Int Urol Nephrol (2008) 40:1015–1025
DOI 10.1007/s11255-008-9424-x

NEPHROLOGY - REVIEW

Inhibition of the renin–angiotensin system and chronic kidney disease

Kostas C. Siamopoulos · Rigas G. Kalaitzidis

Received: 27 February 2008 / Accepted: 23 June 2008 / Published online: 14 August 2008

Abstract Chronic kidney disease (CKD), a major worldwide public-health problem which affects about 10% of the population, has an increased annual incidence rate of about 5–8%. This increased incidence is mainly due to type 2 diabetes and hypertension and the increasing incidence of elderly patients with CKD. Although the progression to end-stage renal failure (ESRF) is mainly based upon the underlying disease, comorbid conditions such as an initial low renal function, severe proteinuria, and high levels of blood pressure also play important roles in the development of ESRF. Since experimental and clinical evidence suggest that angiotensin II plays a central role in the progression of CKD, pharmacological inhibition of the renin–angiotensin–aldosteron system (RAAS) with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists has been suggested as first-line treatment for hypertension and prevention of ESRF in these patients. Aliskiren, a novel renin inhibitor is also a promising medical intervention. However, independently of the category of the drugs used, low target blood pressure levels seem to be equally or more important for the delay or prevention of CKD. In this review the results of studies with pharmacological inhibition of the RAAS in patients with diabetic and nondiabetic nephropathy is discussed.

Keywords Angiotensin converting enzyme inhibitors · Angiotensin II receptor antagonists · Renin inhibitor · Chronic kidney disease

K. C. Siamopoulos (✉) · R. G. Kalaitzidis
Department of Internal Medicine, Medical School, University of Ioannina, 451 10 Ioannina, Greece
e-mail: ksiamop@cc.uoi.gr

Introduction

Chronic kidney disease (CKD), a progressive to end-stage renal failure (ESRF) disease, is a worldwide major public-health problem affecting 11% of the population [1]. Although in recent years stability in the rate of decline of CKD has been reported, there is a 5–8% increased annual incidence [2]. The rate of progression is mainly based upon the underlying disease. However, independently of the primary kidney disease, the presence of comorbid conditions such as an initial low renal function, severe proteinuria, and high levels of blood pressure (BP) also play important roles in the development of ESRF [3–6]. Hypertension is a concomitant disorder in more than 80% of the patients with CKD and its incidence increases as the CKD progresses [7].

The renin–angiotensin–aldosterone system (RAAS) is a major regulatory system of cardiovascular and renal function mainly through the activation of the angiotensin II receptors by angiotensin II (AgII), which is the final step of the RAAS cascade. In the kidney,

AgII plays an important role in the regulation of glomerular filtration rate (GFR) and renal blood flow [8]. Also, it promotes renal NaCl and H_2O reabsorption and therefore expansion of the plasma volume.

However, there is experimental and clinical evidence that hemodynamic and nonhemodynamic effects of AgII play a central role in the progression of CKD [9, 10]. The pharmacological inhibition of the RAAS with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) are now first-line treatments for hypertension, especially in patients with hypertensive target organ damage [11]. Regarding the progression of renal disease this treatment also attenuates/delays the decline in renal function and ameliorates/suppresses proteinuria [10, 12–16]. However, a recent population-based cohort study which assessed the long-term effect of ACEIs on patients with diabetes did not detect a decreased risk of ESRF [17]. In fact, the authors suggested that ACEIs might actually increase the risk for ESRF. However, several limitations on the methodology of the study have been raised [18, 19]. In addition, a recent meta-analysis of 127 placebo-controlled trials indicated that the benefits of ACEIs or ARBs on renal outcomes result mainly from a blood-pressure-lowering effect [20]. Recently the development of an oral active renin inhibitor has provided an alternative method of inhibiting the RAAS and thus creating a potential therapy for CKD patients [10, 21–25]. In the present review the role of the different pharmacological inhibitors/blockers of the RAAS as well as the control of BP on renoprotection are discussed.

Treatment with ACEIs

In the early 1990s Lewis et al. showed that captopril, one of the first ACEIs available on the market, has kidney-protecting properties independent of its effect on BP in diabetic nephropathy. In this randomized controlled trial comparing captopril with placebo in patients with insulin-dependent diabetes mellitus in whom urinary protein excretion was $\geq$500 mg per day and serum creatinine concentration $\leq$2.5 mg/dl captopril treatment was associated with a 50% reduction in the risk of the combined endpoints of death, dialysis, and transplantation that was independent of the small disparity in BP between the groups. The authors concluded that captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and was significantly more effective than BP control alone [26]. However, the placebo patients were receiving conventional antihypertensive treatment excluding calcium antagonists. Later, Tarnow et al. showed that long-term treatment with the long-acting calcium antagonist nisoldipine and the ACEI lisinopril had a similar effect on the progression of diabetic nephropathy in hypertensive type 1 diabetic patients [27].

In the Ramipril Efficacy In Nephropathy (REIN) study, the ACEI ramipril in patients with chronic nephropathies and proteinuria of 3 g or more per 24 h safely reduced the rate of decline of the glomerular filtration rate (GFR) and halved the combined risk of doubling of serum creatinine or ESRF, as compared with placebo plus conventional antihypertensive drugs at the same level of BP control [5]. One year later, the same group of investigators reported that ACEIs confer renoprotection even to nondiabetic CKD patients with non-nephrotic proteinuria [28]. Also, in a 3-year trial involving 583 patients with renal insufficiency and diabetic and nondiabetic nephropathy, the use of the ACEI benazepril provided protection against the progression of renal insufficiency [29]. However, in a meta-analysis study including six studies performed in hypertensive type 2 diabetic patients with proteinuria the use of ACEIs did not reveal significant differences in the decline in GFR between patients treated with and without ACEI, except for one of these studies [30].

