

PERSPECTIVES IN RENAL MEDICINE

Antihypertensive treatment of patients with proteinuric renal diseases: Risks or benefits of calcium channel blockers?

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Antihypertensive treatment of patients with proteinuric renal diseases: Risks or benefits of calcium channel blockers? In patients with proteinuric renal diseases the rate of progression of renal insufficiency is determined by the level of blood pressure and proteinuria. It has been demonstrated that strict blood pressure control with angiotensin converting enzyme (ACE)-inhibitors or beta-blockers, aimed at reaching values below 130/80 mm Hg, attenuates the deterioration of renal function. In general, the beneficial effects of these drugs are reflected in a parallel lowering of proteinuria. Calcium channel blockers are effective antihypertensive drugs, however, their safety in patients with proteinuric renal diseases and renal insufficiency may be questioned because of reported untoward effects on urinary protein excretion. The present review discusses the potential benefits and risks of calcium channel blockers (CCBs) in the treatment of patients with renal diseases. To this end we have evaluated the effects of these drugs in animal models of progressive renal injury. In these animal models adverse effects of CCBs have been reported which are attributed to an impairment of autoregulation. In patients with proteinuria, the dihydropyridine CCBs do not lower proteinuria despite a reduction of blood pressure. Studies on the effects on the course of renal function are limited, however, the available data do suggest that this class of CCBs may be less advantageous than other antihypertensive drugs, thus arguing against the use of these agents as first-line drugs in patients with proteinuric renal diseases. Information on the effects of the non-dihydropyridine CCBs is limited to a small number of studies in patients with diabetic renal disease. Although the data suggest that these classes of CCBs might be more beneficial, more studies are needed, particularly in patients with non-diabetic renal diseases, before founded conclusions can be reached.

In patients with proteinuric renal diseases and renal insufficiency, renal function almost invariably worsens, a process that is independent of the activity of the original renal disease [1]. More than a decade ago Brenner, Meyer and Hostetter proposed the hypothesis that glomerular hypertension resulting in glomerulosclerosis is the final common pathway in this progression of renal diseases [2]. Their hypothesis was mainly based on experimental work in the rat remnant kidney model. Lowering of systemic, and in particular glomerular, pressure by ACE inhibitors or low protein diets ameliorated glomerulosclerosis and retarded renal insufficiency. According to this theory proteinuria is a mere

reflection of glomerular pressure or glomerular injury. More recently, the focus has shifted to the role of tubulointerstitial injury in progressive renal diseases [3]. Proteinuria is no longer considered just an innocent bystander, but rather is held responsible for tubular cell injury and ensuing interstitial damage [4–7].

In humans, both hypertension and proteinuria determine the rate of progression of renal insufficiency [8–10]. This was recently confirmed in the largest prospective study to date, that is, the Modification of Diet in Renal Disease (MDRD) study [11, 12]. The rate of decrease of glomerular filtration rate was highest in patients with proteinuria. Furthermore, in this particular group of patients antihypertensive treatment was most effective in inhibiting the loss of GFR. In the MDRD study, the achieved systolic blood pressure rather than the diastolic blood pressure correlated best with the extent of renal protection. Of note, renal function was best preserved in patients who achieved very low blood pressures: lowering of blood pressure from normal levels of 135/85 mm Hg to “below normal” levels of 125/75 mm Hg was associated with a preservation of renal function. As a consequence, patients with proteinuric renal diseases will need effective antihypertensive treatment.

Calcium channel blockers (CCBs) are effective antihypertensive drugs also in patients with renal failure, who are generally considered to be relatively resistant to antihypertensive treatment [13]. On top of their antihypertensive efficacy, calcium channel blockers do have other advantages: unlike other vasodilating drugs they do not cause renal sodium and water retention [14], and in contrast to ACE inhibitors they do not cause hyperkalemia. However, at present it is unclear whether patients with renal diseases will actually benefit from treatment with calcium channel blockers. Doubt has been raised because the effects of calcium channel blockers in animal models of progressive renal failure have been controversial [15]. Thus far, most studies in humans have concentrated on the effects of calcium channel blockers on proteinuria, a surrogate marker of present and future renal injury. In some of these studies untoward effects on proteinuria have been reported [16–19], which has increased the uncertainty about the use of this class of drugs.

It is our aim to provide an overview of the effects of the different classes of CCBs in animal models of progressive renal disease, and to discuss the relevance of these data for the human situation. Furthermore, we have evaluated the effects of CCBs on proteinuria and renal function in humans. Based on data from the literature and our own experience, our view on the potential role

Key words: proteinuria, blood pressure, renal failure, dihydropyridine calcium channel blockers, antihypertensive drugs.

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of CCB in the treatment of patients with renal diseases and proteinuria is presented.

CALCIUM CHANNEL BLOCKERS: CLASSES AND MECHANISM OF ACTION

Calcium is an important intracellular messenger [20]. Influx of calcium into cells is partly mediated by so-called voltage operated calcium channels, which are classified according to their activation characteristics in L, T, N, and P type channels [21]. The N, P, and L channels are high-voltage channels. Both the N-type and P-type channels are largely restricted to neurons and play a role in neurotransmitter release and long-term depression of Purkinje cells, respectively. The N and P channels are specifically inhibited by ω -conotoxin and ω -agatoxin-IVA, respectively. Classical calcium channel blockers do not bind to these channels. The L-type channels are expressed in various tissues such as skeletal muscle, heart, smooth muscle, endocrine cells and some neurons [22]. L-type channels are involved in the cardiac action potential and the contractility of cardiac and vascular smooth muscle. Studies of these channels have been facilitated by the development of the various classes of calcium channel blockers that specifically bind to these calcium channels. The T-type channel is a low-voltage channel that has no specific blocker, which has hampered the study of this channel [23]. The T-type channel has been implicated in repetitive firing and pacemaker activity in heart and neurons. Recently, it was suggested that the T-type channel may be involved in angiotensin II-mediated aldosterone release [24, 25]. To date, three classes of calcium channel blockers have been widely used in clinical practice: the dihydropyridines (DHP; such as nifedipine, felodipine, amlodipine, nitrendipine, nicardipine, isradipine), the phenylalkylamines (verapamil), and the benzothiazepines (such as diltiazem). All these CCBs interact with the L-type calcium channel, and different binding sites for the various classes of CCBs have been identified [21]. Recently, a new class of CCB has been introduced. The prototype mibefradil, a tetraline derivative, blocks not only L- but also T-type calcium channels [26]. However, the clinical relevance of this T-channel blocking property is as yet unclear. All classes of CCBs have in common that they block voltage-operated calcium channels. Calcium channel blockers reduce blood pressure primarily by vasodilation, as a result of the blockade of calcium channels in vascular smooth muscle cells. However, the various CCBs clearly differ in their tissue selectivity, probably because of the differences in binding sites [21]. The DHP act primarily on vascular smooth muscle cells, whereas verapamil and diltiazem also influence the cardiac action potential. Also, the various CCBs differ in their influence on myocardial cells, and thus in negative inotropic effects on the heart. All these differences determine the clinical use of CCBs, such as in arrhythmia or hypertension.

