manidipine and suggested that the renal protective mechanism relates to favorable effects on lipid peroxidation [69]. Manidipine administration in rats with PHN attenuated the increase in urinary albumin excretion and fractional clearance of albumin. The researchers speculated that one of the mechanisms by which manidipine lessens proteinuria in PHN is attributable to the decrease in the accumulation of lipid peroxidation products in the renal cortex [69].

In contrast to these studies, other investigators have failed to demonstrate a beneficial effect of calcium antagonists in diverse experimental models of chronic renal failure [70–72]. Brunner et al found that administration of verapamil to rats with remnant kidneys exacerbated renal injury and increased renal size [71]. However, treatment was begun several weeks after renal ablation, after the onset of hypertrophy and injury. Tolins and Raij compared the calcium antagonist TA 3090 to enalapril in Dahl S rats after 5/6 renal ablation and found that glomerular volume was significantly reduced by the calcium antagonist when compared with either control or enalapril-treated rats [72]. However, they reported that although enalapril prevented glomerular sclerosis, the calcium antagonist only delayed the onset of injury. The discrepancies might have resulted from the use of the remnant model of chronic renal failure in the Dahl S rat, a model of highly aggressive renal disease.

One possible explanation for the different results might relate to the lack of equivalence of blood pressure control. Clearly the interpretation of these studies as to the pathogenetic role of hypertensive mechanisms depends on the adequacy of periodic tail-cuff blood pressure measurements to accurately assess the differences in systemic blood pressure within and between groups. Recent studies by Griffin et al using the radiotelemetric technique of continuous blood pressure monitoring have demonstrated a marked spontaneous lability of blood pressure in the remnant kidney model [73, 74]. Such lability severely limits the capacity of the tail-cuff method to accurately assess the ambient systemic blood pressure profiles and, therefore, to examine the relationship of glomeruloprotection to the relative antihypertensive effectiveness of different antihypertensive regimens. To obviate this problem, Griffin et al utilized radiotelemetric blood pressure monitoring for 6 weeks to compare the effects of enalapril to nifedipine in the rat 5/6 renal ablation model [73]. Glomerulosclerosis was prevented by enalapril (2% ± 1% versus 26% ± 5% in controls) but not by nifedipine (25% ± 6%). Glomerulosclerosis correlated well with the overall averaged blood pressure in individual animals of all groups, but the slope of the relationship was significantly steeper in nifedipine-treated compared with control and enalapril-treated rats ($P < 0.02$); this result suggested greater pressure transmission to the glomeruli and glomerulosclerosis for any given blood pressure. Because autoregulatory mechanisms provide the primary protection against pressure transmission, renal autoregulation was examined at 3 weeks in an additional group of rats. Autoregulation was impaired in control rats, was not additionally altered by enalapril, but was completely abolished by nifedipine. These data demonstrate the importance of autoregulatory mechanisms in the pathogenesis of hypertensive injury. The investigators suggested that calcium antagonists, which adversely affect pressure transmissions, do not provide protection despite significant blood pressure reduction [73]. Recent studies of protein restriction support earlier work by these investigators [75]. Studies in rats with remnant kidneys placed on a low-protein (LP) intake disclosed that autoregulation is the critical component for LP-diet-conferred glomeruloprotection and that its impairment abrogates such protection despite the maintenance of the LP-diet-induced inhibition of growth responses.

Recently Picken et al used radiotelemetric systolic blood pressure monitoring for 7 weeks to compare the relationship between blood pressure reduction and glomerulosclerosis for three different classes of calcium antagonists in the remnant kidney model: diltiazem, verapamil, and felodipine [76]. Excellent correlations were observed between blood pressure and percentage of glomerulosclerosis in each group ($r = 0.75$ to 0.84, $P < 0.01$). These authors utilized the slope of the relationship between blood pressure and glomerulosclerosis as an index of the effect of calcium-channel blockers on the glomerular transmission of systemic blood pressure. This slope did not differ between control and diltiazem-treated animals; verapamil caused a modest shift to the left, while felodipine resulted in both a shift to the left and in a markedly steeper slope, suggesting a greater glomerular transmission of systemic pressure. The adverse effects of the slope (felodipine > verapamil) explain why glomeruloprotection was not achieved with verapamil and felodipine despite blood pressure reduction. The investigators interpreted the results as suggesting that significant differences exist between calcium-channel blockers in their relative impact on systemic blood pressure and on glomerulosclerosis because of their different effects on renal vascular autoregulatory responses [76].

In a recent editorial, Bidani and Griffin summarized the results of many of these trials and concluded that the key to these discrepancies lies in the interplay between the loss of intrarenal autoregulation, which occurs with the administration of calcium antagonists, and the magnitude of the reduction in the blood pressure achieved [77]. Calcium antagonists decrease the afferent arteriolar tone, allowing a greater transmission of systemic blood pressure to the glomerular capillaries. This effect in turn may be offset by the ability of calcium antagonists to lower systemic blood pressure, thereby causing no net change or even a reduction in the intraglomerular pressure.

Clinical studies assessing the renoprotective effects of calcium antagonists

Only recently have long-term clinical trials assessed the renoprotective effects of calcium antagonists. Although few in number, in concert the available studies suggest that calcium antagonists are beneficial in stabilizing renal function. Zucchelli and colleagues reported the results of their prospective, randomized controlled trial in which they compared the effects of an ACE inhibitor, captopril, and a dihydropyridine calcium antagonist, nifedipine, on both hypertension and the progression of renal insufficiency [78]. During the one-year pre-randomization period, patients were treated with various standard antihypertensive combinations including β-blockers, furosemide, clonidine, and hydralazine. Subsequently, 121 hypertensive patients with chronic renal failure were randomly allocated to either captopril or slow-release nifedipine treatment for a 3-year period. The rate of progression of renal insufficiency, assessed as 1/serum creatinine versus time, creatinine clearance versus time, and ^{99m}TC diethylenetriaminepenta-acetic acid clearance versus time was attenuated to a similar degree in both treatment groups. These investigators proposed that their data were "consistent with the hypothesis that both calcium antagonists and ACE inhibitors possess a renoprotective effect."

A number of events related to the experimental design and the conduct of the study, however, raise questions about this conclusion. First, because the mean arterial pressure was higher during the pre-randomization period, when treated with standard therapy, better control of blood pressure might have contributed to the retardation of the progression rate of renal insufficiency by both ACE inhibitors and calcium antagonists. Furthermore, the interpretation of the renal survival curves is fraught with difficulty. Of the 121 patients who underwent randomization at the end of the initial year of study, only 37 patients concluded 3 years of study in the captopril group, and only 32 patients in the nifedipine group did. In the third year, 11 of the remaining 46 patients in the nifedipine group and only 2 of the remaining 44 patients in the captopril group reached end-stage renal disease ($P < 0.005$). The reduction in statistical power might account for the absence of a difference in overall renal survival between the two groups. The resultant diminution in the number of patients during the final year of study confounds interpretation of the renal survival curves.