Microalbuminuria (24 h urine protein 30–300 mg), which is considered as a sign of endothelial dysfunction, progresses to overt proteinuria in 20–40% of patients with type 2 diabetes [31, 32]. In addition, microalbuminuria has been shown to be associated with an increased incidence of cardiovascular disease not only in diabetes but also in nondiabetic subjects [33–39]. In the Heart Outcomes Prevention Evaluation study (HOPE study), microalbuminuria was also found to be a significant risk factor for the primary outcome, which was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Indeed, it was more significant than coexisting coronary artery disease (CAD) and diabetes mellitus [40]. However, this study was not designed to assess the incidence of microalbuminuria on cardiovascular events in high-risk patients.

In the EURODIAB controlled trial of lisinopril in insulin dependent diabetes (EUCLID) study, a randomized placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria, the investigators demonstrated significant reduction in progression of diabetic nephropathy with the use of the above ACEI [41]. Moreover, treatment with the ACEI enalapril decreased the incidence of microalbuminuria over a period of 6 years in normotensive normoalbuminuric patients with type 2 diabetes [42]. The multicenter double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether ACEIs and non-dihydropyridine calcium-channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, type 2 diabetes mellitus, and normal urinary albumin excretion. The investigators studied 1,204 subjects, who were randomly assigned to receive at least 3 years of treatment with trandolapril (an ACEI) plus verapamil (a sustained-release calcium antagonist), trandolapril alone, verapamil alone, or placebo. The target BP was 120/80 mmHg. The primary endpoint was the development of persistent microalbuminuria (overnight albumin excretion, $\geq$20 μg per minute at two consecutive visits). Trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria by factors of 2.6 and 2.1, respectively. The effect of verapamil alone was similar to that of placebo [16].

Due to severe side-effects such as an increase of serum creatinine and hyperkalemia in some patients, many physicians are reluctant to use ACEIs and ARBs in advanced renal insufficiency. Hou et al. assessed the efficacy and safety of benazepril in patients without diabetes who had advanced renal insufficiency. Four hundred and twenty-two patients were enrolled in a randomized, double-blind study. After an 8-week run-in period, 104 patients with serum creatinine levels of 1.5–3.0 mg/dl (group 1) received 20 mg of benazepril per day, whereas, 224 patients with serum creatinine levels of 3.1–5.0 mg/dl (group 2) were randomly assigned to receive either 20 mg of benazepril per day (112 patients) or placebo (112 patients) and then followed for a mean of 3.4 years. All patients received also conventional antihypertensive therapy. The primary outcome was the composite of a doubling of the serum creatinine level, end-stage renal disease, or death. Secondary endpoints included changes in the level of proteinuria and the rate of progression of renal disease. Benazepril therapy was associated with a 52% reduction in the level of proteinuria and a reduction of 23% in the rate of decline in renal function and conferred substantial renal benefits in patients without diabetes who had advanced renal insufficiency [43].

Treatment with ARBs

Large clinical trials have established also the benefits in morbidity and mortality of the ARBs in patients with hypertension, CKD, and heart failure [13, 44–46]. Four clinical trials (RENAAL, IDNT, IRMA-2, and MARVAL) examined the effect of AT1 receptor blockers in patients with Non-Insulin Dependent Diabetes Melitus (NIDDM) nephropathy. These studies confirmed the beneficial effect of AT1 receptor blockers in patients with NIDDM nephropathy that was extended beyond the BP reduction. The RENAAL study compared the effects of losartan with placebo (both administered in addition to conventional antihypertensive therapy, including calcium channel blockers, diuretics, alpha-blockers, beta-blockers, and centrally acting agents) in patients with type 2 diabetes and nephropathy, defined as a urinary albumin/creatinine ratio of at least 300 mg/g and serum creatinine between 1.3 and 3.0 mg/dl. The primary endpoint was a composite of the time to the first event of doubling of serum creatinine, ESRF, or death, with secondary endpoints of cardiovascular events, progression of renal disease, and changes in proteinuria. Patients treated with losartan demonstrated a 16% reduction ($P = 0.02$) in the composite endpoint, a 25% risk reduction in doubling of serum creatinine ($P = 0.006$), a 28% reduction in the risk of ESRF ($P = 0.002$), and a 20% risk reduction in the composite endpoint of ESRF and death ($P = 0.01$), compared with patients receiving placebo. Losartan-treated patients also experienced a 35% decrease in proteinuria, as shown by a significant fall in the urine albumin/creatinine ratio ($P < 0.001$). Both study groups had similar systolic and diastolic blood pressures throughout the study, a finding that indicates that the renoprotective effects of losartan were attributable to effects beyond BP control [13].

Similar renoprotective effects were obtained with irbesartan in the IDNT study [44]. The IDNT study, which compared irbesartan with amlodipine on the

progression of nephropathy in patients with type 2 diabetes, showed that irbesartan was associated with a lower risk of the primary composite endpoint of doubling of the base-line serum creatinine concentration, the development of ESRF, or death from any cause (20% lower risk vs. placebo, $P = 0.02$); 23% lower risk vs. amlodipine, $P = 0.006$), a lower risk of doubling of serum creatinine concentration (33% lower risk versus placebo, $P = 0.003$; 37% lower risk versus amlodipine, $P = 0.001$), and a lower relative risk of ESRF, although not statistically significant (23% versus either group, $P = 0.07$).