CALCIUM CHANNEL BLOCKERS: ANIMAL MODELS OF RENAL INJURY

Tables 1 and 2 summarize the studies that have evaluated the particular effects of calcium channel blockers in animal models of progressive renal disease [27–60]. It is evident that these studies are quite heterogeneous because of the use of 14 different animal models, both diabetic and non-diabetic, the type and dose of the calcium channel blocker, the interval between the induction of renal injury and the start of treatment, and the duration of

follow-up have been examined. To assess the protective potential of the CCBs, most studies have relied on proteinuria and glomerular histological abnormalities (mostly glomerulosclerosis). Less frequently, loss of renal function and survival have been used. The available data suggest that effects on proteinuria and glomerulosclerosis are closely linked; in all studies in which a reduction of proteinuria was observed during treatment with a CCB, this effect was paralleled by a decrease of glomerulosclerosis, whereas in studies in which proteinuria was not influenced favorably, the severity of glomerulosclerosis did not differ between treatment groups and control groups.

Summarized in Table 1 are 18 studies reporting a positive and protective (that is, a decrease of proteinuria or glomerulosclerosis) effect of the CCBs, whereas the other 15 studies that report either no benefit or even harmful effects are summarized in Table 2. In 17 studies (including 10 studies that could not demonstrate a benefit of the CCBs) the effects of ACE inhibitors were also studied, and in all but two studies in which ACE inhibitors were used, they offered protection [27–29, 40, 41, 43, 46, 48–50, 52, 54, 56–60].

At first sight, the results of the various studies seem rather conflicting. How can we reconcile these animal data?

Role of systemic blood pressure

Mechanistically speaking, one important aspect to consider are the effects of the calcium channel blockers on systemic and glomerular pressures, probably the best studied factors proven to be involved in progressive renal injury. Figure 1 illustrates the decrease in proteinuria and the decrease in systemic blood pressure reported by the various investigators. Clearly, there is no simple relationship between the antiproteinuric effects and the blood pressure lowering effects. Two explanations can be offered for the absence of a relationship. At one hand, systemic blood pressure might not be a good reflection of intraglomerular pressure, since the relationship between systemic blood pressure and glomerular pressure is dependent on the resistances of the afferent and efferent arterioles (*vide infra*). On the other hand, differences in methods may be involved. In most animal studies the number of blood pressure measurements is limited and performed by techniques that by themselves can influence blood pressure. Some investigators measure blood pressure by the tail cuff method, resulting in increased blood pressures as a result of the needed restraint, whereas others measure blood pressure intra-arterially in anesthetized animals, resulting in a falsely low blood pressure. The impact of blood pressure measurements has been elegantly studied by Bidani et al [61, 62]. These investigators measured blood pressure almost continuously (every 10 min) with a telemetric device. They observed that blood pressures were quite variable, and labile, especially in the rat remnant kidney model. The continuously measured blood pressures differed from the blood pressures measured by the other techniques. When looking at renal injury, it became evident that glomerulosclerosis correlated highly significantly with the average systolic blood pressure and with the frequency of systolic blood pressures above 140 mm Hg. Based on these data, one explanation for the observed failure of CCBs to protect against renal injury might be that these drugs fail to consistently lower blood pressure over a 24 hour period [53]. However, this explanation probably does not hold for all studies. One example is the study of Remuzzi et al, who compared the calcium channel blocker nitrendipine and the

Table 1. Effects of calcium channel blockers (CCBs) in animal models of progressive glomerulosclerosis: Overview of studies demonstrating a beneficial effect of the CCBs on proteinuria and/or glomerulosclerosis

| Ref. no. | Exper. model | Start of treatment ^a | Duration of therapy | Drugs | SBP end of the study | MAP end of the study | Proteinuria end of the study ^b | Histology | | |
|----------|------------------------|---------------------------------|---------------------|--------------------------------|-----------------------------------|-----------------------------------|--|----------------|----------------|---|
| | | | | | | | | GS | TI | Additional remarks |
| [27] | UniNx-Rats | 0 | 6–8 weeks | Nifedip. | 122 ± 7 ^c | 106 ± 2 ^c | 37 ± 8 ^c | – ^c | NA | |
| [28] | DOCA-salt UniNx-SHR | 0 | 36 weeks | vs Untr. Nifedip. | 192 ± 6 ~175 ^c | 139 ± 4 126 ± 3 ^c | 77 ± 12 37 ± 5 ^c | – ^c | NA | |
| [29] | RK-MW Rats | 0 | 4–8 weeks | vs Untr. Nifedip. | ~220 ~130 ^c | 172 ± 4 136 ± 5 ^c | 70 ± 10 18 ± 3 ^c | – ^c | NA | Vg – |
| [30] | RK Rats | 0 | max 20 weeks | vs Untr. Nisoldip. | 237 ± 20 147 ± 20 ^c | NA NA | 68 ± 60 ^c 109 ± 45 ^c | – | = | Survival + ^c |
| [31] | RK-Fischer Rats | 1 day | 12 weeks | Manidip. | 0.0004% 141 ± 9 | NA | ~90 ^c | – ^c | – ^c | |
| | | | | 0.002% 128 ± 6 ^c | NA | ~55 ^c | – ^c | – ^c | | |
| | | | | 0.01% 129 ± 8 ^c | NA | ~85 ^c | – ^c | – ^c | | |
| | | | | 0.05% 132 ± 6 ^c | NA | ~175 ^c | + ^c | + ^c | | |
| [32] | RK-SHR High salt | 0 | 10 weeks | vs Untr. Amlodip. | 287 ± 5 237 ± 23 ^c | NA NA | ~361 ~130 ^c | – ^c | – ^c | Arter. scler. – ^c |
| [33] | RK-SD Rats | 2 weeks | 12 weeks | vs Untr. Verapamil | NA NA | ~131 ~142 | 294 ± 67 354 ± 42 | – ^c | = | Calcium content – ^c Survival + ^c |
| [34] | RK-SD Rats | 1 week | 4–6 weeks | vs Untr. Anipamil | NA NA | 144 ± 36 ^c 192 ± 35 | 95 ± 22 126 ± 35 | NA | NA | Calcium content – ^c Survival + ^c |
| [35] | SHR | at age of 15 months | 6 months | vs Untr. Felodip. | NA NA | 146 ± 4 ^c 184 ± 10 | 15 ± 2 ^c 34 ± 2 | – ^c | NA | |
| [36] | SHR | at age of 12 weeks | 8 weeks | vs Untr. Nicardip. | 260 ± 5 205 ± 5 ^c | NA NA | 4.7 ± 0.2 ^{c,c} 6.0 ± 0.2 ^c | NA | NA | Glom./vascular alterations ^c |
| [37] | SHR | at age of 7 weeks | 20 weeks | vs Untr. Efonidip. | ~210 ^c ~240 | NA NA | ~60 ^c ~400 | – ^c | – ^c | Arter.scler. – ^c |
| [38] | SD-rats Heymann | 7 days before induction | 3 weeks | Manidip. | – low 111 ± 5 | NA | 59 ± 13 ^d | = | NA | |
| | | | | – high 98 ± 12 | NA | 47 ± 9 ^{de} | = | NA | | |
| | | | | vs Untr. 105 ± 6 | NA | 62 ± 8 ^d | | | | |
| [39] | SD-rats PAN + PS | during induction | 3 months | Benidip. | – low ~112 | NA | 3.5 ± 0.9 ^c | = | = | |
| | | | | – high ~106 ^c | NA | 2.1 ± 0.4 ^c | – | – | | |
| | | | | vs Untr. ~118 | NA | 5.3 ± 1.6 ^c | | | | |
| [40] | UniNx-Diab | 0 | 1 year | TA-3090 | NA | 116 ± 5 | ~2 ^c | Foc. – | + | Vg – ^c |
| [41] | Dogs | | | vs Untr. | NA | 126 ± 7 | ~32 | Glob. + | | |
| [42] | Diab-Wistar Rats | 1 week | 20 weeks | Diltiazem | ~125 ^c | NA | ~2 ^c | NA | NA | |
| [43] | UniNx-Diab WKY Rats | 1 week | 12 weeks | vs Untr. Benidip. | ~145 ~135 ^c | NA NA | ~44 30 ± 4 ^c | NA | NA | |
| [44] | Subtot.Nx SD-Rats | 48 hours | 8 weeks | vs Untr. Nifedip. | ~160 98 ± 23 ^c | NA NA | 59 ± 7 NA | – ^c | = | Vascular damage– ^c , mesangial proliferation– ^c |
| [45] | SHR | at age of 6 months | 3 months | vs Untr. Nifedip. | 119 ± 9 144 ± 21 ^c | NA NA | NA NA | – ^c | – ^c | Tubular atrophy – ^c , Vg + ^c |

