REVIEW ARTICLE

Drugs 2005; 65 Suppl. 2: 29–39
0012-6667/05/0002-0029/$39.95/0

Renal Protection in Hypertensive Patients: Selection of Antihypertensive Therapy

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Abstract

Hypertension is common in chronic renal disease and is a risk factor for the faster progression of renal damage, and reduction of blood pressure (BP) is an efficient way of preventing or slowing the progression of this damage. International guidelines recommend lowering BP to 140/90mm Hg or less in patients with uncomplicated hypertension, and to 130/80mm Hg or less for patients with diabetic or chronic renal disease. The attainment of these goals needs to be aggressively pursued with multidrug antihypertensive regimens, if needed. The pathogenesis of hypertensive renal damage involves mediators from various extracellular systems, including the renin–angiotensin system (RAS). Proteinuria, which occurs as a consequence of elevated intraglomerular pressure, is also directly nephrotoxic. As well as protecting the kidneys by reducing BP, antihypertensive drugs can also have direct effects on intrarenal mechanisms of damage, such as increased glomerular pressure and proteinuria. Antihypertensive drugs that have direct effects on intrarenal mechanisms may, therefore, have nephroprotective effects additional to those resulting from reductions in arterial BP. Whereas BP-lowering effects are common to all antihypertensive drugs, intrarenal effects differ between classes and between individual drugs within certain classes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) have beneficial effects on proteinuria and declining renal function that appear to be mediated by factors additional to their effects on BP. These RAS inhibitors are recommended as a first-line antihypertensive approach in patients with chronic kidney disease. The addition of diuretics and calcium channel antagonists to RAS inhibitor therapy is also considered to be a rational strategy to reduce BP and preserve renal function. Calcium channel antagonists are a highly heterogeneous class of compounds, and it appears that some agents are more suitable for use in patients with chronic renal disease than others. Manidipine is a third-generation dihydropyridine (DHP) calcium channel antagonist that blocks both L and T-type calcium channels. Unlike older-generation DHPs, which preferentially act on L-type channels, manidipine has been shown to have beneficial effects on intrarenal haemodynamics, proteinuria and other measures of renal functional decline in the first clinical trials involving hypertensive patients with chronic renal failure. Preliminary results from a trial in diabetic patients who had uncontrolled hypertension and microalbuminuria despite optimal therapy with an ACE inhibitor or an ARB suggest that manidipine may be an excellent antihypertensive drug in combination with RAS inhibitor treatment in order to normalise BP and albumin excretion in patients with diabetes.

1. Introduction

Hypertension is second only to diabetes as the leading independent cause of end-stage renal disease (ESRD),[1,2] the risk of which increases continuously with the extent and duration of elevated blood pressure (BP).[3–5] In addition, a substantial number of patients with diabetes also have hypertension,[6] which can accelerate the progression of nephropathy and the onset of ESRD.[7,8] In general, chronic renal disease can be a cause or a consequence of hypertension, the majority of patients with chronic renal disease have hypertension[9,10] and without anti-hypertensive intervention, this can result in a vicious cycle of worsening renal function and hypertension.[8]

ESRD has a negative impact on the prognosis of patients in terms of survival and quality of life,[11] it is associated with substantial economic cost,[12–15] and it is becoming increasingly prevalent in countries with western lifestyles.[1,16,17] In order to reduce the increasing medical and economic burden of ESRD, therapeutic strategies that effectively slow or prevent the onset and progression of renal disease must be implemented in patients at high risk of renal disease and those already displaying symptoms of early disease.

Irrespective of whether a patient is at risk of renal damage from hypertension or already has renal disease as a result of hypertension, diabetes or other causes, the reduction of BP is viewed as an efficient way of preventing damage and halting or slowing the progression of renal damage towards ESRD.[11,18,19] This article will review evidence supporting the nephroprotective efficacy of antihypertensive drugs, including the third-generation dihydropyridine (DHP) calcium channel antagonist, manidipine.