Subsequently, two studies in hypertensive diabetic patients have circumvented many of the methodologic concerns of the Zucchelli study. Velussi et al compared the effects of cilazapril versus amlodipine on GFR and albumin excretion in hypertensive patients with non-insulin-dependent diabetes mellitus (NIDDM) [79]. Twenty-six patients had normoalbuminuria and 18 had microalbuminuria. Glomerular filtration rate was measured by plasma clearance of ^{51}Cr EDTA at baseline and every 6 to 12 months during a 3-year followup interval. The GFR decline (mean $\pm$ SE) per year in the normoalbuminuric patients during cilazapril treatment was similar to that observed during amlodipine therapy. Furthermore the GFR decline per year in the microalbuminuric patients during cilazapril therapy did not differ from that observed with amlodipine. Cilazapril and amlodipine lowered the albumin excretion rate to a similar extent in normoalbuminuric and microalbuminuric patients.

In a recent carefully conducted study, Rossing et al compared the effects of the long-acting dihydropyridine nisoldipine with those of the ACE inhibitor lisinopril on proteinuria and on decline in GFR in 49 hypertensive patients with IDDM [80]. Interim results at the end of the first year disclosed a striking dissociation between the antiproteinuric effects and the effects on GFR. Albuminuria was reduced by 47% in the lisinopril group versus no decrement in the nisoldipine group. In marked contrast, the decline in GFR tended to be less steep in the nisoldipine group compared with the decline in the lisinopril group. Although the numbers are small, these observations suggest that a dihydropyridine, presumably acting through mechanisms independent of its renal microcirculatory effects, is renoprotective.

Campbell and colleagues recently reported on the results of a large multicenter trial comparing the effects of ACE inhibitors versus calcium antagonists in normotensive diabetic subjects (systolic blood pressure < 140 mm Hg if age < 40, otherwise systolic blood pressure < 160 mm Hg, and diastolic blood pressure < 90 mm Hg) with microproteinuria (albumin excretion rate, 20–200 μg/min) [81]. Subjects were randomly assigned to receive placebo, perindopril, or nifedipine. Perindopril (2–8 mg/day) and nifedipine (slow release, 10–40 mg/day) were titrated to achieve a fall in supine diastolic blood pressure > 4 mm Hg). Data for 2 to 7 years were obtained from 60 subjects. For patients with IDDM, perindopril reduced the rate of change in albumin excretion rate, but neither drug affected blood pressure or rate of change in creatinine clearance. For patients with NIDDM, although both drugs reduced blood pressure similarly, neither drug affected the rate of change in albumin excretion rate or creatinine clearance. The authors concluded that reduction of proteinuria by antihypertensive agents does not necessarily predict a reduced rate of decline in creatinine clearance, and that protection of renal function by these agents is determined in part by the absolute blood pressure achieved.

In summary, although only relatively few studies are available for review, and the numbers of patients are small, their results suggest that calcium antagonists attenuate or stabilize the progression of chronic renal failure. Clearly more studies are needed to confirm this postulate.

A number of similar studies are underway to compare the effects of therapy with an ACE inhibitor combined with

a calcium antagonist versus either intervention alone in patients with nondiabetic renal disease. Two years ago, a large, randomized prospective study was initiated to assess renal protection in nondiabetic renal disease. The European Multicenter Study on Progression in Nondiabetic Renal Disease (NEPHROS study) will compare the renal protective effects of ramipril, felodipine, or the combination of ramipril plus felodipine (personal communication). Two hundred patients with nondiabetic renal disease will be recruited in the United Kingdom, France, Germany, Israel, and Sweden. A second study will soon be initiated comparing the renal protective effects of trandolapril, verapamil, or the combination of trandolapril plus verapamil.

Do chemically dissimilar calcium antagonists differ in their renal effects?

In addition to the question of whether calcium antagonists as a class are renoprotective, interest has focused on the question of whether differences exist within the class, for example, dihydropyridine versus nondihydropyridine calcium antagonists. Maki et al conducted a meta-analysis of investigations with followup times of at least 6 months to assess the effects of different antihypertensive agents on proteinuria and GFR in patients with renal disease [82]. They included studies in diabetic and nondiabetic patients with renal disease. Analysis of the results of 14 randomized controlled trials disclosed that ACE inhibitors caused a greater decrease in proteinuria, improvement in GFR, and decline in mean arterial pressure compared with controls. In a multivariate analysis of controlled and uncontrolled trials, each 10 mm Hg reduction in blood pressure decreased proteinuria, but ACE inhibitors and nondihydropyridine calcium antagonists were associated with additional declines in proteinuria that were independent of blood pressure changes and diabetes. Each 10 mm Hg reduction in blood pressure caused a relative improvement in glomerular filtration rate (0.18 ml/min/month), but in diabetic patients dihydropyridine calcium antagonists tended to cause a relative reduction in glomerular filtration rate (-0.68 ml/min/month). Maki and colleagues emphasized that the results of their retrospective analysis should be interpreted with caution and proposed that direct long-term comparison studies are needed to determine whether class differences exist between ACE inhibitors and calcium antagonists, and whether specific differences exist within the classes.

Only one investigative group has demonstrated that nondihydropyridine calcium antagonists confer a greater renoprotective effect in randomized prospective studies. Lash and Bakris conducted a 4-year followup study in patients with nephropathy from type-II diabetes and observed that therapy with lisinopril and verapamil reduces nephrotic-range proteinuria. The combination of the two agents induced a greater effect than did either agent alone [83]. This benefit occurred in the absence of additional antihypertensive effects of the combination.

It is too early for us to ascertain whether dihydropyridines indeed differ from nondihydropyridines in their renal effects. Clearly, additional long-term studies enrolling larger numbers of patients are required to rigorously compare the effects of chemically dissimilar calcium antagonists on proteinuria and on their ability to stabilize GFR.

Does it matter whether calcium antagonists are renoprotective?

In light of the compelling data indicating that ACE inhibitors are renoprotective in the clinical setting of diabetes and hypertension, should we concern ourselves with the possibility that calcium antagonists are also beneficial? I believe we should. Recent reports have emphasized that our failure to achieve blood pressure control is partly attributable to a misplaced focus on monotherapy. Most patients with renal insufficiency or diabetes require at least two drugs for adequate blood pressure control. In fact a report by Stefanski et al noted that their patients with chronic renal insufficiency and severe hypertension require more than four antihypertensive agents to control their blood pressure [1]. These observations have been confirmed by recent data. Bakris et al reported that an average of 4.3 antihypertensive medications were required by diabetic hypertensive patients to reduce blood pressure to levels of $< 130/80$ mm Hg [2]. These findings underscore the need to include in our antihypertensive armamentarium not one but several antihypertensive agents that share the attributes of efficacy, maintenance of metabolic neutrality, and the ability to stabilize renal function in the setting of progressive renal disease.