Abbreviations are: GS, glomerulosclerosis; TI, tubulointerstitial injury; Foc., focal sclerosis; Glob., global sclerosis; –, decrease; =, unchanged; +, increased compared to controls; NA, not available; ~, approximately; UniNx, uninephrectomy; DOCA-salt, deoxycorticosterone acetate with high salt; SHR, spontaneously hypertensive rats; RK-MW, remnant kidney-Munich Wistar; SD, Sprague Dawley; PAN, puromycin aminonucleoside; PS, protamine sulfate; Diab, Diabetic; WKY, Wistar Kyoto; Subtot.Nx, subtotaly nephrectomized; Vg, glomerular volume; Arter. scler., arterio(lo)sclerosis; Glom., glomerular. All drug-names abbreviated as “dip.” are dihydropyridine CCBs and have to end as “-dipine.”

^a Start of treatment represents the interval between the induction of injury and the start of therapy. For SHR rats time of birth is considered as the time of induction of injury.

^b Proteinuria is expressed as mg/24 h, mg/24 h/100 mg bodyweight^c, or mg/mg creatinine^d

^c $P < 0.05$ vs Untr. (=untreated); means ± SEM or SD are given

Systolic blood pressure (SBP) and mean arterial pressure (MAP) in mm Hg.

ACE inhibitor lisinopril. Blood pressure was measured four to five times daily. Despite equal lowering of blood pressure, nitrendipine was clearly less effective than lisinopril [56].

Role of glomerular capillary pressure and renal autoregulation

The work of Bidani and coworkers points to another possible explanation for the unexpected ineffective or even detrimental

effects of calcium channel blockers. These investigators have shown that in their models of renal injury an enhanced glomerular transmission of the systemic hypertension plays a major role in the induction and progression of renal injury. It is known that the transmission of the systemic blood pressure to the glomerulus is dependent on the resistance of the afferent arteriole. Under normal circumstances glomerular pressure does not increase in

Table 2. Effects of calcium channel blockers (CCBs) in animal models of progressive glomerulosclerosis: Overview of studies demonstrating no beneficial effect of the CCBs on proteinuria and/or glomerulosclerosis

| Ref. no. | Exper. model | Start of treatment ^a | Duration of therapy | Drugs | SBP end of the study | MAP end of the study | Proteinuria end of the study ^b | Histology | | |
|----------|--------------------------------|---------------------------------|----------------------|--|--|--|---|---------------------|-------------|--|
| | | | | | | | | GS | TI | Additional remarks |
| [46] | RK-Wistar Rats | 5 weeks | 15 weeks | Verapamil vs Untr. | 158 175 | NA NA | 58.2 ^{cd} 17.2 ^c | + ^d | NA | Survival - ^d |
| [47] | RK-Wistar Rats | 5 weeks | 16 weeks | Verapamil - low - high vs Untr. | 162 140 ^d 185 | 156 ± 7 124 ± 3 180 ± 8 | 20.7 ^c 29.4 ^c 13.8 ^c | = = = | = + = | Kidn.weight + ^d Survival - ^d Vg - ^d |
| [48] | RK-postsalt SD-Rats | 4 days | 2 weeks | TA-3090 vs Untr. | ~160 ^d ~230 | 158 ± 7 177 ± 9 | ~200 ~200 | - ^d | NA | Vg - ^d |
| | RK-postsalt SD-Rats | 4 days | 4 weeks | TA-3090 vs Untr. | ~140 ^d ~215 | NA NA | 333 ± 64 ^d 180 ± 23 | = | NA | Cholesterol + ^d , Survival + |
| [49] | Adriamycine SD-Rats | 10 weeks 24 weeks | 28 weeks 14 weeks | Diltiazem - wk 10 - wk 24 vs Untr. | NA NA NA | 122 ± 6 ^d 133 ± 5 ^d 154 ± 7 | max 450 ^d ~230 ~190 | = - ^d | NA NA | Mesangial expansion - ^d |
| [50] | Subtot.Nx SD-Rats | 1 week | 5 weeks | Felodip. vs Untr. | ~130 ^d 176 ± 7 | 104 ± 6 ^d 139 ± 5 | 221 ± 35 ^d 84 ± 22 | = | NA | |
| [51] | 2K-1C Rats | 6 weeks | 6 weeks | Nitrend. vs Untr. | 183 ± 5 192 ± 5 | NA NA | 163 ± 55 ^d 19 ± 9 | + ^d | = | Vg ⁺ , Tubular atrophy & dilation + |
| [52] | 2K-1C Rats | 8 weeks | 5 weeks | RO405967 vs Untr. | 160 ± 2 ^d 216 ± 13 | NA NA | 139 ± 44 83 ± 35 | = | = | Vascular lesions -, Vg + |
| [53] | UniNx-Rats DOCA-salt UniNX-SHR | 0 | 8 weeks 5 months | Amlodip. vs Untr. Amlodip. vs Untr. | ~145 ^d ~175 ~150 ^d ~235 | 112 ± 5 ^d 146 ± 6 136 ± 2 ^d 170 ± 8 | ~100 ~105 ~80 ^d ~55 | = | NA | Vg = |
| [54] | RK-Rats | 1 week | 7 weeks | Nifedip. vs Untr. | ~130 ~190 | NA NA | ~68 ~65 | = | NA | Vg = |
| [55] | UniNx-SHR | 0 | 12 weeks | Manidip. - low - high vs Untr. | 213 ^d 160 ^d 219 | NA NA NA | 55 ± 4 59 ± 6 54 ± 3 | = = = | = | Mesangial proliferation - ^d |
| [56] | MWF/Ztm Rats | At age of 10 weeks | 6 months | Nitrend. vs Untr. | 140 ± 11 ^d 170 ± 8 | NA NA | 271 ± 36 ^d 321 ± 54 | +; NS | = | Vg = |
| [57] | Diabetic SHR Rats | 0 | 16 weeks | Lacidip. vs Untr. | 131 ± 5 ^d 172 ± 10 | NA NA | 18 ± 1 29 ± 1 | NA | NA | |
| [58] | Diabetic SD-Rats | 0 | 4-6 weeks | Lacidip. vs Untr. | 117 ± 5 ^d 142 ± 5 | NA NA | 16 ± 6 29 ± 12 | NA | NA | |
| | | 0 | 12 months | Lacidip. vs Untr. | 122 ± 6 ^d 155 ± 9 | NA NA | 338 ± 66 355 ± 98 | = | = | |
| [59] | UniNx-Diab. MW-Rats | 0 | 8 weeks | Nifedip. vs Untr. | NA NA | 106 ± 2 ^d 118 ± 5 | NA NA | NA | NA | |
| | | 0 | 8 months | Nifedip. vs Untr. | 118 ± 4 ^d 145 ± 5 | NA NA | 136 ± 26 113 ± 18 | = | NA | Vg = |
| [60] | UniNx-Diab. SD-Rats | 1 month | 2 months | Verapamil vs Untr. | 114 ± 2 131 ± 2 | NA NA | 58 ± 10 71 ± 18 | NA | NA | |

Abbreviations are: GS, Glomerulosclerosis; TI, Tubulo-interstitial injury; -, decrease; =, unchanged; +, increased compared to controls; NA, Not available; ~, approximately; NS, not significant; RK, remnant kidney; SD-rats, Sprague-Dawley; Subtot.Nx, subtotally nephrectomized; 2K-1C, two kidney-one clip model; UniNx, Uninephrectomized; DOCA-salt, Deoxycorticosterone acetate with high salt; SHR, Spontaneously hypertensive rats; MWF/Ztm-rats, a model of spontaneous glomerular injury; MW, Munich-Wistar rats; Vg, Glomerular volume. All drug-names abbreviated as "-dipine".