The Irbesartan in patients with type 2 diabetes and Microalbuminuria study group (IRMA-2) investigated the renoprotective effect of the irbesartan in hypertensive patients with type 2 diabetes and microalbuminuria. After a follow-up of 2 years 5.2% in the 300 mg irbesartan group and 9.7% in the 150 mg irbesartan group reached the primary endpoint (the time to the onset of diabetic nephropathy), as compared with 14.9% in the placebo group of patients ($P < 0.001$). The authors concluded that irbesartan is renoprotective independently of its blood-pressure-lowering effect in hypertensive patients with type 2 diabetes and microalbuminuria [45].

In the MicroAlbuminuria Reduction with VALsartan (MARVAL) study the investigators found that, for the same level of attained BP and the same degree of BP reduction, valsartan lowered urinary albumin excretion more effectively than amlodipine in patients with type 2 diabetes and microalbuminuria, including the subgroup with baseline normotension. This indicates a BP-independent antiproteinuric effect of valsartan [46].

The antiproteinuric effect of ARBs independently of the degree of proteinuria and the underlying disease was recently investigated in a meta-analysis study of 49 randomized control trials involving 6,181 patients. The reduction in proteinuria from ARBs was similar to that of ACEIs [47].

Dose titration: comparison and combination of ACEIs/ARBs

Andersen et al. evaluated the optimal dose of losartan in 50 consecutive hypertensive type 1 diabetic patients with diabetic nephropathy. They received increasing doses of losartan, 50, 100, and 150 mg once daily in three periods each lasting 2 months. All doses of losartan reduced albuminuria and BP. Albuminuria was reduced by 30% [95% confidence interval (CI) 15–41%] on losartan 50 mg, 48% (95% CI 35–57%) on losartan 100 mg, and 44% (95% CI 32–56%) on losartan 150 mg (all P values < 0.01 versus baseline). Losartan 100 mg daily was significantly more effective than 50 mg daily in reducing albuminuria ($P < 0.01$) without differences between the two high doses. Losartan 100 mg daily was also more effective than 50 mg daily in reducing systolic, diastolic, and mean arterial BP ($P = 0.05$), without differences between the high doses. These results suggest that the optimal dose of losartan is 100 mg daily for renoprotection and BP reduction in type 1 diabetic patients with diabetic nephropathy [48]. However, the use of higher or ultrahigh doses of different ARBs such as irbesartan, candesartan, and valsartan resulted in additional antiproteinuric effect in patients with diabetic and nondiabetic nephropathy. It is also of interest that the enhanced renoprotective effect was independent of changes in systemic BP and with no dose-related increases in adverse events [49–51]. In addition, the IRMA-2 study showed that long-term treatment with 300 mg irbesartan in microalbuminuric type 2 diabetic patients resulted in greater reduction of microalbuminuria and normalisation of urinary albumin in a greater percentage (33%) of patients compared with patients who received 150 mg of the drug, in whom normalization of proteinuria was reached in 24% of patients [45]. Nevertheless, before we change our current policy on the recommended doses of the above drugs we should wait for results of long-term studies.

The antiproteinuric effect of the combination of an ACE with an ARB has also been studied. The combination of the ACE inhibitor lisinopril and the ARB losartan was compared to that of the optimal antiproteinuric doses of monotherapy in nine nondiabetic renal patients with median proteinuria 4.5 g/day (95% CI 3.5–6.4 g/day), creatinine clearance of 80 ml/min (95% CI 66–96 ml/min), and mean arterial pressure (MAP) of 102 mmHg (95% CI 93–112 mmHg). In this study, losartan and lisinopril were used in randomized order, each preceded by a baseline period without medication. The doses of losartan (mg/day) were 50, 100, 150, and again 50. The lisinopril doses were 10, 20, 40, and again 10. In a second protocol, patients were treated with a combination, using the optimal antiproteinuric doses

established for the individual drugs. The antiproteinuric response by losartan was optimal at 100 mg (−46%; 95% CI −60% to −24%), being larger than at the 50 mg dose (−27%; 95% CI −42% to −4%; $P < 0.05$), but not different from the 150 mg dose (−46%; 95% CI −58% to −20%). Proteinuria decreased further at each up-titration step of lisinopril to −75% (95% CI −85% to −43%) at the 40 mg dose. Combination therapy reduced proteinuria more effectively (−85%; 95% CI −96% to −58%) than monotherapy with losartan, and to a lesser extent than with lisinopril. Optimal BP responses were obtained at similar doses [52].

The comparative effectiveness of ACEIs versus ARBs in essential hypertension was recently reviewed. According to the authors of that study both drugs of RAAS inhibition had similar effects on BP control, but the ACEIs had higher rates of cough than ARBs [53].

Few studies however, have directly compared the renoprotective effects of ACEIs with ARBs in patients with type 2 diabetes. In the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study, a prospective, multicenter, double-blind, 5-year study, 250 subjects with type 2 diabetes and early nephropathy were randomly assigned to receive either the ARB telmisartan (80 mg daily) or the ACEI enalapril (20 mg daily). The primary endpoint was the change in the GFR (determined by measuring the plasma clearance of iohexol) between the baseline value and the last available value during the 5-year treatment period. Telmisartan was not inferior to enalapril in providing long-term renoprotection in persons with type 2 diabetes. These findings supported the clinical equivalence of ARBs and ACEIs in persons with conditions that place them at high risk for cardiovascular events [54]. Similar are the results of the IMPROVE study which showed that hypertensive patients, mainly diabetics, and relatively low degree of proteinuria may only require monotherapy with RAAS-blocking agents [55].