An additional consideration that merits attention is how ACE inhibitors differ from calcium antagonists in renal potassium handling. The very patients (for example, diabetics or patients with progressive renal failure) who might be suitable candidates for ACE inhibitor therapy (for retarding progression of their disease) are the ones most likely to develop hyperkalemia as a consequence. In contrast, calcium antagonists do not provoke hyperkalemia. Indeed, studies by Solomon et al in subjects with end-stage renal disease have suggested that the benzothiazepine diltiazem enhances potassium disposal [84]. Consequently, patients who tend to develop hyperkalemia when treated with ACE inhibitors might benefit from calcium antagonists because these agents do not increase plasma potassium levels.

Critique of the ABCD and FACET studies and concluding remarks

Increasing evidence indicates a need for more rigorous blood pressure control in the hypertensive diabetic patient. Although much attention has focused on the renal protective attributes of ACE inhibitors, the side effects of this

drug class render ACE inhibitors inappropriate for some diabetic patients. Furthermore, it is becoming increasingly apparent that appropriate blood pressure control in the diabetic hypertensive patient frequently requires more than one class of antihypertensive drugs. Recent studies have focused on identifying appropriate antihypertensive agents that not only lower blood pressure but also retard the progression of renal disease.

These considerations have focused our attention on calcium antagonists and their effects on renal function and renal hemodynamics. In addition to their efficacy and maintenance of metabolic neutrality, recent preliminary reports suggest that, despite their renal microcirculatory effects, some calcium antagonists can slow progressive renal failure. Such considerations have prompted the initiation of several randomized, prospective, long-term studies to elucidate the renoprotective effects of monotherapy with calcium antagonists. It is becoming apparent that several pharmacologic interventions may be capable of retarding the progression of renal failure.

In light of these considerations, the recent report of the ABCD trial [85] warrants consideration and discussion as to whether it militates against the use of calcium antagonists in diabetic patients with hypertension. The ABCD trial, still underway at the University of Colorado Life Sciences Center, is a prospective, 5-year, randomized, double-blind study scheduled to end in June 1998. The study is designed to evaluate the effects of intensive versus moderate blood pressure control on the prevention or progression of non-insulin-dependent diabetes mellitus (NIDDM) nephropathy, neuropathy, retinopathy and cardiovascular events in 950 patients. A secondary objective of this trial is to evaluate the effects of a long-acting calcium antagonist, nisoldipine, and an ACE inhibitor, enalapril, as first-line antihypertensive agents in the prevention and progression of diabetic vascular complications. In this population of patients with diabetes and hypertension, the authors found a significantly higher incidence of fatal and nonfatal myocardial infarction among those assigned to therapy with the calcium-antagonist nisoldipine than among those assigned to receive enalapril.

As the authors rightfully acknowledge, the findings are based on a secondary end point, and therefore require confirmation [85]. Although patients who received the calcium antagonist had a significantly higher rate of nonfatal myocardial infarction than did those receiving the angiotensin-converting-enzyme inhibitor, the incidence of other cardiovascular events did not differ between the patients taking a calcium antagonist and those treated with an ACE inhibitor. Specifically, cerebrovascular accidents, congestive heart failure, and death from cardiovascular causes did not significantly differ between these groups. In fact, death from any cause was not statistically significantly different (nisoldipine = 17; enalapril = 13). Furthermore, the study failed to distinguish between a deleterious effect of nisoldipine, a protective effect of enalapril, or a combination of both as a reason for the difference observed. Although comparisons with historic controls are not ideal, it is interesting to note that the rate of myocardial infarction among patients with NIDDM who were randomly assigned to therapy with nisoldipine in the study is not significantly different from that in other recent studies of patients with NIDDM [86, 87]. This observation suggests that the findings resulted from a protective effect of the ACE inhibitor. Although the ABCD study cannot distinguish among these possibilities, the ongoing ALLHAT study [88] should allow us to elucidate the reason for the results reported. Because there are more than two drug-treatment goups, it should be possible to distinguish harm from benefit if differences in end-point rates are observed in the future, since a treatment with known benefit in terms of cardiovascular outcomes—a diuretic—is included.

Unfortunately, many physicians have assumed that the adverse effects attributed to nisoldipine are reflective of the calcium antagonist class as a whole and have extrapolated inappropriately these effects to drugs with more advanced extended release formulations [89, 90] or drugs that are intrinsically long acting (amlodipine, lacidipine) that have a markedly different pharmacokinetic profile. Indeed, a review of the few available data suggests a theoretic framework for anticipating that these pharmacokinetic differences may be exaggerated in the setting of diabetes mellitus (Epstein M, Preston R, unpublished observations). Amplification of such differences in the diabetic patient could explain differences in clinical efficacy as well as adverse cardiovascular events.

Another study that has recently stirred the waters is the FACET study. For purposes of this discussion, I have elected to analyze and critique the FACET study because it exemplifies some of the problems, inconsistencies, and indeed lack of rigor that confound some recent reports. Unfortunately, many clinicians fail to take the time necessary to critically review such reports, and therefore they arrive at misleading conclusions.

The recent Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) [91] adds additional fuel to the fire regarding a possible adverse effect of calcium antagonists. The FACET study compared the effects of fosinopril and amlodipine on serum lipids and diabetes control in NIDDM patients with hypertension. Prospectively defined cardiovascular events were assessed as secondary outcomes. A total of 380 hypertensive diabetics were randomly assigned to open-label fosinopril (20 mg/day) or amlodipine (10 mg/day) and followed for as long as 3.5 years. If blood pressure was not controlled, the other study drug was added. Both treatments were effective in lowering blood pressure. At the end of followup, the two groups had no significant difference in total serum lipids or glycemic control. The patients receiving fosinopril had a significantly lower risk of the combined outcome of acute

myocardial infarction, stroke, or hospitalization for angina than did the patients receiving amlodipine (14/189 versus 27/191; hazards ratio = 0.49).