^a Start of treatment represents the interval between the induction of injury and the start of therapy; for SHR rats time of birth is considered as the time of induction of injury.

^b Proteinuria is expressed as mg/24 hr, ^cor mg/mg creatinine

^d $P < 0.05$ vs. Untr. (=untreated); means ± SEM or SD

Systolic blood pressure (SBP) and mean arterial pressure (MAP) are in mm Hg.

parallel with an increase of systemic blood pressure. Indeed, such an increase of glomerular pressure is prevented by the so-called autoregulatory response, mediated by afferent vasoconstriction. In the remnant kidney model renal autoregulation is attenuated, and defective autoregulation correlates with injury. A low protein diet that restores autoregulation attenuates renal injury [63].

At this point it is important to realize that the afferent arteriole is the renal vessel most responsive to CCBs. Studies in the hydronephrotic rat kidney, a model that allows direct visualization of the glomerular vessels, have demonstrated that CCBs preferentially cause dilation of the afferent arteriole [64, 65]. Indeed, CCBs are the only antihypertensive drugs that impair renal

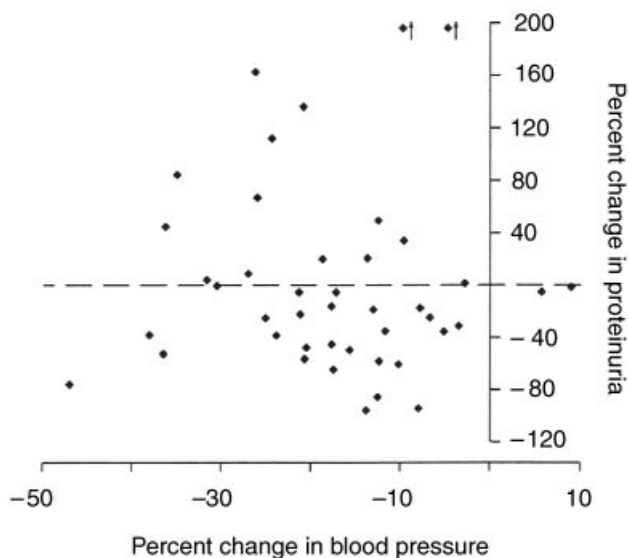


Fig. 1. Relationship between the change in blood pressure and the change of proteinuria during treatment with calcium channel blockers in animal models of glomerulosclerosis. Data are derived from the studies in Tables 1 and 2.

autoregulation [66]. Both verapamil (a fenylalkylamine) and the dihydropyridines nifedipine and nicardipine attenuate the autoregulatory response in dogs [67, 68]. Such an impairment of autoregulation has been confirmed in rats for nifedipine and verapamil [69, 70]. Griffin, Picken and Bidani have followed up on these ideas. In the rat remnant kidney model, they demonstrated that nifedipine further impairs the already somewhat disturbed autoregulatory response [54]. In their model they have consistently found a perfect correlation between systolic blood pressure and the degree of glomerulosclerosis (Fig. 2). In fact, the data points of untreated rats as well as of rats treated with either an ACE inhibitor or triple therapy could all be fitted to the same curve describing this relationship. For rats treated with nifedipine a correlation was also found between blood pressure and glomerulosclerosis; however, the curve describing this relationship was shifted to the left, indicating that at a given level of blood pressure glomerular injury is higher during treatment with the CCB nifedipine (Fig. 2). Recent studies, as yet only published in abstract form, confirm the harmful effects of autoregulatory disturbances. It was demonstrated that the relationship between glomerulosclerosis and blood pressure is also shifted to the left by felodipine and by verapamil [71]. Furthermore, verapamil attenuated the protective efficacy of a low protein diet, again suggesting a role for interference with autoregulation by this drug [72]. One of the abovementioned abstracts suggested that diltiazem might not impair autoregulation [71]. However, a closer look at the data of the latter study reveals that diltiazem had no effect at all, not even on blood pressure, suggesting that the dose used was too low. Other animal data indicate that diltiazem will also cause an increased transmission of the systemic blood pressure to the glomerulus. Diltiazem, like the other classes of CCBs, preferentially causes afferent arteriolar vasodilation [73, 74]. In diabetic beagle dogs Brown et al observed a definite trend towards impairment of autoregulation by the benzothiazepine TA-3090 [40, 41].

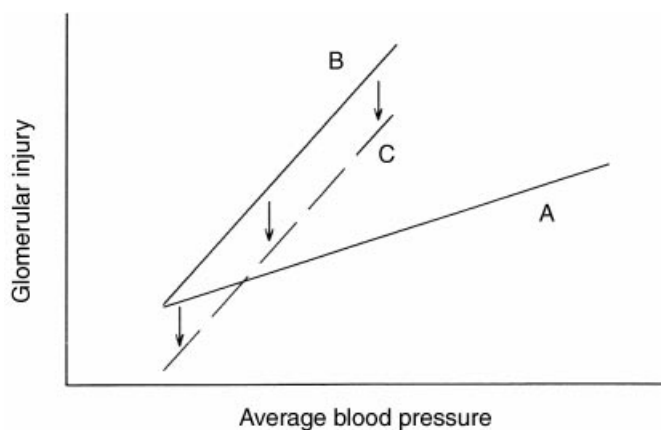


Fig. 2. Correlation of glomerular injury with overall averaged systolic blood pressure in the rat remnant kidney model. Figure adapted from Griffin et al [54]. Curve A describes the correlation for rats either untreated or treated with the ACE inhibitor enalapril. Curve B describes the relationship for nifedipine treated rats. Clearly, the slope is shifted to the left, indicating an increased susceptibility to glomerular injury in the nifedipine group. Curve C is a hypothetical curve, based on the assumption that the calcium channel blockers might be protective via other mechanisms than influencing blood pressure.

In case of an impairment of the autoregulatory response one would expect that CCBs can only be protective if blood pressure is lowered to such an extent that the impairment of autoregulation is compensated for. Indeed, in a number of the studies in Table 1, all showing renal protection by the CCBs, a major reduction in blood pressure was achieved of more than 25% [27–30, 45]. When the blood pressure is very high, at a level above the autoregulatory range, one would expect that more modest reductions in blood pressure also offers protection. This assumption is supported by a few studies in which control blood pressures were very high and reductions of a lesser degree (10 to 25%) were accompanied by antiproteinuric effects and decreased morphologic damage [32, 35–37].