2. Pathophysiology of Hypertensive Nephropathy

Increases in arterial BP are normally prevented from affecting the renal microvasculature by the proportionate autoregulatory vasoconstriction of the preglomerular vasculature, such that the pressure load transmitted from the systemic circulation to the glomerular capillary is blunted, and glomerular hydrostatic pressure remains relatively constant in the face of changing BP.[20] Such autoregulatory responses provide primary protection against hypertensive renal damage.[21,22] Failure of the autoregulatory response results in elevated glomerular hydrostatic pressure, hyperfiltration, proteinuria and glomerular injury.[23] If the upper limit of autoregulation is exceeded, hypertensive damage is expected to result, even when autoregulation is not impaired.[20] If renal autoregulation is already impaired, as occurs in patients with diabetic or non-diabetic chronic renal disease, the susceptibility to hypertensive damage is enhanced.[20]

The pathogenesis of hypertensive glomerular damage is clearly multimodal, and it has been suggested that parallel extracellular pathways converge on common intracellular signalling pathways resulting in excessive matrix synthesis.[24] The role of the sympathetic nervous system (SNS), which is activated in patients with renal disease,[24,25] is crucial.[2,26] Activation of the SNS occurs early, when renal function is not, or only slightly, impaired.[27] The renin–angiotensin system (RAS) is activated in parallel with the SNS.[28,29] Endothelial dysfunction also occurs during the early stages of renal dysfunction.[30–32] Via various mediators, the SNS, the RAS and the endothelial system (including endothelin 1) can all contribute to the pathophysiology of hypertension, and may also have directly damaging effects on the glomerulus.[24,25,31,32]

Proteinuria, which consists mainly of albuminuria, can be used as an intermediate endpoint indicating elevated intraglomerular pressure and renal damage, as well as a marker indicating treatment efficacy.[33] Proteinuria has also been identified as a pathway that has an independent role in the development of renal damage.[34–36] A decline of the glomerular filtration rate (GFR) is delayed when proteinuria is decreased with antihypertensive therapy, and the protection of renal function achieved with antihypertensive therapy has been shown to be dependent on the extent of initial proteinuria.[33,35,37]

The pathophysiology of hypertensive renal damage suggests that therapeutic intervention should aim to reduce BP load, reduce the transmission of pressure to the renal microvasculature and interrupt local pathways that mediate tissue injury.[22] It has been suggested that antihypertensive drugs should be chosen to control BP according to the new guidelines and minimise proteinuria.[33,35,36,38]

3. Goals for the Reduction of Blood Pressure and Proteinuria

Lowering BP to below the autoregulatory threshold is likely to prevent malignant nephrosclerosis and ESRD in patients with uncomplicated hypertension, whereas in order to prevent the progression of renal damage, BP may need to be reduced much more in patients with chronic renal disease.[22] Accordingly, international guidelines recommend lowering BP to at least 140/90mm Hg in patients with uncomplicated hypertension, and to <130/80mm Hg for patients with diabetes or chronic renal disease.[9,10,39,40] A goal BP of <125/75mm Hg has been recommended for patients with renal disease and proteinuria >1 g/day.[40] Although reducing BP to the goal is of primary importance in the prevention of serious renal damage, proteinuria should be monitored during the course of chronic renal disease and a target protein-to-creatinine ratio of <500–1000 mg/g has been specified as another goal for antihypertensive therapy.[9]

4. Nephroprotective Antihypertensive Strategies

The major antihypertensive drug classes are the angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), β-blockers, central sympatholytic agents, calcium channel antagonists, other vasodilators and diuretics. In order to achieve goal BP, combination therapy with different classes of antihypertensive agents is often required. Most patients with uncomplicated hypertension will require concomitant treatment with at least two antihypertensive drugs to achieve BP goals, and three or more drugs will often be required to reach the lower target BP goals in patients with diabetes or chronic renal disease.[10,41] Combination therapy may be considered as the initial therapy for systolic blood pressure (SBP) >20mm Hg above goal in patients with diabetes or chronic renal disease.[9]