Various factors related to the experimental design and the conduct of the study confound the certainty of this conclusion, however. First, a number of key aspects of the study have changed since the original abstract was published in 1996. Of note, the original abstract concluded that the combination of amlodipine and fosinopril provided the best outcomes for diabetic hypertensive patients [92]. This group was composed entirely of subjects who had failed one of the randomized monotherapies, and so might be presumed to have been at higher risk. In contrast, the newly published material now concludes that the ACE inhibitor is superior to the calcium antagonist [91]. In addition, the number of patients assigned to each study group has changed. In the first 6 months post randomization, the amlodipine group had 20 dropouts and 50 crossovers (to amlodipine + fosinopril), whereas the fosinopril group had 13 dropouts and 60 crossovers. Thus, 70/190 (37%) and 76/190 (40%) were no longer in their randomized groups by June 1993, 6 months after recruitment ended (and the starting point for followup in the original trial). It is also important to note that this is an open-label, single-center study, which exposes the results to sponsor and investigator bias [91]. Finally, and perhaps most important, there were no significant differences between the study groups for any of the individual cardiovascular events, and all-cause mortality was the same for the amlodipine and fosinopril groups. Only when various events were arbitrarily grouped together did any of the events reach statistical significance [91].

Until the ongoing morbidity and mortality studies with calcium antagonists such as ALLHAT establish definitively what the effects of calcium antagonists are on cardiovascular risk, what should physicians do? The available evidence is clear that ACE inhibitors should be used as initial monotherapy in managing the diabetic hypertensive patient. Nesto and Zarich recently summarized the evidence indicating that ACE inhibitors can be helpful in the diabetic patient with cardiovascular disease [93]. Experimental data indicate that ACE inhibitors can suppress plasminogen activator expression and improve fibrinolytic capacity in patients after MI [93]. Also, ACE inhibitors markedly improve insulin sensitivity and glycemic control. Because improved glycemic control is associated with improved mortality after MI in diabetic patients receiving insulin [93], ACE inhibitors might improve survival in this group by concomitantly decreasing insulin resistance, improving glycemic control, and restoring fibrinolytic capacity. The data are even more compelling with respect to renal protection. Randomized prospective studies have shown that ACE inhibitors clearly confer benefits beyond those of blood pressure reduction. However, as I have said, monotherapy with ACE inhibitors often does not suffice to achieve the new target blood pressures advocated by the Joint National Commission VI. In such settings I believe it is prudent to add a calcium antagonist as a second agent because of its efficacy, metabolic neutrality, and the fact that its mechanisms of action complement those of ACE inhibitors.

QUESTIONS AND ANSWERS

Dr. Nicolaos E. Madias (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts*): Could you please expand on the issue of whether calcium antagonists of different molecular structure differ in terms of their effects on the kidney?

Dr. Epstein: Yes, that is a key point. Clearly, there are differences on the renal microcirculatory profile, as I noted. Efonidipine and manidipine appear to have a greater efferent vasodilatory effect than do the traditional drugs verapamil or diltiazem. The second issue, and I think the most relevant one, is whether chemically dissimilar calcium antagonists differ in their effects on proteinuria and stabilization of renal function. We don't know about stabilization of renal function, but some newer data have suggested that some of the nondihydropyridines have a greater beneficial effect. Most of these studies stem primarily from one group, Bakris and colleagues, who in a series of recent publications have suggested that verapamil or diltiazem appears to have a greater effect in terms of diminishing proteinuria over the period of observation [2, 94]. It's an intriguing observation that requires confirmation by other investigators in other laboratories, but if it's true, and I have no reason to doubt that it is, it raises an important issue as to what the mechanisms are. The renal microcirculatory profile of verapamil and diltiazem is similar to that of most dihydropyridines. Thus the possibility exists that non-hemodynamic mechanisms account for the greater antiproteinuric affect.

Dr. Madias: The antiproteinuric effect of ACE inhibitors evolves over a period of weeks and appears to reflect hemodynamic changes as well as changes in the permselective properties of the glomerular basement membrane. Also, the antiproteinuric effect is potentiated by sodium restriction or diuretics. Could you please comment on whether there are similar observations regarding the antiproteinuric effect of calcium antagonists?

Dr. Epstein: It is well established that the ability of ACE inhibitors to reduce albumin excretion depends on sodium intake [95]. In contrast, relatively few studies have investigated the effect of sodium intake on albuminuria in the presence of calcium antagonist administration. Bakris and Smith conducted a prospective, crossover, open-labeled trial to determine whether sodium intake alters albumin excretion in NIDDM patients with diabetic nephropathy [94]. They compared the effects of once-daily diltiazem with once-daily nifedipine to decrease blood pressure to less than 140/90 mm Hg. A diet of 50 mEq of sodium per day in combination with once-daily diltiazem reduced

albumin excretion. Albumin excretion was not reduced after a similar period of blood pressure reduction with once-daily nifedipine. Although these observations must be viewed with caution because of the non-randomized study design and small number of patients, these authors suggest that sodium restriction enhances the antiproteinuric effect of some calcium antagonists.

Recently, Smith et al investigated the effects of chemically dissimilar calcium antagonists on glomerular permeability [96]. They randomized 28 patients with type-II diabetes to treatment with either diltiazem CD or nifedipine GITS and assessed changes in glomerular permeability using dextran clearances. At similar levels of blood pressure (goal of mean blood pressure < 107 mm Hg), diltiazem significantly reduced proteinuria by decreasing glomerular membrane permeability, whereas nifedipine did not. Additional studies must be conducted to further clarify these interesting effects.

Dr. John T. Harrington (*Dean, Tufts University School of Medicine, Boston*): Murray, you discussed many of the clinical studies, either published or in progress, but you had concerns about several of them. How would you define the ideal study of the renoprotective effects of calcium antagonists? Has that ideal study yet been done?

Dr. Epstein: The earlier concerns that I had about some of those studies were related to duration—that the studies were not of sufficient duration to allow us to make reasonable inferences. Some were one to 2 years long, but I think that optimally 4 to 5 years of followup are required. Many studies have relied on very crude measures of renal function, serum creatinine concentration or creatinine clearance, which certainly are not adequate, especially in patients with diabetic nephropathy. I believe some other marker that would pass scrutiny must be used.

Dr. Harrington: You mentioned in passing that calcium antagonists reduce renal cortical calcium content. How do they do that? What's the mechanism for that protective effect? Do we know?

Dr. Epstein: I don't know. Interestingly, that study by Goligorsky was published in 1985. I'm unaware whether anyone has confirmed or extended those initial observations in the 13 years since that study was published.

Dr. Andrew J. King (*Division of Nephrology, New England Medical Center*): The antihypertensive effects of calcium-channel blockers have been purported to be greater in volume-expanded patients, including those with end-stage renal disease. Could you speculate on the mechanisms involved in their response?