On the other hand, Kincaid-Smith et al., in a randomized controlled trial in normotensive patients with CKD and proteinuria [56], showed that the addition of the ARB candesartan to ACEI treatment reduced proteinuria and both systolic and diastolic BP. The COOPERATE study, a randomized controlled trial [57], assessed the efficacy and safety of combined treatment of an ACEI and an ARB, and monotherapy of each drug at its maximum dose, in patients with nondiabetic renal disease. Two hundred and sixty-three patients were randomly assigned losartan, 100 mg daily, trandolapril 3 mg daily, or a combination of both drugs at equivalent doses. Survival analysis compared the effects of each regimen on the combined primary endpoint of time to doubling of serum creatinine concentration or end-stage renal disease. According to those authors' conclusion, combination treatment safely retards progression of nondiabetic renal disease compared with monotherapy. However, the interesting finding that some patients on combined treatment also reached the combined primary endpoint made the authors suggest the need for a more integrated treatment of our patients, a recommendation also proposed by the authors of the present review.

The study of Kincaid-Smith et al. compared the effect of increasing the ACEI dose by 50% with that of adding an ARB to a standard ACEI dose. Proteinuria and BP were compared in both groups of patients in the three periods, on standard ACEI, on ACEI plus candesartan, and on a dose of ACEI increased by 50%. Standard ACEI plus candesartan was more effective in reducing systolic BP and proteinuria than a 50% increase in ACEI dose [58].

Based on the above as well as other studies the National Kidney Foundation suggests that ACEI and ARB may be used in combination to reduce proteinuria in both diabetic and nondiabetic kidney disease independently of the control of BP [59]. A recent meta-analysis further supports the combination of ARBs and ACEIs as an effective antiproteinuric therapy [48]. In a randomized double-blind placebo-controlled trial (AVOID) in patients with type 2 diabetes and albuminuria the addition of 300 mg once daily of the renin inhibitor aliskiren (*for details see below*) to the ARB losartan 100 mg for 6 months was associated with a 20% reduction in albuminuria [60]. The rationale for combination treatment of drugs affecting the RAAS including mineralocorticoid antagonists and the recently available renin inhibitor aliskiren in patients with CKD is fully discussed in depth in a very recent review [61]. However, additional important information on combination therapy in kidney disease are excepted this year after the results of the ongoing study ONTARGET which compares the efficacy of telmisartan plus ramipril with ramipril alone in the composite outcome of cardiovascular morbidity and mortality as a

primary outcome as well as the doubling of serum creatinine and ESRF as a secondary endpoint [62].

Treatment with renin inhibitor

The biochemical consequences of renin inhibition differ from those of ACEI and ARB, particularly in terms of angiotensin profiles and interactions with the bradykinin-nitric oxide-cGMP pathway and possibly the (pro)renin receptor. The renin inhibitor aliskiren reduces angiotensin I and II, and (unlike ACEI and ARB) the levels of plasma renin activity, a potential considered cardiovascular risk factor [63, 64]. Aliskiren represents the first in a novel class of renin inhibitors. It is a highly potent and selective inhibitor of human renin in vitro and in vivo; once-daily oral doses of aliskiren inhibit renin and lower BP in sodium-depleted marmosets and hypertensive human patients. The drug has a high solubility in water and biological fluids and is a nonpeptide drug suitable for oral administration [22, 65–68].

Aliskiren ameliorated organ damage, lowered BP and albuminuria, and normalized serum creatinine in transgenic rats for human renin and angiotensinogen genes [25] and provides similar renoprotection as compared with an ARB in a rat model of hypertensive nephropathy [23].

Studies in humans attest to an effective antihypertensive effect comparable to ACEIs, ARBs, diuretics, and amlodipine with no side-effects at the dosage of 300 mg daily and the option of combination with other antihypertensives [69–71]. Randomized clinical trials in patients with cardiovascular and renal diseases are also in progress.

Limitations of the use of drugs inhibiting the RAAS

ACEIs and ARBs are widely used in CKD patients. These agents have the advantage of being well tolerated, and moreover, they do not worsen the insulin resistance and the associated metabolic abnormalities in lipid and carbohydrate metabolism [70, 72]. However, a number of side-effects do occur and include hypotension, acute renal failure especially in patients with bilateral renal-artery stenosis, and hyperkalemia [1, 57, 71, 73]. The combination of ACEIs with nonsteroidal anti-inflammatory drugs is one of the main causes of drug induced acute renal failure, especially in the elderly population [72, 74]. Since cardiac failure, mild renal failure and hypertension often coincide with chronic pain, co-prescription of an ACEI or ARB with a nonsteroidal anti-inflammatory drug is not infrequent and can lead to functional renal insufficiency. Moreover, since sodium depletion is a precipitating factor, addition of a diuretic increases the risk of renal failure [73, 75]. Therefore, drug combinations of ACEIs and ARBs with nonsteroidal anti-inflammatory drugs and diuretics (a combination referred to as ‘triple whammy’ due to its adverse effect), should be avoided, especially in the elderly population. Finally, there are conflicting reports concerning the effect of ACEIs and ARBs on the risk of contrast nephropathy. Gupta et al. showed that the use of ACEIs may protect against contrast nephropathy [76]. However, other retrospective and prospective studies suggest that ACEIs and ARBs can deteriorate renal function [77–79] especially in the elderly patients [80]. The effect of continuing or discontinuing chronic therapy with an ACEI or ARB on the incidence of contrast nephropathy prior to coronary angiography was more recently evaluated [81]. Of note, the findings of the above prospective randomized trial suggest that among patients with CKD stages 3–4 withdrawal or not of these drugs 24 h prior to angiography did not significantly change the rate of contrast-induced nephropathy. Further more the incidence rate was 6.2%, 3.7%, and 6.3% for the continuation, discontinuation, and RAS blockade naïve group, respectively. According to these results the authors conclude that in CKD patients it is not necessary to discontinue these class of drugs before angiography, as has been previously suggested [82, 83]. Regarding the renin inhibitor aliskiren, this drug is also likely to have the same contraindications as ACEIs and ARBs.