Antihypertensive agents can offer renal protection via two mechanisms: a reduction of BP and effects on intrarenal mechanisms of damage, such as glomerular pressure and proteinuria (figure 1).[11] Arterial BP-lowering effects are common to all antihypertensive drugs. However, intrarenal effects differ among different classes of antihypertensive agents and among individual drugs within certain antihypertensive drug classes (table I).[19] The assessment of intrarenal effects is very difficult and only possible under experimental conditions. The optimal combination of antihypertensive drugs for renal protection has not been unequivocally defined, although some general recommendations can be made on the basis of clinical evidence to date (table II).[9,10,40,42]

4.1. Agents that Inhibit the Renin–Angiotensin System

It is postulated that, in addition to increased glomerular pressure, increased glomerular permeability to macromolecules, the activation of fibrogenesis, and increased oxidative stress all contribute to the net result of increased RAS activity on the kidney.[9,22] ACE inhibitors and ARB, which are classes of antihypertensive drugs that inhibit the RAS, are the agents that have been most widely studied in the prevention or treatment of progressive renal disease.

Overall, the results of numerous clinical trials have indicated that ACE inhibitors and ARB are effective in lowering BP, slowing the progression of diabetic and non-diabetic renal disease, reducing proteinuria, irrespective of the type of renal disease, and also reducing the risk of overt nephropathy.[9,10,37,43–49] The beneficial effects of ACE inhibitors and ARB on the decline of

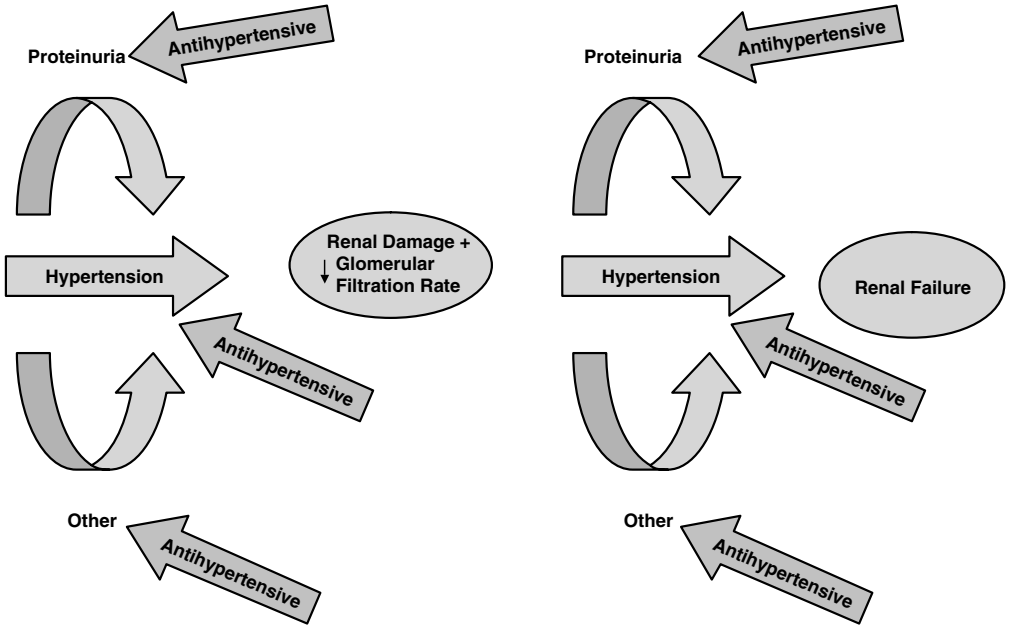

Fig. 1. Mechanisms by which antihypertensive agents can provide renal protection (antihypertensive effects, antiproteinuric effects, and numerous other class effects). Adapted with permission from the K/DOQI clinical practice guidelines.[9]

renal function do appear to be mediated by factors that are additional to their effects on arterial pressure.[9] Consequently, ACE inhibitors and ARB are recommended as preferred agents for inclusion in antihypertensive treatment regimens for patients with diabetic renal disease or non-diabetic renal disease with proteinuria.[9,10,40] Diuretics (see section 4.2), calcium channel antagonists (see section 4.3) and β-blockers (see section 4.4) should be added, as needed, to reach BP targets.