The relationship between the degree of blood pressure reduction and glomerular injury is also demonstrated when analyzing consecutive studies performed by the same investigators in the same model. Wenzel and coworkers have used the two kidney one clip model of hypertension [51, 52, 75]. Harmful effects (such as increased proteinuria and glomerulosclerosis) were observed during treatment with nitrendipine, which lowered blood pressure by only 5% [51]. Mibefradil, used in the same renal model, lowered blood pressure by 26% and did not lower proteinuria nor attenuate glomerulosclerosis [52]. When nitrendipine was combined with enalapril the renal effects compared favorably with enalapril alone: proteinuria and blood pressure were fully normalized, and complete renal protection was obtained [75]. Brunner et al studied the effects of different dosages of verapamil in the rat remnant kidney model, and found that an intermediate dose resulted in minor effects on blood pressure, more proteinuria and more glomerulosclerosis. The higher dose, which lowered blood pressure more effectively, did not significantly increase proteinuria nor glomerulosclerosis [46, 47]. Dworkin used both nifedipine and amlodipine in the uninephrectomized DOCA-salt rat model and in the uninephrectomized spontaneously hypertensive rat (SHR) rat [27, 28, 53]. The protective renal effects noticed

during nifedipine were not seen during amlodipine. When the numbers presented in these studies are compared, nifedipine lowered blood pressure more effectively than amlodipine in both models [27, 28, 53]. Altogether, these observations might provide an explanation for the controversial results of the studies presented in Tables 1 and 2.

As mentioned above, defective autoregulation will result in an increased transmission of the systemic blood pressure to the glomerulus. We assume that the effects of CCBs on renal injury are related to the changes in glomerular pressure. Unfortunately, measurements of intraglomerular pressure have been performed in only seven studies [27–29, 40, 53, 56, 59]. In six studies intraglomerular pressure was unaffected by the calcium channel blocker despite blood pressure reduction, results that are compatible with the abovementioned adverse effects on autoregulation [27, 29, 40, 53, 56, 59]. Only one study observed a decrease of glomerular capillary pressure during treatment with a CCB [28]. In this latter study, nifedipine was used in the uninephrectomized SHR rat, which protected the animal against the development of glomerulosclerosis.

Admittedly, in three of the abovementioned studies the CCBs lowered proteinuria and attenuated glomerulosclerosis, despite the unchanged glomerular capillary pressure [27, 29, 40]. The latter studies suggest that progression of renal failure cannot only be explained by increased systemic or glomerular pressure. Other mechanisms may be involved, and the effects of CCBs on these mechanisms must be considered. Alternative pathways of protection by CCBs may cause a downward shift of the curve relating glomerulosclerosis to blood pressure (Fig. 2), and thus balance or even outweigh the impact of the impairment of autoregulation.

Role of glomerular hypertrophy

Some investigators have stressed the role of glomerular hypertrophy. Indeed, in some experimental models it has been shown that hypertrophy is required for injury to occur [76–78]. Prevention of glomerular hypertrophy averts renal injury and glomerulosclerosis. Calcium channel blockers are able to attenuate kidney hypertrophy after uninephrectomy [27–29]. Indeed, Dworkin suggested that CCBs afford protection in various models by way of limiting hypertrophy independently from effects on glomerular pressure [79]. However, such an effect on hypertrophy is not uniformly observed. It has been demonstrated that CCBs did not lower kidney weight after uninephrectomy [53, 80] or even induced an increase of glomerular hypertrophy [45, 51, 52]. These differences in hypertrophic response may be related to the timing of the administration of the CCB in relation to the induction of renal injury and the onset of the hypertrophic response.

Role of timing of treatment

One factor that may explain the differences in outcome of the various studies is the interval between the induction of injury and the start of the treatment. In most studies in Table 1 (the protective studies) treatment was started immediately after induction of the injury, whereas in the negative studies the start of treatment was often delayed [46, 47, 51, 52]. The importance of the timing of the start of treatment is highlighted by the studies of Dworkin. In his earlier studies employing the rat remnant kidney model it was demonstrated that nifedipine started at the time of injury afforded complete protection [29]. However, when treatment was started four weeks after the induction of injury,

nifedipine was no longer protective [81]. The timing of drug treatment might also explain the beneficial effects of CCBs in models of Heymann nephritis and aminonucleoside nephrosis [38, 39]. It seems quite possible that by administering the drugs before the induction of injury one affects the induction phase, thus limiting the harmful effects of puromycin, or limiting the immune response in case of the Heymann model.

Other mechanisms of renoprotection

It has been suggested that CCBs may protect against progressive renal injury by diminishing cellular uptake of calcium and preventing calcinosis [82]. Such an effect could explain the results of Harris et al and Jarusiripitap et al, who observed better survival in remnant kidney rats treated with verapamil or anipamil [33, 34]. These studies are remarkable because of the high mortality (due to renal failure) in the untreated control groups, suggesting that in these particular studies additional mechanisms of renal injury have been operative.

Other beneficial effects of CCBs are the reduction of vascular damage, particularly in models of severe hypertension [32, 36, 37, 44, 52], and attenuation of mesangial proliferation [44, 49, 55]. The relevance of this latter finding is unclear, however, since in the study of Amann et al the effects on mesangial cell proliferation were not matched by protective effects on the podocyte or the tubulointerstitium [44]. An untoward effect on tubulointerstitial fibrosis was noted by Gaber et al, who observed more tubulointerstitial injury during treatment of diabetic beagle dogs with a diltiazem derivative [40].

Calcium channel blockers might be protective in specific conditions where afferent vasoconstriction and ischemic injury are important. Administration of the nitric oxide (NO) synthase inhibitor L-NMMA in rats induces hypertension, proteinuria, and progressive renal failure [83]. Renal histological damage is characterized by glomerular collapse, interstitial expansion, and glomerulosclerosis [84]. In this model nifedipine largely prevented these abnormalities without having a major influence on renal hemodynamics or blood pressure [84]. The use of the immunosuppressive drug cyclosporine is associated with nephrotoxicity, which is attributed to constriction of the afferent arteriole [85]. Experimental data suggest that calcium channel blockers may be effective in reducing cyclosporine-induced renal damage [85].

CALCIUM CHANNEL BLOCKERS: HUMAN STUDIES

Effects on proteinuria

The development of end-stage renal disease (ESRD) is the best and most definitive end point for studies evaluating the effects of antihypertensive drugs on renal function deterioration. However, controlled studies in humans on the effects of CCB and the risk of developing ESRD are virtually lacking. It has been demonstrated that systemic and more importantly glomerular pressure are important factors in the progression of renal failure [1]. Proteinuria may be a reflection of intraglomerular pressure, but it may also induce renal damage on its own by causing tubulointerstitial injury [3, 7]. Indeed, recent studies have demonstrated that proteinuria is an important determinant of renal function deterioration [9], and that the lowering of proteinuria precedes and predicts a subsequent decrease in the rate of renal function deterioration [12, 86, 87]. Therefore, proteinuria is frequently used as a surrogate end point in studies investigating potentially

Table 3. Studies on the effects of calcium channel blockers on proteinuria in humans

| | Nifedipine | Other DHP | Verapamil | Diltiazem |
|-----------------------|------------|-----------|-----------|---------------------|
| Diabetic patients | | | | |
| Low albuminuria | 12 (224) | 17 (233) | 4 (71) | 0 |
| High albuminuria | 9 (104) | 5 (52) | 1 (8) | 5 (62) ^a |
| Non-diabetic patients | | | | |
| Low albuminuria | 3 (63) | 10 (174) | 1 (10) | 0 |
| High albuminuria | 5 (69) | 6 (69) | 1 (10) | 0 |

Numbers of treatment groups are given (in brackets numbers of patients). Abbreviation is DHP, dihydropyridines.