Dr. Epstein: The effects of most antihypertensive agents are potentiated by a reduction in salt intake, and their blood-pressure-lowering effect is blunted by a high salt intake. The Blaustein hypothesis predicts that a high salt intake will increase intracellular calcium [97]. This raises the possibility that calcium antagonists are more effective with patients on a high-salt intake. Cappuccio et al assessed the effects of a normal-sodium intake (150 mEq/day) and a high-sodium intake (350 mEq/day) on the blood pressure response to a single capsule of nifedipine [98]. The difference in blood pressure between subjects taking a placebo and those taking nifedipine was greater on the high-sodium diet than on the low-sodium diet, but this difference failed to reach statistical significance.

Studies with verapamil also have shown that the blood pressure fall tends to be amplified on a high-sodium intake [99]. The finding, therefore, that a high-sodium intake appears at the very least not to blunt, and possibly enhances, the effect of the calcium antagonists is of interest. I am not aware of subsequent studies that have extended these earlier observations, however.

Dr. King: Could you comment on the relative antihypertensive effectiveness of the various classes of calcium-channel antagonists?

Dr. Epstein: Generally, the dihydropyridines are more effective. But this issue is broader than mere differences in the chemical structure. I'm an advocate for drug formulation as a determinant of clinical decision-making. Specifically, clinical experience has demonstrated that once-a-day formulations dramatically change these drugs' effects. This was beautifully exemplified by a study a few years ago by Kleinbloesem et al [100]. If one alters the rapidity of attainment of a plasma concentration of nifedipine, that is, rapid versus slow and gradual attainment, the effect on heart rate and blood pressure is dramatically different. Whereas a slow infusion of nifedipine lowered blood pressure and caused no appreciable change in heart rate, rapid intravenous infusion barely decreased blood pressure but markedly raised heart rate. I am less concerned about which dihydropyridine than I am by differences in formulation. That is, I favor a drug that is taken once a day and that acts over the entire 24-hour period. The concerns that I've raised—the Griffen-Bidani studies, the studies from Milan—all suggest that if we don't control blood pressure throughout the 24-hour period in a sustained manner, then we fail to treat our patient optimally [101].

Dr. Madias: Cyclosporine A is primarily an afferent arteriole constrictor and, as you noted, calcium antagonists are afferent arteriole dilators. Could you please address the existing information on the effects of calcium antagonists on the vasoconstrictive and nephrotoxic effects of cyclosporine A?

Dr. Epstein: I earlier depicted data from some studies in cadaveric kidney transplant recipients to make the point that these agents may have utility in acute prophylaxis in that setting. Another major area that has attracted a lot of investigative attention is cyclosporine and its acute renal vasoconstrictive effects. There is a clear-cut rationale for why calcium antagonists act as renal vasodilators in this setting. Thromboxane mimetics induce afferent arteriolar constriction, and we have reported that calcium antagonists can reverse this constriction in a dose-dependent manner

[17]. Furthermore, endothelin induces afferent arteriolar constriction and calcium antagonists can reverse that effect as well [16]. To the extent that both of these are thought to constitute important mediators of cyclosporine-induced vasoconstriction, it is reasonable to anticipate that calcium antagonists would be able to reverse the renal vasoconstriction. Indeed, this has been reported by Ruggenenti and colleagues in Italy [102] and by other investigators [103, 104].

DR. HARRINGTON: You showed a difference in blood pressure, monitored radiotelemetrically, between enalapril and nifedipine. Was that difference related to nifedipine per se or to a specific formulation of nifedipine? Shouldn't we be able to obtain the same results with nifedipine as with enalapril?

DR. EPSTEIN: In that instance, we are looking at the chemical agent per se and not formulation, because nifedipine in the GITS formulation cannot be administered to laboratory animals. When the GITS formulation of nifedipine is administered to patients, much of the variability in that study is dramatically attenuated clinically by the administration of appropriate long-acting formulations or by drugs that are intrinsically long-acting, such as amlodipine or lacidipine (available in Europe but not available in the United States).

DR. ANDREW S. LEVEY (*Division of Nephrology, New England Medical Center*): Thank you very much for a balanced view of calcium-channel blockers in retarding the progression of renal disease. Most recent clinical trials that demonstrate the usefulness of ACE inhibitors in slowing the progression of diabetic or non-diabetic nephropathy have not been "head-to-head" comparisons with calcium-channel blockers. What clinical trial design do you favor for comparing these agents? Specifically, do you believe it is proper to omit an ACE inhibitor from the treatment of patients with progressive renal disease for the purpose of determining whether other agents are equally efficacious?

DR. EPSTEIN: As I noted previously, I believe the most important intervention for retarding progression of renal disease is adequate and sustained blood-pressure lowering. Once we attain that goal, a secondary issue is whether some antihypertensive classes preferentially confer additional renal protection. I agree with you that recent studies have documented that ACE inhibitors are especially efficacious in retarding progressive renal disease. The data with respect to calcium antagonists are suggestive but inconsistent. Although I believe that comparisons of ACE inhibitors versus calcium antagonists are acceptable in disorders other than type-I diabetes mellitus, physicians are unlikely to allow their patients to be randomized to a non-ACE-inhibitor treatment arm. Consequently, an alternative study approach should be considered. In light of recent reports indicating that monotherapy is often inadequate for lowering blood pressure in many of these patients, a reasonable approach might be to compare ACE inhibitors plus diuretics versus ACE inhibitors plus calcium antagonists. This comparison will allow us to discern whether calcium antagonists are equally or more renoprotective than other agents at similar levels of blood-pressure reduction.

Reprint requests to Dr. M. Epstein, Nephrology Section, VA Medical Center, 1201 NW 16th Street, Miami, Florida 33125, USA