4.2. Diuretics

Extracellular fluid volume overload as a result of sodium retention is one of the major causes of hypertension in renal disease.[9,22] Diuretics act primarily by decreasing tubular sodium reabsorption, thereby increasing sodium excretion, reversing extracellular fluid volume expansion, and lowering BP. Diuretics potentiate the antihypertensive effects of ACE inhibitors and ARB by stimulating renin and reducing fluid volume, thus

Table I. Comparative renal effects of the classes of antihypertensive drugs that have been most extensively studied in relation to renal disease (renin-angiotensin system [RAS] inhibitors and calcium channel antagonists [CCAs])

	Afferent resistance	Efferent resistance	RPF	GFR	FF	Albuminuria/ proteinuria
RAS inhibitors	↓	↓↓↓	↑	↔	↓	↓↓
Calcium channel antagonists						
Old-generation DHPs	↓↓↓	↓	↑↑	↑	↑↑	↑
Manidipine, efonidipine	↓↓	↓↓	↑	↔	↓	↓
Non-DHP	↓	↓↓	↑	↔	↓	↓

DHP = Dihydropyridine; **FF** = filtration fraction; **GFR** = glomerular filtration rate; **RPF** = renal plasma flow; ↓ and ↑ indicate decrease and increase, respectively, and the numbers of arrows indicates the magnitude of the effect.

Table II. Recommendations regarding antihypertensive agents in diabetic renal disease and non-diabetic renal disease with proteinuria (compiled on the basis of recommendations from major international guidelines)[9,10,40,42]

Type of renal disease	Target BP	Preferred agents for chronic renal disease	Other agents to reach BP target
Diabetic renal disease	<130/80mm Hg	ACE inhibitor or ARB	Diuretic, then CCA (or β-blocker[a])
Non-diabetic renal disease with spot urine total protein-to-creatinine ratio ≥200 mg/g	<130/80mm Hg	ACE inhibitor or ARB	Diuretic, then CCA (or β-blocker[a])
Non-diabetic renal disease with spot urine total protein-to-creatinine ratio <200 mg/g	<130/80mm Hg	None preferred	Diuretic, then ACE inhibitor, ARB, CCA (or β-blocker[a])

ACE = Angiotensin-converting enzyme; **ARB** = angiotensin receptor blocker; **BP** = blood pressure; **CCA** = calcium channel antagonist.
[a]If necessary, β-blockers should be used in patients with heart failure, acute coronary syndromes or resting tachycardia.

making BP more sensitive to the actions of these agents.[9,18,22,42] In studies of disease progression in diabetic or non-diabetic kidney disease, the majority of patients received diuretics in addition to ACE inhibitors or ARB.[9] The first one-year randomised study designed specifically to test the effectiveness of a diuretic-based treatment on microalbuminuria in diabetic patients with hypertension found that diuretic-based therapy was equivalent to an ACE inhibitor-based therapy.[50] It was suggested that the effectiveness of the diuretic-based treatment on microalbuminuria in that study may have been dependent on the pathophysiological increase in systemic sodium that is characteristic of hypertension in diabetic patients. It is generally recommended that patients with chronic renal disease receive a diuretic along with an ACE inhibitor or ARB as part of the strategy to reach target BP.[9,10,40]

4.3. Calcium Channel Antagonists

Calcium channel antagonists are potent vasodilators, and like ACE inhibitors are generally able to improve endothelial function in patients with hypertension.[11,51] Calcium channel antagonists are highly effective antihypertensive agents; they have various properties that may afford renal protection, and their effects on the development and progression of renal injury has been studied extensively.[19]