^a In one of these studies eight patients were treated with verapamil, the other 10 patients with diltiazem

beneficial effects of antihypertensive drugs on the progression of renal disease. Thus, it seems quite relevant to critically assess the effects of CCBs on proteinuria in patients with renal disease and overt proteinuria. We performed a *Medline* database search and screened recent articles and reviews for cross references. From these, 69 full length articles were selected in which patients were treated in randomized or non-randomized fashion for at least one week with a calcium channel blocker [16, 19, 88–155]. To be included in the analysis both data on blood pressure and proteinuria had to be provided. Because of differences in prognosis, etiology, and treatment effects, we were particularly interested in patients with a high proteinuria (>500 mg/24 hr). Since the number of studies in this patient group was low, non-randomized studies were also included. Some studies provided data on two or more groups of patients treated with a CCB, and these were analyzed separately. Consequently, the total number of treatment groups (Table 3) exceeds the number of studies. In 46 randomized studies data on the effects of ACE inhibitors were also reported that were used for comparison. Relevant data were gathered from these publications. To make data comparable we used the mean arterial pressure as given by the authors, or MAP was calculated as diastolic pressure plus one third of the pulse pressure. Since many papers only provided data on albuminuria, we have used this as the relevant parameter. In case data were given as total urinary protein excretion, we calculated albuminuria from proteinuria by using an appropriate correction factor [156]. These correction factors are probably only a rough estimate. However, conversion of proteinuria to albuminuria was only needed to assign patients to a group with low albuminuria (<500 mg/24 hr) or a group with high albuminuria (>500 mg/24 hr). In the high albuminuria group only 17 studies reported total protein excretion rates. The lowest value in these studies was 1330 mg/24 hr. Even when total protein excretion was divided by a factor 2.0 instead of 1.2, this group of patients still belonged to the high albuminuria group. In the low albuminuria group only three studies reported total protein excretion rates. The highest value of these three studies was 340 mg/24 hr. Therefore, any reasonable correction factor would not change the classification of this patient group. Percent changes in blood pressure and proteinuria were calculated from baseline or from time controlled placebo values. Correlations were assessed by determining the Spearman correlation coefficient. Weighed means were calculated by the formula $\Sigma(x_i * n_i/n_t)$, where Σ is the sum, x_i is the value of a group, n_i is the number of patients in that group and n_t is the total number of patients of all groups.

An overview of the treatment groups is given in the Table 3. It

is evident that most studies were done with DHP, in diabetic patients and/or in patients with low albuminuria. Thus, information on the effects of CCBs on proteinuria in patients with non-diabetic renal disease and high albuminuria was limited to 11 studies with dihydropyridines (5 with nifedipine) and one with verapamil.

The overall results of the various studies are summarized in Figure 3, in which patient groups are divided according to the level of albuminuria, type of renal disease (diabetic vs. non-diabetic) and the type of CCB used. Apparently, the results obtained with DHP are quite heterogeneous. It has been suggested that dihydropyridine CCB might be more effective in diabetic patients [157, 158]; however, with all of the studies taken together there was no difference in the response between diabetic and non-diabetic patients. Dihydropyridines have some antiproteinuric effects in patients with low albuminuria, whereas almost no effect is observed in patients with albuminuria >500 mg/24 hours. Since increases in proteinuria have been observed in particular with the DHP nifedipine, we analyzed the data further by dividing the DHP patients in two groups according to the use of nifedipine. Although proteinuria was seemingly less decreased by nifedipine, the difference between the mean changes is not impressive and is mainly due to the results of only one study in which the use of a non-nifedipine DHP resulted in an unexpectedly high decline in proteinuria (Fig. 3). In diabetic patients verapamil and diltiazem seem more effective than dihydropyridines, although blood pressure reduction was also more pronounced with these treatments. No pertinent data on the effects of verapamil or diltiazem are available for non-diabetics. It is evident that ACE inhibitors had a clear antiproteinuric effect in all groups.

When combining data of all studies with DHP, only a very weak correlation between the decrease in blood pressure and the decrease in proteinuria was seen ($r = +0.2487$, $P < 0.05$; Fig. 4). A possible explanation for this is the fact that measurements of blood pressure and proteinuria are not performed in parallel, and measurements of blood pressure are done only at a single time point. In this respect the short duration of action of the nifedipine formulations used may be relevant. Urine collections were mostly done during 24 hours. Six of all DHP treated groups reported timed overnight urine collections. Timed urine collections by day were reported in 13 of the 67 DHP groups. If one only considers data from these 13 studies in which urine was collected over short intervals by day, probably more closely related to the time of blood pressure measurement, a significant correlation ($r = +0.8022$, $P < 0.01$) is observed. The regression line suggests an intercept far above zero. Figure 4 clearly demonstrates that when blood pressure is only modestly reduced proteinuria increases, whereas a greater reduction in blood pressure is needed to see a decrease in proteinuria. In this respect, these data fit with the findings of Griffin et al [54], describing the relation between blood pressure and glomerular injury in rats after treatment with nifedipine (Fig. 2).

One explanation for such an increase of proteinuria could be a decreased tubular protein reabsorption. Calcium channel blockers, especially those of the DHP class, increase urinary sodium and water excretion, partly by decreasing proximal tubular sodium reabsorption [159, 160]. It has been suggested that dihydropyridine CCBs might also block tubular protein reabsorption. Some