The role of BP target level in renoprotection

According to the guidelines [59, 84] BP of less than 130/80 mmHg is recommended for CKD nondialysis patients in order to receive the greatest reno-cardioprotection. Moreover, lower values to at least 120/80 mmHg have recently been advised, particularly when proteinuria is present [11]. However, as stated

in the latest guidelines [11] and also as experienced in everyday clinical practice, the achievement of the suggested very low BP control usually requires the combination of two to three drugs, especially in patients with CKD [85, 86].

The value of levels of BP has been investigated in the African American Study of Kidney Disease and Hypertension (AASK). This study compared two levels of BP in patients treated with an ACEI [87]. A lower BP goal did not reduce the mean decline in GFR or the risk for the composite outcome of reduction in GFR of at least 50%, kidney failure, or all-cause mortality during median follow-up of 4 years when compared with a usual BP goal. However, in that study the primary renal disease was hypertensive nephrosclerosis and the median baseline proteinuria was very low.

In a meta-analysis of 11 randomized, controlled trials with 1,860 patients comparing the efficacy of antihypertensive drugs in CKD nondiabetic patients Jafar et al. found that systolic BP of 110–129 mmHg but not levels of diastolic BP and urine protein excretion less than 2.0 g/d were associated with the lowest risk for kidney disease progression. Antihypertensive regimens that included ACEIs were more effective in slowing the progression of kidney disease than were regimens that did not include ACEIs. It is of interest however, that systolic BP less than 110 mmHg was associated with a higher risk for kidney disease progression [88].

In the systematic review and meta-analysis of Casas et al. [20] the effects of ACEIs or ARBs in 127 placebo-controlled trials were compared with the effects seen with an active comparator drug. Although the comparisons of ACEIs or ARBs with other antihypertensive drugs yielded a significant relative risk for doubling of serum creatinine and a small benefit on ESRF in favor of the two drugs it is concluded that the benefits probably result from a blood-pressure-lowering effect. In addition, in patients with diabetes, additional renoprotective actions of these substances beyond lowering blood pressure remain unproven, and there is uncertainty about the greater renoprotection seen in nondiabetic renal disease. However, the meta-analysis received a large correspondence of criticism, mainly due to the different sizes of the various studies, concern about the included patients, but also to the inclusion criteria that had been used.

From the above studies, it is evident that the progression of CKD to ESRF is dependent not only on the type of antihypertensive drugs and the target of BP but also on the degree of proteinuria and the presence of diabetes. Especially in patients with diabetes the presence or not of proteinuria at the initial diagnostic screen plays a very important role in the progression of renal damage. Last year Schrier et al. [89] published the summary of the hypertensive and normotensive Appropriate Blood Pressure Control in Diabetes type 2 (ABCD) trial, an interventional clinical trial with 5 years of follow-up that examined the role of intensive versus standard BP control in a total of 950 patients with type 2 diabetes mellitus. The results of the normotensive ABCD study included associations between intensive BP control and significant slowing of the progression of nephropathy (as assessed by urinary albumin excretion). In patients with normoalbuminuria (<30 mg/24 h) or microalbuminuria (30–300 mg/24 h) at baseline, mean renal function remained stable during 5 years in both the intensive and the moderate BP control groups. By contrast, the rate of creatinine clearance in patients with overt diabetic nephropathy (>300 mg/24 h albuminuria) at baseline dropped by an average of 5 ml/min/year in both groups. The progression from normoalbuminuria to microalbuminuria and from microalbuminuria to overt diabetic nephropathy was markedly slower in the intensive than in the moderate BP group independently of the type of the antihypertensive used (nisoldipine or enalapril). In the hypertensive group of patients with normoalbuminuria (<30 mg/24 h) or microalbuminuria (30–300 mg/24 h) at baseline, mean renal function remained stable during 5 years of either intensive or standard BP intervention. By contrast, the rate of creatinine clearance in patients with overt diabetic nephropathy (>300 mg/24 h albuminuria) at baseline decreased by an average of 5 ml/min/year in spite of either intensive or standard BP control, although the patients were receiving the ACEI enalapril.

In 1994, the results of the Modification of Diet in Renal Disease (MDRD) study were published. A low target BP (less than 125/75 mmHg) did not produce a slower projected mean decline in GFR at 3 years compared with the usual target BP. However, patients with greater proteinuria significantly benefited from the low target BP [90]. On the other hand, in the long-term follow-up of the MDRD study [91], 840 patients

with predominantly nondiabetic kidney disease and a glomerular filtration rate of 13–55 ml/min per 1.73 m^2 were evaluated approximately 10 years later. Assignment to a low target BP (mean arterial pressure <92 mmHg) slowed significantly the cumulative probability of kidney failure and the composite outcome (kidney failure or all-cause mortality) compared with the usual target BP group (mean arterial pressure <107 mmHg). During the trial, 51% of participants in the low target BP and 32% of participants in the high target BP group received ACEIs for more than 50% of follow-up visits. However, sensitivity analysis for use of ACEIs did not substantially change the results.