REFERENCES

1. STEFANSKI A, AMANN K, RITZ E: To prevent progression: ACE inhibitors, calcium antagonists or both? *Nephrol Dial Transplant* 10:151–153, 1995
2. BAKRIS GL, COPLEY JB, VICKNAIR N, SADLER R, LEURGANS S: Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy: Results of a six year study. *Kidney Int* 50:1641–1650, 1996
3. KLUTSCH K, SCHMIDT P, GROSSWENDT J: Der einfluss von BAY a 1040 auf die Nierenfunktion des Hypertonikers. *Artzneimittelforschung* 22:377–380, 1972
4. REAMS GP, BAUER JH: Acute and chronic effects of calcium antagonists on the essential hypertensive kidney, in *Calcium Antagonists and the Kidney*, edited by EPSTEIN M, LOUTZENHIZER R, Philadelphia, Hanley & Belfus, 1990, pp 247–256
5. BLACKSHEAR JL, GARNIC D, WILLIAMS GH: Exaggerated renal vasodilator response to calcium entry blockade in first-degree relatives of essential hypertensive subjects. *Hypertension* 9:384–389, 1987
6. MONTANARI A, VALLISA D, RAGNI G, GUERRA A, COLLA R, NOVARINI A, CORUZZI P: Abnormal renal responses to calcium entry blockade in normotensive offspring of hypertensive parents. *Hypertension* 12:498–505, 1988
7. EDWARDS RM: Segmental effects of norepinephrine and angiotensin II on isolated renal microvessels. *Am J Physiol* 244:F526–F534, 1983
8. YUAN BH, ROBINETTE JB, CONGER JD: Effects of angiotensin II and norepinephrine on isolated rat afferent and efferent arterioles. *Am J Physiol* 258:F741–F750, 1990
9. ITO S, CARRETERO OA: An in vitro approach to the study of macula densa-mediated glomerular hemodynamics. *Kidney Int* 38:1206–1210, 1990
10. ITO S, REN Y: Evidence for the role of nitric oxide in macula densa control of glomerular hemodynamics. *J Clin Invest* 92:1093–1098, 1993
11. CARMINES PK, MORRISON KD, NAVAR LG: Angiotensin II effects on microvascular diameters of in vitro blood-perfused juxtamedullary nephrons. *Am J Physiol* 251:F610–F618, 1986
12. YAMMAMOTO T, TANAKA H, YOSHIYUKI J, TSUJIOKA K, KAJIYA F, YAMAMORI S, HOSAKA H: Visualization of intrarenal microvessels and evaluation of the effect of angiotensin II by a needle probe microscope with a CCD camera (*abstract*). *J Am Soc Nephrol* 4:574, 1993
13. STEINHAUSEN M, SNOEI H, PAREKH N, BAKER R, JOHNSON PC: Hydronephrosis: A new method to visualize vas afferens, efferens, and glomerular network. *Kidney Int* 23:794–806, 1983
14. LOUTZENHISER R, HAYASHI K, EPSTEIN M: Atrial natriuretic peptide reverses afferent arteriolar vasoconstriction and potentiates efferent arteriolar vasoconstriction in the isolated perfused rat kidney. *J Pharmacol Exp Ther* 246:522–528, 1988
15. LOUTZENHISER R, HAYASHI K, EPSTEIN M: Divergent effects of KCl-induced depolarization on afferent and efferent arterioles. *Am J Physiol* 257:F561–F564, 1989
16. LOUTZENHISER R, EPSTEIN M, HAYASHI K, HORTON C: Direct visualization of effects of endothelin on the renal microvasculature. *Am J Physiol* 258:F61–F68, 1990
17. LOUTZENHISER R, EPSTEIN M: Renal hemodynamic effects of calcium antagonists, in *Calcium Antagonists and the Kidney*, edited by EPSTEIN M, LOUTZENHISER R, Philadelphia, Hanley & Belfus, 1990, pp 33–75
18. HAYASHI KH, SARUTA T, EPSTEIN M: The renal hemodynamic effects of calcium antagonists, in *Calcium Antagonists in Clinical Medicine* (2nd ed), edited by EPSTEIN M, Philadelphia, Hanley & Belfus, 1998, pp 393–411
19. EPSTEIN M: Calcium antagonists and the kidney: Implications for