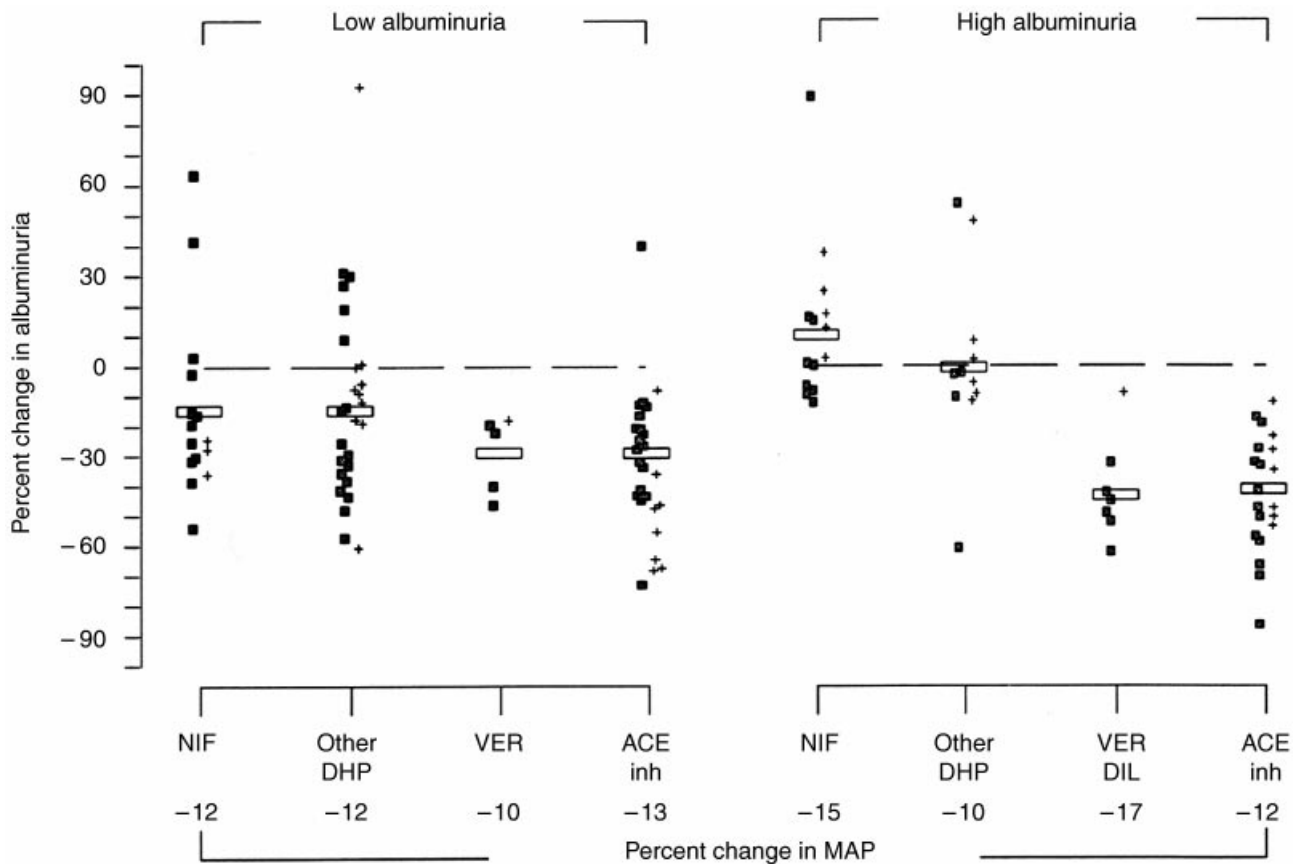


Fig. 3. Relative changes in albuminuria for groups treated with nifedipine (NIF), other dihydropyridines (DHP), verapamil (VER) or diltiazem (DIL) and angiotensin converting enzyme inhibitors (ACEinh) in humans. Filled symbols indicate groups with diabetes, crosses indicate non-diabetic groups. Bars in the Figure indicate weighed means. Relative changes in mean arterial pressure (MAP) are also given as weighed means. Low/high albuminuria is less/more than 500 mg/24 hours.

studies reported an increased excretion of urinary β_2 -microglobulin, a marker of proximal tubular protein reabsorption, after administration of nifedipine [115, 116, 161]. However, in one of these studies the increase of the β_2 -microglobulin excretion was not significant [116], and in another the increase was only 10%, and may be explained by a period effect [115]. In a third study a definite increase of β_2 -microglobulin excretion was paralleled by an abrupt increase in urinary flow, suggesting that the increased excretion was caused by a wash-out of urine [161]. Recently, in a short-term study with a natriuretic dose of nifedipine we did not find a change in urinary β_2 -microglobulin excretion either acutely or after repeated administration during one week [126]. Overall, the arguments in favor of an effect of DHP on tubular protein reabsorption are weak.

It is tempting to speculate that the absence of an antiproteinuric effect of dihydropyridine CCBs in patients with overt proteinuria, like in animals, is explained by a disturbance of autoregulation allowing enhanced transmission of the systemic blood pressure to the glomerulus. In such a case the potentially beneficial effects of blood pressure lowering are balanced or outweighed by the increased transmission of pressure to the glomerulus due to the afferent vasodilation. Other findings support this idea. In patients with a nephrotic syndrome a high protein load acutely increased proteinuria [162]. Co-administration of nifedipine further en-

hanced the proteinuria despite the observed small blood pressure reduction of 4 mm Hg, suggesting more prominent afferent glomerular vasodilation. The complexity of the interplay between systemic blood pressure reduction and afferent glomerular arteriolar vasodilation is evident from the following example: nephrotic patients were studied when adhering to a high protein diet [66]. When using the high protein diet, verapamil lowered proteinuria. The study was repeated during adherence to a low protein diet, and the low protein diet preserved autoregulation. In the latter case it can be expected that vasodilation of the afferent arteriole will counteract the decrease of systemic blood pressure. Indeed, during the low protein diet verapamil did not lower proteinuria.

In our recent study in patients with renal disease we observed a difference in proteinuria dependent on posture [126]. Nifedipine increased proteinuria during standing or walking. Possibly this has to be ascribed to higher norepinephrine levels during standing: if nifedipine attenuates the effect of norepinephrine on the afferent arterioles, systemic blood pressure will be transduced more easily to the glomerulus, thereby enhancing the filtration of proteins.

The available data, admittedly limited to patients with diabetes, suggest that there may be a difference in the antiproteinuric effects of DHP versus non-dihydropyridine CCBs. One may ask if differences between DHP versus verapamil or diltiazem can be

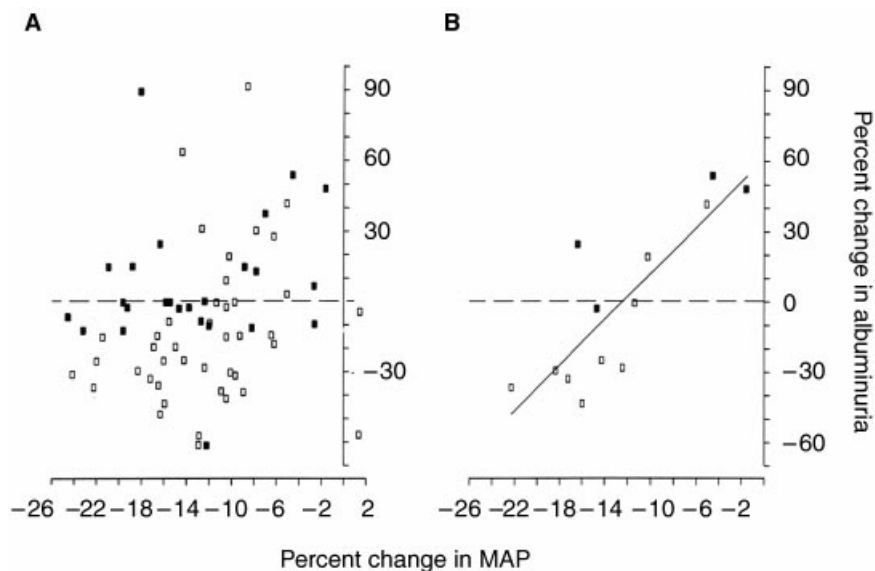


Fig. 4. Relationship between the change in mean arterial pressure (MAP) and the change in albuminuria during treatment with dihydropyridine calcium channel blockers in humans. (A) The results of all studies. (B) The relationship is shown for studies in which urine was collected in timed intervals during daytime. Open symbols represent studies of patients with an albuminuria of less than 500 mg/24 hours, whereas closed symbols represent studies of patients with an albuminuria of more than 500 mg/24 hours.

explained by differences in sodium intake. In general, the long-term antihypertensive effects of DHP and verapamil are hardly dependent on sodium intake [163–165]. One study reported on the effects of low and high sodium intake during treatment with nifedipine and diltiazem [94]. During nifedipine no effect on urinary protein excretion rate was seen, whereas diltiazem decreased proteinuria only during low salt intake, despite a comparable blood pressure reduction. Therefore, it is conceivable that the antiproteinuric effect of the latter drug is mediated by an effect on the renin-angiotensin system. However, studies using DHP, diltiazem or verapamil in hypertensive patients did not show a clear effect of these drugs on PRA in the long run [166, 167]. To our knowledge studies with these drugs on the effects on PRA in patients with proteinuria are not available.

Thus far, no studies have been reported on the effects of the new calcium channel blocker mibefradil on proteinuria. However, we have preliminary data from a recently completed multicenter study in patients with renal insufficiency and proteinuria who were treated with either the new CCB mibefradil or nifedipine. When compared to baseline values, obtained after withdrawal of antihypertensive drugs such as ACE inhibitors, both drugs caused a similar increase in proteinuria, whereas mibefradil was more effective in lowering blood pressure.