In the early 1990s, Parving et al. [92] showed that effective antihypertensive treatment postpones renal insufficiency in diabetic nephropathy. The effect of long-term aggressive antihypertensive treatment with a combination of drugs such as metoprolol, hydralazine, and furosemide on kidney function in diabetic nephropathy was studied prospectively in 11 insulin-dependent diabetics (mean age 30 years). During the mean pretreatment period of 32 (range 23–66) months, glomerular filtration rate decreased significantly and albuminuria and the arterial BP increased also significantly. During the 72 (range 32–91) month period of antihypertensive treatment with the above drugs, the average arterial BP fell from 143/96 mmHg to 129/84 mmHg and albuminuria decreased from 1,038 to 504 micrograms/min. The rate of decline in the glomerular filtration rate decreased from 0.89 (range 0.44–1.46) ml/min/month before treatment to 0.22 (range 0.01–0.40) ml/min/month during treatment. The rate of decline in the GFR was significantly smaller during the second 3 years compared with the first 3 years in patients who received long-term antihypertensive treatment (greater than or equal to 6 years).

In conclusion, control of BP in CKD patients at targets lower than these suggested for patients with uncomplicated hypertension is mandatory for the delay of kidney disease progression or the development of CKD in cases of diabetes. As others, we suggest that the inhibition of RAAS is a reliable tool for the treatment of CKD patients [19]. However, during follow-ups and especially in elderly patients, checks for adverse effects should be performed with meticulous attention. Combination of the RAAS inhibitors is more effective in patients with heavier proteinuria yet the combination of more than two or three antihypertensive drugs of different categories is needed for the achievement of very low BP levels in most CKD patients. Finally, as practising nephrologists we should also consider integrated care of CKD patients with treatment or improvement of all preventable and modifiable risk factors for CKD progression [93, 94].

References

1. USRD 2006 ADR/reference tables. Available at: http://www.usrds.org/reference_2006.htm 2008
2. El-Nahas M (2005) The global challenge of chronic kidney disease. Kidney Int 68:2918–2929
3. Ishani A, Grandits GA, Grimm RH, Svendsen KH, Collins AJ, Prineas RJ, Neaton JD (2006) Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. J Am Soc Nephrol 17:1444–1452
4. Perry HM Jr, Miller JP, Fornoff JR, Baty JD, Sambhi MP, Rutan G, Moskowitz DW, Carmody SE (1995) Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension 25:587–594
5. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G (1998) Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril efficacy in nephropathy. Lancet 352:1252–1256
6. Schaeffner ES, Kurth T, Bowman TS, Gelber RP, Gaziano JM (2007) Blood pressure measures and risk of chronic kidney disease in men. Nephrol Dial Transplant 4:1246–1251
7. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS (2003) Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 41:1–12
8. Willenheimer R, Dahlof B, Rydberg E et al (1999) AT1-receptor blockers in hypertension and heart failure: clinical experience and future directions. Eur Heart J 20:997–1008
9. Karalliedde J, Viberti G (2006) Evidence for renoprotection by blockade of the renin–angiotensin–aldosterone system in hypertension and diabetes. J Hum Hypertens 20:239–253
10. Zanchetti A, Ruilope LM (2002) Antihypertensive treatment in patients with type–2 diabetes mellitus: what guidance from recent controlled randomized trials? J Hypertens 20:2099–2110
11. Mancia G, De BG, Dominiczak A, Cifkova R et al (2007) 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 25:1105–1187
12. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia) (1997) Randomised placebo-controlled trial