renal protection, in *Calcium Antagonists in Clinical Medicine*, edited by EPSTEIN M, Philadelphia, Hanley & Belfus, 1998, pp 433–465
20. EPSTEIN M: Calcium antagonists and the kidney: Future therapeutic perspectives. *Am J Kidney Dis* 21(suppl 3):16–25, 1993
21. TOJO A, KIMURA K, MATSUOKA H, SUGIMOTO T: Effects of manidipine hydrochloride on the renal microcirculation in spontaneously hypertensive rats. *J Cardiovasc Pharmacol* 20:895–899, 1992
22. LEONETTI G, GRADNIK R, TERZOLI L, FRUSCIO M, RUPOLI CUSPIDI C, SAMPERI L, ZANCHETTI A: Effects of single and repeated doses of the calcium antagonist felodipine on blood pressure, renal function, electrolytes and water balance, and renin-angiotensin-aldosterone system in hypertensive patients. *J Cardiovasc Pharmacol* 8:1243–1248, 1986
23. EPSTEIN M, DE MICHELI AG: Natriuretic effects of calcium antagonists, in *Calcium Antagonists in Clinical Medicine*, edited by EPSTEIN M, Philadelphia, Hanley & Belfus, 1992, pp 349–366
24. EPSTEIN M, DE MICHELI AG, FORSTER H: Natriuretic effects of calcium antagonists in humans: A review of experimental evidence and clinical data. *Cardiovasc Drug Rev* 9:399–413, 1991
25. NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM: National High Blood Pressure Education Program Working Group report on hypertension and chronic renal failure. *Arch Intern Med* 151:1280–1287, 1991
26. JACOBSON HR, STRIKER GE: Report on a workshop to develop management recommendations for the prevention of progression in chronic renal disease. *Am J Kidney Dis* 25:103–106, 1995
27. NEURINGER JR, BRENNER BM: Hemodynamic theory of progressive renal disease: a 10-year update in brief review. *Am J Kidney Dis* 22:98–104, 1993
28. BRENNER BM, MEYER TW, HOSTETTER TH: Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation and intrinsic renal disease. *N Engl J Med* 307:652–659, 1982
29. HOSTETTER TH, OLSON JL, RENNKE HG, VENAKTACHALAM MA, BRENNER BM: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 241:F85–F93, 1981
30. HOSTETTER TH, RENNKE HG, BRENNER BM: The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 72:375–380, 1982
31. MEYER TW, ANDERSON S, RENNKE HG, BRENNER BM: Reversing glomerular hypertension stabilizes established glomerular injury. *Kidney Int* 31:752–759, 1987
32. ANDERSON S, RENNKE HG, BRENNER BM: Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 77:1993–2000, 1986
33. RAY PE, AGUILERA G, KOPP JB, HORIKOSHI S, KLOTMAN PE: Angiotensin II stimulates proliferation of human fetal mesangial cells by a receptor-mediated mechanism (*abstract*). *J Am Soc Nephrol* 1:424, 1990
34. AMANN K, IRZYNIEC T, MALL G, RITZ E: The effect of enalapril on glomerular growth and glomerular lesions after subtotal nephrectomy in the rat: a stereological analysis. *J Hypertens* 11:969–975, 1993
35. EPSTEIN M: The benefits of ACE inhibitors and calcium antagonists in slowing progressive renal failure: focus on fixed-dose combination antihypertensive therapy. *Renal Fail* 18:813–832, 1996
36. ICHIKAWA I, HARRIS RC: Angiotensin actions in the kidney: Renewed insight into the old hormone. *Kidney Int* 40:583–596, 1991
37. ORTH S, NOWICKI M, WIECEK A, RITZ I: Nephroprotective effect of ACE inhibitors. *Drugs* 46(suppl 2):189–196, 1993
38. ICHIKAWA I: Nephrology Forum: Will angiotensin II receptor antagonists be renoprotective in humans? *Kidney Int* 50:684–692, 1996
39. LEWIS EJ, HUNSICKER, LG, BAIN RP, ROHDE RD, FOR THE COLLABORATIVE STUDY GROUP: The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456–1462, 1993
40. CATTRAN DC, GREENWOOD C, RITCHIE S: Long-term benefit of angiotensin-converting enzyme inhibitor therapy in patients with severe immunoglobulin A nephropathy: A comparison to patients receiving treatment with other antihypertensive agents and to patients receiving no therapy. *Am J Kidney Dis* 23:247–254, 1994
41. MASCHIO G, ALBERTI D, JANIN G, LOCATELLI F, MANN JF, MOTOLESE M, PONTICELLI C, RITZ E, ZUCCHELLI P: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition Progressive Renal Insufficiency Study Group. *N Engl J Med* 334:939–945, 1996
42. EPSTEIN M, COOPER ME: Diabetic nephropathy: Focus on ACE inhibition and calcium channel blockade, in *Calcium Antagonists in Clinical Medicine* (2nd ed), edited by EPSTEIN M, Philadelphia, Hanley & Belfus, 1998, pp 243–271
43. ANDERSON S: Renal hemodynamic effects of calcium antagonists in rats with reduced renal mass. *Hypertension* 17:288–295, 1991
44. ANDERSON S, RENNKE HG, BRENNER BM: Nifedipine versus fosinopril in uninephrectomized diabetic rats. *Kidney Int* 41:891–897, 1992
45. DWORKIN LD, FEINER HD, PARKER M, TOLBERT E: Effects of nifedipine and enalapril on glomerular structure and function in uninephrectomized SHR. *Kidney Int* 39:1112–1117, 1991
46. DWORKIN LD, LEVIN RI, BENSTEIN JA, PARKER M, ULLIAN ME, KIM Y, FEINER HD: Effects of nifedipine and enalapril on glomerular injury in rats with deoxycorticosterone-salt hypertension. *Am J Physiol* 259:F598–F604, 1990
47. EPSTEIN M, LOUTZENHISER R: Potential applicability of calcium antagonists as renal protective agents, in *Calcium Antagonists and the Kidney*, edited by EPSTEIN M, LOUTZENHISER R, Philadelphia, Hanley & Belfus, 1990, pp 275–298
48. EPSTEIN M: Calcium antagonists and renal protection. Current status and future perspectives. *Arch Intern Med* 152:1573–1584, 1992
49. EPSTEIN M: Calcium antagonists and the kidney: Implications for renal protection, in *Calcium Antagonists in Clinical Medicine* (2nd ed), edited by EPSTEIN M, Philadelphia, Hanley & Belfus, 1998, pp 433–465
50. DWORKIN LD: Effects of calcium channel blockers on experimental glomerular injury. *J Am Soc Nephrol* 1:S21–S27, 1990
51. DWORKIN LD: Impact of calcium entry blockers on glomerular injury in experimental hypertension. *Cardiovasc Drugs Ther* 4:1325–1330, 1990
52. DWORKIN LD, LEVIN RI, BENSTEIN JA, ET AL: Effects of nifedipine and enalapril on glomerular injury in rats with deoxycorticosterone-salt hypertension. *Am J Physiol* 259:F598–F604, 1990
53. SWEENEY C, SHULTZ P, RAIJ L: Interactions of the endothelium and mesangium in glomerular injury. *J Am Soc Nephrol* 1:S13–S20, 1990
54. RAIJ L, KEANE W: Glomerular mesangium: its function and relationship to angiotensin II. *Am J Med* 79(suppl 36):24–30, 1985
55. DWORKIN LD, BENSTEIN JA: Antihypertensive agents, glomerular hemodynamics and glomerular injury, in *Calcium Antagonists and the Kidney*, edited by EPSTEIN M, LOUTZENHISER R, Philadelphia, Hanley & Belfus, 1990, pp 155–176
56. DWORKIN LD, BENSTEIN JA, PARKER M, TOLBERT E, FEINER HD: Calcium antagonists and converting enzyme inhibitors reduce renal injury by different mechanisms. *Kidney Int* 43:808–814, 1993
57. DWORKIN LD, TOLBERT E, RECHT PA, HERSCH JC, FEINER LEVIN RI: Effects of amlodipine on glomerular filtration, growth, and injury in experimental hypertension. *Hypertension* 27:245–250, 1996
58. KEANE WJ, RAIJ L: Relationship among altered glomerular barrier permselectivity, angiotensin II and mesangial uptake of macromolecules. *Lab Invest* 52:599–604, 1985
59. SWEENEY C, RAIJ L: Interactions of the endothelium and mesagium in glomerular injury: potential role of calcium antagonists, in *Calcium Antagonists in Clinical Medicine*, edited by EPSTEIN M, Philadelphia, Hanley & Belfus, 1992, pp 413–426
60. SHULTZ P, RAIJ L: Inhibition of human mesangial cell proliferation by calcium blockers. *Hypertension* (suppl):76–80, 1990
61. SHULTZ P, RAIJ L: Effect of amlodipine on mesangial cell proliferation and protein synthesis. *Am J Hypertens* 5:912–914, 1992
62. TOLINS J, MELEMED A, SULCINER A, GUSTAFSON K, VERCELLOTTI G: Calcium channel blockade inhibits platelet activating factor production by human umbilical vein endothelial cells. *Lipids* 26:1218–1222, 1991
63. BURKE TJ, SINGH H, SCHRIER RW: Calcium handling by renal tubules during oxygen deprivation injury to the kidney prior to reoxygenation. *J Cardiovasc Drugs Ther* 4:1319–1324, 1990
64. SCHRIER RW, BURKE TJ: Calcium channel-blockers in experimental and human acute renal failure. *Adv Nephrol* 17:287–300, 1988
65. SCHWERTSCHLAG U, SCHRIER RW, WILSON P: Beneficial effects of