The calcium channel antagonist class of antihypertensive drugs is a highly heterogeneous group, and substantial differences regarding their effects on proteinuria and other markers of renal disease progression have been observed.[52] Although calcium channel antagonists can be divided into two broad subclasses (DHP and non-DHP agents), there also appear to be differences in the nephroprotective activity of calcium channel antagonists within the same subclass (table I).[23] Factors that may account for these differences include the variable intrarenal distribution of different calcium channels, and divergent effects on glomerular membrane permeability, transcapillary pressure reduction and renal autoregulation.[52,53]

Studies in patients with diabetes that have examined the effects of non-DHP calcium channel antagonists on proteinuria and other measures of renal disease progression have generally demonstrated positive outcomes.[9,54–56] In a 6-year study in which patients with diabetic nephropathy were randomly assigned to treatment with an ACE inhibitor, a non-DHP calcium channel antagonist (verapamil or diltiazem) or a β-blocker,[55] the yearly rate of decline in creatinine clearance was greatest with β-blockers, and there were no differences between the ACE inhibitor and calcium channel antagonist groups. In addition, although the degree of BP reduction was similar in all groups, proteinuria was reduced to a similar extent

only in the ACE inhibitor and calcium channel antagonist groups.[55] Furthermore, the addition of verapamil to an ACE inhibitor has been shown to result in at least an additive reduction of proteinuria in patients with diabetic nephropathy,[9,56] although a recent long-term study could not confirm these beneficial effects of verapamil.[57] Consequently, the addition of a non-DHP calcium channel antagonist to an ACE inhibitor or ARB to lower BP and slow the progression of diabetic renal disease is considered to be a reasonable treatment decision.[9,18,40,42] The latest National Kidney Foundation guidelines state that this is also the case for non-diabetic kidney disease.[9]

Unlike non-DHP calcium channel antagonists, older-generation DHP calcium channel antagonists, such as amlodipine and nifedipine, have not been observed to have a beneficial effect on proteinuria and a decline of renal function in diabetic or non-diabetic renal disease.[9,47–49,52,53,58,59] However, in contrast to conventional DHP calcium channel antagonists, the novel DHP calcium channel antagonist manidipine does appear to have beneficial renal effects (see section 5).

4.4. Beta-blockers

Although β-blockers may afford some nephroprotection, it remains unclear how adrenergic blockade can best be used with respect to renal disease.[23,24] If necessary, β-blockers should be substituted for calcium channel antagonists in patients with renal disease who also have heart failure, acute coronary syndromes or resting tachycardia.[18,42] Several trials,[60,61] which were conducted before ACE inhibitors became available, have indicated that β-blockers do have some nephroprotective properties.

5. Effects of Manidipine on Renal Function

Manidipine is a lipophilic, long-acting, third-generation DHP calcium channel antagonist, which unlike older-generation long-acting DHP agents does not result in sympathetic activation.[62,63] In comparison with older-generation DHP calcium channel antagonists, manidipine has similar antihypertensive efficacy and a favourable tolerability profile, and also appears to be beneficial in renal disease.[64]

5.1. Effects on Renal Calcium Channels

Calcium channels are thought to play an important role in mediating renal arteriole tone.[65] Unlike older-generation DHP calcium channel antagonists, which generally preferentially act on L-type channels, manidipine blocks both L and T-type calcium channels.[66] L-type calcium channels are predominantly present at the afferent arteriole, whereas T-type channels are present at efferent arterioles.[65] The exact role of P/Q-type channels in the mediation of renal arteriole tone has not been defined, but P-type channels have been implicated in the contraction of afferent arterioles,[67] and novel DHP calcium channel antagonists may be able to block these channels.[68]

5.2. Effects on Intrarenal Haemodynamics

High glomerular pressure can be attenuated by antihypertensive drugs that result in vasodilation of the efferent glomerular arteriole.[11] Older-generation DHP calcium channel antagonists act predominantly by relaxing the afferent glomerular arteriole so they do not reduce glomerular capillary pressure and can impair renal autoregulation mechanisms of the preglomerular vasculature.[11,69] Because renal autoregulatory resistance changes provide the primary protection against the transmission of systemic hypertension to the renal microvasculature, they can counteract the beneficial effects of arterial BP reduction.[69] It has also been suggested that a reduction in glomerular capillary pressure may contribute to the antiproteinuric effects of inhibitors of the RAS, which do cause vasodilation of efferent arterioles.[11] Manidipine may also improve glomerular capillary pressure by inducing vasodilation of the efferent renal arterioles, thereby preserving autoregulation and affording renal protective effects additional to those that occur

in association with systemic antihypertensive activity.[65,70]