of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 349:1857–1863
13. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, RENAAL Study Investigators (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345:861–869
14. Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF (1993) Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. Ann Intern Med 118:129–138
15. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G (1998) Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). Kidney Int 53:1209–1216
16. Ruggenenti P, Fassi A, Ilieva AP et al (2004) Preventing microalbuminuria in type 2 diabetes. N Engl J Med 351:1941–1951
17. Suissa S, Hutchinson T, Brophy JM, Kezouh A (2006) ACE-inhibitor use and the long-term risk of renal failure in diabetes. Kidney Int 69:913–919
18. Covic A, Gusbeth-Tatomir P, Goldsmith DJ (2007) Current dilemmas in inhibiting the renin–angiotensin system: do not forget real life. Int Urol Nephrol 39:571–576
19. Rossing P, Parving HH, de Zeeuw D (2006) Renoprotection by blocking the RAAS in diabetic nephropathy–fact or fiction? Nephrol Dial Transplant 21:2354–2357
20. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, MacAllister RJ (2005) Effect of inhibitors of the renin–angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet 366:2026–2033
21. Luft FC, Weinberger MH (2007) Antihypertensive therapy with aliskiren. Kidney Int. doi:10.1038/sjki5002732
22. Luther RR, Glassman HN, Boger RS (1991) Renin inhibitors in hypertension. Clin Nephrol 36:181–186
23. Muller DN, Luft FC (2006) Direct renin inhibition with aliskiren in hypertension and target organ damage. Clin J Am Soc Nephrol 1:221–228
24. Oh BH (2007) Aliskiren, the first in a new class of direct renin inhibitors for hypertension: present and future perspectives. Expert Opin Pharmacother 8:2839–2849
25. Pilz B, Shagdarsuren E, Wellner M, Fiebeler A, Dechend R, Gratze P, Meiners S, Feldman DL, Webb RL, Garrelds IM, Jan Danser AH, Luft FC, Müller DN (2005) Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. Hypertension 46:569–576
26. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD (1993) The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 329:1456–1462
27. Tarnow L, Rossing P, Jensen C, Hansen BV, Parving HH (2000) Long-term renoprotective effect of nisoldipine and lisinopril in type 1 diabetic patients with diabetic nephropathy. Diabetes Care 23:1725–1730
28. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP, Remuzzi G (1999) Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 354:359–364
29. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, Ponticelli C, Ritz E, Zucchelli P (1996) Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The angiotensin-converting-enzyme inhibition in progressive renal insufficiency study group. N Engl J Med 334: 939–945
30. Parving HH, Hovind P, Rossing K (2001) Evolving strategies for renoprotection: diabetic nephropathy. Curr Opin Nephrol Hypertens 10:515–522
31. Mogensen CE (1984) Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 310:356–360
32. Nelson RG, Knowler WC, Pettitt DJ, Saad MF, Charles MA, Bennett PH (1991) Assessment of risk of overt nephropathy in diabetic patients from albumin excretion in untimed urine specimens. Arch Intern Med 151:1761–1765
33. Bigazzi R, Bianchi S, Baldari D, Campese VM (1998) Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. J Hypertens 16:1325–1333
34. de Leeuw PW, Ruilope LM, Palmer CR, Brown MJ, Castaigne A, Mancia G, Rosenthal T, Wagener G (2004) Clinical significance of renal function in hypertensive patients at high risk: results from the INSIGHT trial. Arch Intern Med 164:2459–2464
35. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S, HOPE Study Investigators (2001) Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 286:421–426
36. Jager A, Kostense PJ, Ruhé HG, Heine RJ, Nijpels G, Dekker JM, Bouter LM, Stehouwer CD (1999) Microalbuminuria and peripheral arterial disease are independent predictors of cardiovascular and all-cause mortality, especially among hypertensive subjects: five-year follow-up of the Hoorn Study. Arterioscler Thromb Vasc Biol 19:617–624
37. Jensen JS, Feldt-Rasmussen B, Strandgaard S, Schroll M, Borch-Johnsen K (2000) Arterial hypertension, microalbuminuria, and risk of ischemic heart disease. Hypertension 35:898–903
38. Sarnak MJ, Levey AS, Schoolwerth AC et al (2003) Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association councils on kidney in cardiovascular disease high blood pressure research, clinical cardiology and epidemiology and prevention. Circulation 108:2154–2169
39. Wachtell K, Ibsen H, Olsen MH et al (2003) Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med 139:901–906
40. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. N Engl J Med 342:145–153
41. The EUCLID Study Group (1997) Randomised placebo-controlled trial of lisinopril in normotensive patients with

insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet 349:1787–1792
42. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R (1998) Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 128:982–988
43. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, Jiang JP, Liang M, Wang GB, Liu ZR, Geng RW (2006) Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 354:131–140
44. Berl T, Hunsicker LG, Lewis JB et al (2003) Cardiovascular outcomes in the Irbesartan diabetic nephropathy trial of patients with type 2 diabetes and overt nephropathy. Ann Intern Med 138:542–549
45. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 345:870–878
46. Viberti G, Wheeldon NM (2002) Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 106:672–678
47. Kunz R, Friedrich C, Wolbers M, Mann JF (2008) Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med 148:30–48
48. Andersen S, Rossing P, Juhl TR, Deinum J, Parving HH (2002) Optimal dose of losartan for renoprotection in diabetic nephropathy. Nephrol Dial Transplant 17:1413–1418
49. Hollenberg NK, Parving HH, Viberti G, Remuzzi G, Ritter S, Zelenkofske S, Kandra A, Daley WL, Rocha R (2007) Albuminuria response to very high-dose valsartan in type 2 diabetes mellitus. J Hypertens 25:1921–1926
50. Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving HH (2005) Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. Kidney Int 68:1190–1198
51. Schmieder RE, Klingbeil AU, Fleischmann EH, Veelken R, Delles C (2005) Additional antiproteinuric effect of ultrahigh dose candesartan: a double-blind, randomized, prospective study. J Am Soc Nephrol 16:3038–3045
52. Laverman GD, Navis G, Henning RH, de Jong PE, de Zeeuw D (2002) Dual renin–angiotensin system blockade at optimal doses for proteinuria. Kidney Int 62:1020–1025
53. Matchar DB, McCrory DC, Orlando LA, Patel MR, Patel UD, Patwardhan MB, Powers B, Samsa GP, Gray RN (2008) Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med 148:16–29
54. Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J; Diabetics Exposed to Telmisartan and Enalapril Study Group (2004) Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 351:1952–1961
55. Bakris GL, Ruilope L, Locatelli F, Ptaszynska A, Pieske B, de Champlain J, Weber MA, Raz I (2007) Treatment of microalbuminuria in hypertensive subjects with elevated cardiovascular risk: results of the IMPROVE trial. Kidney Int 72:879–885
56. Kincaid-Smith P, Fairley K, Packham D (2002) Randomized controlled crossover study of the effect on proteinuria and blood pressure of adding an angiotensin II receptor antagonist to an angiotensin converting enzyme inhibitor in normotensive patients with chronic renal disease and proteinuria. Nephrol Dial Transplant 17:597–601
57. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T (2003) Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet 361:117–124
58. Kincaid-Smith P, Fairley KF, Packham D (2004) Dual blockade of the renin–angiotensin system compared with a 50% increase in the dose of angiotensin-converting enzyme inhibitor: effects on proteinuria and blood pressure. Nephrol Dial Transplant 19:2272–2274
59. Kidney Disease Outcome Quality Initiative (2004) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43(5 Suppl 1):S65–S230
60. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK, AVOID Study Investigators (2008) Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 358(23):2433–2446
61. Toto R, Palmer BF (2007) Rationale for combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor treatment and end-organ protection in patients with chronic kidney disease. Am J Nephrol 28:372–380
62. Teo K, Yusuf S, Sleight P et al (2004) Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. Am Heart J 148:52–61
63. Azizi M, Webb R, Nussberger J, Hollenberg NK (2006) Renin inhibition with aliskiren: where are we now, and where are we going? J Hypertens 24:243–256
64. Brewster UC, Setaro JF, Perazella MA (2003) The renin–angiotensin–aldosterone system: cardiorenal effects and implications for renal and cardiovascular disease states. Am J Med Sci 326:15–24
65. Stanton A (2003) Therapeutic potential of renin inhibitors in the management of cardiovascular disorders. Am J Cardiovasc Drugs 3:389–394
66. Stanton A, Jensen C, Nussberger J, O'Brien E (2003) Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. Hypertension 42:1137–1143
67. Stanton A (2003) Potential of renin inhibition in cardiovascular disease. J Renin Angiotensin Aldosterone Syst 4:6–10
68. Wood JM, Maibaum J, Rahuel J et al (2003) Structure-based design of aliskiren, a novel orally effective renin inhibitor. Biochem Biophys Res Commun 308:698–705
69. Drummond W, Munger MA, Rafique EM (2007) Antihypertensive efficacy of the oral direct Renin inhibitor aliskiren as add-on therapy in patients not responding to