Effects on the course of renal function

Several investigators have reported on the short-term effects of CCB treatment on renal hemodynamics in patients with non-diabetic renal disease. Within a one year period generally no adverse effects on GFR or RPF are noted [96, 134]. However, the time frame of such studies is too short to allow meaningful conclusions. Only a limited number of long-term studies have assessed the impact of DHP on the progression of chronic renal failure in patients with non-diabetic renal disease. Eliahou and coworkers [168, 169] have compared the effect of nisoldipine and standard antihypertensive treatment on blood pressure and progression of renal insufficiency. Part of the patients had non-glomerular diseases (such as polycystic kidney disease, interstitial

nephritis). Urinary protein excretion rates were not reported, but it is likely that in part of the patients proteinuria was absent or low. Overall, an improvement of the slope of the reciprocal of serum creatinine was observed in the nisoldipine treated patients. However, further analysis revealed that this improvement was independent from the type of treatment and achieved only in patients in whom mean arterial pressure decreased (on average from 111 to 104 mm Hg). Apparently, the beneficial effect on the progression of renal insufficiency was related to the blood pressure decline *per se*. This study thus suggests that DHP calcium channel blockers can safely be used in patients with renal diseases, provided that blood pressure is lowered. However, in view of the patients characteristics, such a conclusion cannot be generalized to include patients with proteinuric renal disease. Zucchelli et al [154, 155] have compared captopril and nifedipine in 121 non-diabetic patients with renal insufficiency and proteinuria, who were followed for 156 weeks. Overall, no significant differences in renal function deterioration were observed. It should be noted, however, that blood pressure reduction was considerable on both drugs (blood pressures decreasing from approximately 165/100 mm Hg to 139/82 mm Hg), the majority of patients having blood pressures below 140/80 mm Hg. Furthermore, during follow-up more nifedipine treated patients needed hemodialysis. Although this difference was not significant, one must be aware of the β -error since the number of patients with a follow-up of three years was rather small (37 vs. 31 patients in the captopril and nifedipine group, respectively). Thus, a negative effect of the CCB compared to the ACE inhibitor cannot be excluded. Indeed, in the study of Piccoli et al [136] the 31 patients treated with dihydropyridine calcium channel blockers had a faster decline in renal function than the 31 patients treated with enalapril. The average decrease in proteinuria was greater in the ACE inhibitor group than in the DHP group. Of note, in both treatment groups only a small blood pressure reduction was observed, mean arterial pressure averaging approximately 110 mm Hg at the end of the study. Altogether, the latter studies suggest that the dihydropyridine CCB are less effective than the ACE inhibitors in attenuating

progressive renal failure, in particular when blood pressure reduction is only modest. In non-diabetic patients data on the long-term efficacy of non-DHP calcium channel blockers are lacking.

In diabetics two studies of more than one year have suggested benefits from diltiazem [150] and verapamil or diltiazem [93] during profound blood pressure reductions. In the study of Slataper et al [150] three groups of 10 patients each were treated with diltiazem, lisinopril and atenolol/furosemide, respectively. In all groups mean arterial blood pressure was lowered from approximately 120 to 104 mm Hg. In the diltiazem and lisinopril group the antiproteinuric effect and the rate of decline in glomerular filtration rate was nearly identical. In the atenolol/furosemide group reduction of albuminuria was significantly less and the decline in glomerular filtration rate was greater. However, in this group the patients were older, had a slightly longer duration of hypertension and more black patients were included. Bakris et al [93] treated three groups with lisinopril, atenolol and verapamil, or diltiazem during five years. The majority of patients was also treated with furosemide. In all groups the mean arterial pressure was reduced by approximately 16 mm Hg to 100 mm Hg. The reduction in proteinuria and annual rate of decline in creatinine clearance was similar in the lisinopril and verapamil/diltiazem groups. In contrast, in the atenolol group the reduction in proteinuria was significantly less and the decline in creatinine clearance steeper. However, during the treatment period the systolic blood pressure was significantly higher in the atenolol group, which also included more black patients. Thus, both studies suggest that during profound blood pressure reduction in diabetic patients the beneficial effect of a treatment with verapamil/diltiazem is comparable to the effect of an ACE inhibitor. These studies do not provide definitive proof that these drugs have additional benefits compared to beta-blockers/furosemide treatment.

Effects of calcium channel blockers in chronic ischemic injury

The use of the immunosuppressive drug cyclosporine is hampered by its nephrotoxicity. The adverse effects of cyclosporine on the kidney are in part attributed to the afferent vasoconstriction and ensuing ischemia [85]. Calcium channel blockers might afford protection by attenuating this vasoconstriction. Indeed, several studies have claimed improvement of renal function and attenuation of renal histological injury when cyclosporine is combined with a CCB [170–172]. However, definite proof of long-term benefits has yet to come. When using calcium channel blockers and cyclosporine in combination, one must be aware that certain calcium channel blockers can increase the cyclosporine levels. Verapamil, diltiazem, nifedipine and amlodipine are known to increase the cyclosporine level, whereas no effect is seen during concomitant treatment with nifedipine, isradipine or nitrendipine [173].

As mentioned above, in animal experiments nifedipine attenuated the renal injury caused by the NO-synthase inhibitor L-NMMA. It has been suggested that an endogenous inhibitor of NO might accumulate in the serum of patients with renal failure [174]. Indeed, if such an inhibitor affects hypertension and progression of renal failure in humans, CCBs might be advantageous. However, information is too limited to allow for meaningful conclusions.

CONCLUSIONS

In many animal models of progressive glomerulosclerosis calcium channel blockers neither decreased proteinuria nor delayed the progression of renal insufficiency. Some studies even reported an increase of renal damage. These adverse effects are likely to be explained by the preferential afferent vasodilation resulting in an impairment of autoregulation and increased glomerular capillary pressure.

In the animal models protection is observed only when treatment is started at the onset of injury, a condition which cannot easily be met in humans. Calcium channel blockers afford protection in models of ischemic injury caused by afferent vasoconstriction (cyclosporine, L-NMMA).

Also, in humans proteinuria and hypertension are the best predictive factors of progressive renal disease, as has been shown by the MDRD study [11]. Many reports on dihydropyridine CCBs suggest that these antihypertensive drugs do not reduce proteinuria. The data demonstrate an increase in albuminuria during small blood pressure reductions, whereas only a moderate anti-proteinuric effect is seen during profound blood pressure decreases.

Studies demonstrating a clear beneficial effect of dihydropyridines on the progression of renal insufficiency are lacking. In fact, the available evidence suggests that dihydropyridines may be less effective than ACE inhibitors. Therefore, monotherapy with dihydropyridines as first line treatment in patients with renal insufficiency and proteinuria is not advisable.

If, on the other hand, during treatment with other antihypertensive drugs such patients do not reach the target blood pressure of 125/75 mm Hg as advocated by the MDRD study [11], addition of a dihydropyridine CCB could be valuable. In such a case, we suggest to closely monitor blood pressure and proteinuria. Any increase in proteinuria should lead to a critical reassessment of the value of the treatment with the dihydropyridine CCB.

Data on proteinuria and progression of renal function during treatment with verapamil or diltiazem are virtually absent in patients with non-diabetic renal disease, and prospective studies with these drugs are urgently needed. At least in diabetic patients beneficial effects of these classes of drugs have been suggested.

From our analysis of the effects of dihydropyridine calcium channel blockers on proteinuria it is evident that interpretation of the data are hampered by methodological problems. In future studies it is important to measure protein excretion under standardized conditions (with respect to timing, posture, etc.) and in relation to time averaged blood pressures.

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