In a small study,[71] the daily administration of manidipine 10–20 mg/day for one week decreased renal perfusion pressure from 126 to 109mm Hg ($P < 0.01$) in hypertensive patients without renal impairment. The mean renal blood flow, renal plasma flow and glomerular filtration rate were increased from baseline. Glomerular capillary pressure was significantly decreased from 46 to 38mm Hg. Manidipine reduced the filtration fraction by 0.017, indicating that the favourable effects of manidipine on renal haemodynamics partly stem from a reduction of efferent arteriolar resistance.

The effects of manidipine 10–20 mg/day on the renal haemodynamics of patients with non-diabetic chronic renal disease have been observed to be similar to the effects of the ACE inhibitor enalapril 10–20 mg/day.[72] There were no statistically significant differences in mean renal vascular resistance, renal blood flow or glomerular filtration volume between manidipine and enalapril treatment groups during this randomised, double-blind 12-month head-to-head comparison. More randomised, controlled trials need to be performed in order to confirm preliminary results from early trials.

5.3. Effects on Renal Function in Hypertensive Patients with Chronic Renal Disease

The results of clinical trials investigating the effects of manidipine on the level of proteinuria and BP in patients with chronic kidney disease are summarised in table III.

The effects of manidipine 20 mg/day on the parameters of renal function have been compared with those of nifedipine 60 mg/day over 3 months of treatment in a randomised, open-label trial involving 101 hypertensive patients with chronic renal failure.[73] Proteinuria was significantly increased by 35% from baseline at 3 months in patients treated with nifedipine, and decreased by 25% in patients treated with manidipine, although the difference was not statistically significant. In

Table III. Results of clinical trials investigating the effects of manidipine (MAN) on proteinuria/microalbuminuria and blood pressure in patients with chronic kidney disease (CKD) or uncontrolled hypertension and microalbuminuria

Study	Patient group	Treatment duration	Treatment	No.	Change in proteinuria (mg/24 h)	Change in albumin excretion rate (mg/24 h)	Change in BP (mmHg)
Del Vecchio et al.[72]	CKD	48 weeks	MAN 10–20 mg/day	67	+20	NA	−16.3*/14.2*
			Enalapril 10–20 mg/day	69	−370*	NA	−23.1*,†/15.6*
Bellinghieri et al.[73]	CKD	3 months	MAN 20 mg/day	50	−304.8	NA	−19.0**/14.5**
			Nifedipine 60 mg/day	48	+321.9*	NA	−17.4**/25.5**
Fogari et al.[74]	Diabetic with microalbuminuria	2 years	MAN 10 mg/day	37	NA	−31*	−19‡/15‡
			Lisinopril 10 mg/day	36	NA	−43‡	−18‡/14‡
Martinez-Martin et al.[75]	Diabetic with microalbuminuria	3 months	MAN 20 mg/day[a]	25[b]	NA	≈−59[c]	−17**/6**
			Amlodipine 10 mg/day[a]		NA	≈−17§,[c]	−12**,†/9**,†

BP = Blood pressure.
[a] Added on to previous treatment (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker).
[b] Total evaluable patients.
[c] Measured in μg/min.
* $p < 0.05$ versus baseline;
** $p < 0.001$ versus baseline;
‡ $p < 0.01$ versus baseline;
† $p < 0.05$ versus MAN;
§ $p < 0.001$ versus MAN.

the long term, increases in proteinuria, such as those seen in the nifedipine treatment group, are known to damage the kidney. Significant improvements in mean creatinine parameters were observed in patients receiving manidipine, but these parameters were not significantly altered in nifedipine recipients. Manidipine and nifedipine were similarly effective in significantly reducing SBP and diastolic blood pressure (DBP).