amlodipine monotherapy. J Clin Hypertens (Greenwich) 9:742–750
70. O'Brien E, Barton J, Nussberger J, Mulcahy D, Jensen C, Dicker P, Stanton A (2007) Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. Hypertension 49:276–284
71. Oparil S, Yarows SA, Patel S, Fang H, Zhang J, Satlin A (2007) Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet 370:221–229
72. Berne C, Pollare T, Lithell H (1991) Effects of antihypertensive treatment on insulin sensitivity with special reference to ACE inhibitors. Diabetes Care 14(Suppl 4):39–47
73. Kostis JB, Shelton B, Gosselin G, Goulet C, Hood WB Jr, Kohn RM, Kubo SH, Schron E, Weiss MB, Willis PW 3rd, Young JB, Probstfield J (1996) Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). SOLVD Investigators. Am Heart J 131:350–355
74. Baraldi A, Ballestri M, Rapanà R, Lucchi L, Borella P, Leonelli M, Furci L, Lusvarghi E (1998) Acute renal failure of medical type in an elderly population. Nephrol Dial Transplant 13(Suppl 7):25–29
75. Loboz KK, Shenfield GM (2005) Drug combinations and impaired renal function—the 'triple whammy'. Br J Clin Pharmacol 59:239–243
76. Gupta RK, Kapoor A, Tewari S, Sinha N, Sharma RK (1999) Captopril for prevention of contrast-induced nephropathy in diabetic patients: a randomised study. Indian Heart J 51:521–526
77. Bakris GL, Weir MR (2000) Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 160:685–693
78. Cirit M, Toprak O, Yesil M, Bayata S, Postaci N, Pupim L, Esi E (2006) Angiotensin-converting enzyme inhibitors as a risk factor for contrast-induced nephropathy. Nephron Clin Pract 104:c20–c27
79. Toprak O, Cirit M, Bayata S, Yesil M, Aslan SL (2003) The effect of pre-procedural captopril on contrast-induced nephropathy in patients who underwent coronary angiography. Anadolu Kardiyol Derg 3:98–103
80. Mahajan S, Tiwari S, Bhowmik D, Agarwal SK, Tiwari SC, Dash SC (2006) Factors affecting the outcome of acute renal failure among the elderly population in India: a hospital based study. Int Urol Nephrol 38:391–396
81. Rosenstock JL, Bruno R, Kim JK, Lubarsky L, Schaller R, Panagopoulos G, DeVita MV, Michelis MF (2008) The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. Int Urol Nephrol. doi:10.1007/s11255-008-9368-1
82. Gami AS, Garovic VD (2004) Contrast nephropathy after coronary angiography. Mayo Clin Proc 79:211–219
83. Maeder M, Klein M, Fehr T, Rickli H (2004) Contrast nephropathy: review focusing on prevention. J Am Coll Cardiol 44:1763–1771
84. Chobanian AV, Bakris GL, Black HR et al (2003) The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289:2560–2572
85. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J (2000) Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis 36:646–661
86. Koshy S, Bakris GL (2000) Therapeutic approaches to achieve desired blood pressure goals: focus on calcium channel blockers. Cardiovasc Drugs Ther 14:295–301
87. Wright JT Jr, Bakris G, Greene T et al (2002) Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 288:2421–2431
88. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS, AIPRD Study Group (2003) Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med 139:244–252
89. Schrier RW, Estacio RO, Mehler PS, Hiatt WR (2007) Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. Nat Clin Pract Nephrol 3:428–438
90. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, Striker G (1994) The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med 330:877–884
91. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, Levey AS (2005) The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. Ann Intern Med 142:342–351
92. Parving HH, Andersen AR, Smidt UM, Hommel E, Mathiesen ER, Svendsen PA (1987) Effect of antihypertensive treatment on kidney function in diabetic nephropathy. Br Med J (Clin Res Ed) 294:1443–1447
93. Brenner BM (2003) Retarding the progression of renal disease. Kidney Int 64:370–378
94. Covic A, Gusbeth-Tatomir P, Goldsmith DJ (2007) Current dilemmas in inhibiting the renin-angiotensin system: do not forget real life. Int Urol Nephrol 39(2):571–576