calcium channel blockers and calmodulin binding drugs on in vitro renal cell anoxia. *J Pharmacol Exp Ther* 238:119–124, 1986
66. Harris DCH, Hammond WS, Burke TJ, Schrier RW: Verapamil protects against progression of experimental chronic renal failure. *Kidney Int* 31:41–46, 1987
67. Goligorsky MS, Chaimovits C, Rapoport J, Goldstein J, Kol R: Calcium metabolism in uremic nephrocalcinosis: Preventive effects of verapamil. *Kidney Int* 27:774–779, 1985
68. Münter K, Hergenröder S, Jochims K, Kirchengast M: Individual and combined effects of verapamil or trandolapril on glomeruloprotection in the stroke prone rat. *J Am Soc Nephrol* 7:681–686, 1996
69. Arai T, Kobayashi S, Nakajima T, Hishida A: Reduction of proteinuria by a calcium antagonist, manidipine, in rats with passive Heymann nephritis. *Int Cong Series Excerpta Medica* Diuretic IV: 647–650, 1993
70. Jackson B, Johnston CI: The contribution of systemic hypertension to progression of chronic renal failure in the rat remnant kidney: effect of treatment with an angiotensin converting enzyme inhibitor or a calcium inhibitor. *J Hypertens* 6:495–501, 1988
71. Brunner FP, Thiel G, Hermle M, Bock HA, Mihatsch MJ: Long-term enalapril and verapamil in rats with reduced renal mass. *Kidney Int* 36:969–977, 1989
72. Tolins JP, Raij L: Comparison of converting enzyme inhibitor and calcium channel blocker in hypertensive glomerular injury. *Hypertension* 16:452–461, 1990
73. 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
74. Griffin K, Picken M, Bidani A: Radiotelemetric BP monitoring, antihypertensives and glomeruloprotection in remnant kidney model. *Kidney Int* 46:1010–1018, 1994
75. Bidani AK, Griffin KA, Picken MM: Preservation of renal autoregulation and not blockade of renal hypertrophy mediates the glomeruloprotection provided by a low protein diet in the remnant model (*abstract*). *J Am Soc Nephrol* 7:1577, 1996
76. Picken MM, Griffin K, Bakris G, Bidani AK: Differences in the antihypertensive and glomeruloprotective efficacies of calcium channel blockers in the remnant kidney model (*abstract*). *J Am Soc Nephrol* 7:1586–1587, 1996
77. Bidani A, Griffin KA: Calcium channel blockers and renal protection: is there an optimal dose? *J Clin Lab Med* 125:553–555, 1995
78. Zucchelli P, Zuccalà A, Borghi M, Fusaroli M, Sasdelli C, Sanna G, Gaggi R: Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int* 42:452–458, 1992
79. 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
80. Rossing P, Tarnow L, Boelskifter S, Jensen BR, Nielsen FS, Parving H-H: Differences between nisoldipine and lisinopril on glomerular filtration rates and albuminuria in hypertensive IDDM patients with diabetic nephropathy during the first year of treatment. *Diabetes* 46:481–487, 1997
81. Campbell DJ, on behalf of the Melbourne Diabetic Nephropathy Study Group: ACE inhibitors versus calcium channel blockade (*abstract 22*). *Proc 5th Int Symp Hypertens Assoc Diabetes Mellitus*, Coolum, Australia, 1997
82. Maki DD, Ma JZ, Louis TA, Kasiske BL: Long-term effects of antihypertensive agents on proteinuria and renal function. *Arch Intern Med* 155:1073–1080, 1995
83. Lash JP, Bakris GL: Effects of ACE inhibitors and calcium antagonists alone or combined on progression of diabetic nephropathy. *Nephrol Dial Transplant* 10(suppl 9):56–62, 1995
84. Solomon R, Dubey A: Diltiazem enhances potassium disposal in subjects with end-stage renal disease. *Am J Kidney Dis* 14:420–426, 1992
85. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW: The effects of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 338:645–652, 1998
86. Koshkinen P, Mantarri M, Manninen V, Huttunen JK, Heinonen OP, Frick M: Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care* 15:820–825, 1992
87. Kuusisto J, Mykkanen L, Pyorala K, Laasko M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994
88. Davis BR, Cutler JA, Gordon DJ, et al: Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens* 9:342–360, 1996
89. Van Zwieten PA, Hansson L, Epstein M: Slowly acting calcium antagonists and their merits. *Blood Press* 6:78–80, 1997
90. Epstein M: Safety of calcium antagonists as antihypertensive agents: An update, in *Calcium Antagonists in Clinical Medicine* (2nd ed), edited by Epstein M, Philadelphia, Hanley & Belfus, 1998, pp 553–571
91. Tatti P, Pahor M, Byngton R, Di Mauro P, Guarisco R, Strollo F: Outcome results of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 21:597–603, 1998
92. Tatti P, Guarisco R, Di Mauro P, Strollo F: Reduced risk of major cardiac events with the association of two antihypertensive drugs in a non-insulin dependent diabetic population (*abstract*). Annual Meeting of the American Diabetes Association, 1996
93. Nesto RW, Zarich B: Acute myocardial infarction in diabetes mellitus. Lessons learned from ACE inhibitors. *Circulation* 97:12–15, 1998
94. Bakris GL, Smith A: Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 125:201–204, 1996
95. Heeg JE, de Jong 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
96. Smith AC, Toto R, Bakris GL: Differences in glomerular membrane permeability responses to a non-dihydropyridine (NDHP) and dihydropyridine (DHP) calcium channel antagonist (CCA) in patients with diabetic nephropathy: A randomized single-blind, two-year study (*abstract*). *J Am Soc Nephrol* 8:A562, 1997
97. Blaustein MP: Sodium ions, calcium ions, blood pressure regulation and hypertension: a reassessment and a hypothesis. *Am J Physiol* 232:C165–C173, 1997
98. Cappuccio FP, Markandu ND, MacGregor GA: Calcium antagonists and sodium balance: Effect of changes in sodium intake and of the addition of a thiazide diuretic on the blood pressure lowering effect of nifedipine. *J Cardiovasc Pharmacol* 10:S57–S60, 1987
99. Nicholson JP, Resnick LM, Laragh JH: The antihypertensive effect of verapamil at extremes of dietary sodium intake. *Ann Intern Med* 107:329–334, 1987
100. Kleinbloesem CH, van Brummelen P, Danlöf M, Faber H, Urquhalt J, Breimer DD: Rate of increase in the plasma concentration of nifedipine as a major determinant of its hemodynamic effects in humans. *Clin Pharmacol Ther* 41:26–30, 1987
101. Epstein M: The calcium antagonist controversy: The emerging importance of drug formulation as a determinant of risk. *Am J Cardiol* 79(suppl 10A):9–19, 1997
102. Ruggenenti P, Perico N, Mosconi L, Gaspare F, Benigni A, Amuchastigui CS, Bruzzi I, Remuzzi G: Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hypoperfusion. *Kidney Int* 43:706–711, 1993
103. Weir MR, Klassen DK, Shen SY, et al: Acute effects of intravenous cyclosporine on blood pressure, renal hemodynamics, and urine prostaglandin production of healthy humans. *Transplantation* 49:41–47, 1990
104. Dawidson I, Rooth P, Fry WR, et al: Prevention of acute cyclosporine-induced renal blood flow inhibition and improved immunosuppression with verapamil. *Transplantation* 48:575–580, 1989