In a 12-month randomised, double-blind trial in 136 hypertensive, severely proteinuric patients with chronic kidney disease (hypertensive kidney disease, interstitial nephropathy, nephropathy from unknown causes), no significant difference was observed between manidipine (10–20 mg/day) treatment and enalapril (10–20 mg/day) treatment in the rate of renal function decline, as measured by serum creatinine and creatinine clearance.[72] Compared with baseline, the degree of proteinuria remained substantially unchanged (1.6 versus 1.62 g/24h) in the manidipine group and was significantly reduced in the enalapril group (from 1.37 to 1.00 g/24h; $P < 0.05$). Both treatments provided significant reductions in DBP and SBP from baseline, although enalapril resulted in a mean decrease in SBP that was significantly greater than that obtained with manidipine. It was suggested that the lower BP obtained with enalapril may have amplified the differences between the two treatment groups with regard to proteinuria.

5.4. Effects on Renal Function in Diabetic Hypertensive Patients with Microalbuminuria

The results of clinical trials investigating the effects of manidipine on the albumin excretion rate (AER) and BP in diabetic patients with hypertension and microalbuminuria are also summarised in table III.

Manidipine and the ACE inhibitor lisinopril were both observed to improve renal function, as measured by changes in AER in a study in which 73 diabetic hypertensive patients with microalbuminuria were treated for 2 years.[74] AER was significantly reduced from 82 mg/24h at baseline to 51 mg/24h with manidipine 10 mg/day and from 78 to 35 mg/24h with lisinopril 10 mg/day. The two agents had similar antihypertensive activity.

It is possible that combination therapy with a calcium channel antagonist such as manidipine and a RAS-inhibiting agent may have additive or even synergistic renoprotective effects. Preliminary results from a study in which manidipine 20 mg/day or amlodipine 10 mg/day were given as add-on therapy to diabetic patients with uncontrolled hypertension and microalbuminuria despite 6 months or more of full-dose ACE inhibitor or ARB therapy imply that add-on manidipine is a very effective treatment choice when RAS inhibitors fail to normalise BP and albumin excretion.[75] Manidipine recipients had a 54% reduction in AER after 3 months compared with a 15% reduction with amlodipine. Furthermore, one-third of manidipine recipients achieved a target AER of less than 20 μg/min. Both manidipine and amlodipine resulted in significant reductions in SBP/DBP, but the magnitude of the antihypertensive effect was significantly greater with manidipine than amlodipine. If these preliminary results are further confirmed by controlled trials, manidipine could become a preferred option for addition to RAS inhibitor treatment for the normalisation of BP and albumin excretion in patients with diabetes.

6. Conclusion

Irrespective of the agent used to control BP, the reduction of arterial BP to goal exerts a nephroprotective action, so it is clear that the reduction of BP to target levels is of the utmost importance for improving renal outcomes in hypertensive patients. Therapy with any one antihypertensive agent is generally not an effective strategy, and particularly in patients with diabetes or chronic renal disease multi-drug regimens must be employed early in order to achieve the low target BP goal of less than 130/80mm Hg. A number of mechanisms contribute to the pathogenesis of renal injury, and certain antihypertensive agents may have nephroprotective effects that are additional to their BP-lowering

effects. Current guidelines recommend that an ACE inhibitor or an ARB should be the first choice of antihypertensive agent for inclusion in antihypertensive regimens for patients with diabetic or non-diabetic chronic renal disease. The addition of diuretics, β-blockers and calcium channel antagonists to RAS inhibitor therapy is also considered to be a rational strategy to reduce BP and preserve renal function. Calcium channel antagonists are, however, a highly heterogeneous class of compounds, and it appears that some of these agents are more suitable for use in patients with chronic renal disease than others. Judging from its beneficial effects on renal haemodynamics, proteinuria and other measures of renal function in clinical trials involving diabetic or non-diabetic hypertensive patients with chronic kidney disease, the third-generation calcium channel blocker manidipine is one such agent.

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