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REVIEW

Emerging drug combinations to optimize renovascular protection and blood pressure goals

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Abstract: Hypertension and renal disease are closely related. In fact, there is an inverse linear relationship between renal function and prevalence of hypertension. Hypertensive patients with renal dysfunction exhibit a poor clinical profile, which markedly increases their risk for cardiovascular outcomes. This review considers the available evidence on the best therapeutic approach for optimizing renovascular protection in the hypertensive population. To effectively reduce or at least slow the establishment and progression of renal disease in the hypertensive population it is critical to reach blood pressure targets. Many studies have shown that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prevent or at least delay the development of microalbuminuria in patients with hypertension and type 2 diabetes, reduce the incidence of overt diabetic nephropathy, and are also beneficial in patients with nondiabetic renal disease. Therefore, renin-angiotensin system (RAS) inhibition plays a key role in the prevention of renal outcomes. As the majority of patients with hypertension will need at least two antihypertensive agents to achieve blood pressure goals, the use of RAS inhibitors is a mandatory part of antihypertensive therapy. The question of which antihypertensive agent is the best choice for combining with RAS blockers should be considered. Many studies have shown that diuretics and calcium channel blockers are the best choice. However, more studies are needed to clarify the subgroups of patients who will benefit more from a combination with a diuretic or from a combination with a calcium channel blocker. To date, RAS inhibitors recommended in this context are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Aliskiren, the first oral direct renin inhibitor available, has shown promising results.

Keywords: antihypertensive drugs, renin-angiotensin system, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, combined therapy

Hypertension and renal disease

Hypertension is the most important modifiable risk factor for cardiovascular disease. It has been estimated that about 30% of the general population is hypertensive, a proportion that increases to two-thirds in the elderly.[1] Remarkably, this prevalence is increased in patients with renal insufficiency. Thus, in a large cohort of Spanish patients enrolled in an ongoing prospective, observational, multicenter study of patients with stage 3 (n = 434) and 4 (n = 695) chronic kidney disease, hypertension was almost universal (91.2% and 94.1%, respectively). Moreover, proteinuria (>300 mg/day) was present in more than 60% of patients, without significant differences between stages 3 and 4 (1.2 ± 1.8 and 1.3 ± 1.8 g/day, respectively).[2] In fact, there is an inverse linear relationship between renal function and prevalence of hypertension (from 66% at a glomerular filtration rate of 83 mL/minute per 1.73 m^2 of body surface area to 95% at

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a glomerular filtration rate of 12 mL/minute per 1.73 m^2 of body surface area).[3] In patients with diabetic nephropathy, the prevalence of hypertension ranges from 41% in subjects with type 1 diabetes to 93% in those with type 2 diabetes and proteinuria.[4,5] Therefore, hypertension and kidney health are closely related. Hypertension is one of the main causes of renal disease, and hypertension is more prevalent in patients with a decreased renal function.[6]

There is an inverse relationship between renal function and the risk of cardiovascular disease.[7] This relationship was first demonstrated in patients with end-stage renal disease. Thus, about 40%–75% of patients on dialysis have cardiovascular disease, and around 50% of these patients die from this condition. Overall, patients with end-stage renal disease have an increased risk, up to 20–30 times, of developing cardiovascular disease when compared with the general population.[8–11] There is also a clear relationship between moderate renal disease and cardiovascular disease. In the HOPE (Heart Outcomes and Prevention Evaluation) study, ramipril significantly reduced the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who were not known to have a low ejection fraction or heart failure. In a post hoc analysis, the risk of myocardial infarction was higher for patients with a baseline serum creatinine level ≥1.4 mg/dL (n = 980) than for those with a serum creatinine level <1.4 mg/dL (n = 8307).[12] In the Hypertension Optimal Treatment study involving 18,597 patients, at baseline there were 470 patients who had a serum creatinine level higher than 1.5 mg/dL. Those patients with a high serum creatinine level at randomization more frequently had a history of myocardial infarction or other sequelae of coronary heart disease, stroke, and diabetes mellitus than those with a serum creatinine level ≤1.5 mg/dL.[13] Moreover, cardiac structure alterations are more frequent in patients with renal insufficiency. Thus, left ventricular hypertrophy is more common in subjects with a creatinine clearance <30 mL/minute (38%) than in those with a creatinine clearance >30 mL/minute (16%).[14]

Furthermore, hypertensive patients with renal dysfunction exhibit a poor clinical profile, which markedly increases their risk for cardiovascular outcomes. Thus, in a study involving 2024 patients with hypertension and chronic ischemic heart disease, those patients with an estimated glomerular filtration rate (using the Modification of Diet in Renal Disease study formula) <60 mL/minute per 1.73 m^2 of body surface area (n = 666; 32.9%) were older and had a higher proportion of atrial fibrillation, diabetes, organ damage (left ventricular hypertrophy), associated clinical conditions (heart failure, cerebrovascular disease), and worse blood pressure (BP) control rates.[15]

The diagnosis of hypertension-induced renal damage in hypertensives is based not only on reduced renal function but also on increased urinary excretion of albumin.[11] This is very relevant, as it is well established that any degree of albuminuria is associated with a higher risk of cardiovascular disease and progression of kidney disease. In fact, there is a continuous relationship between urinary albumin excretion and cardiovascular disease.[16–18] Therefore, a reduced glomerular filtration rate and an increased urinary albumin excretion markedly raise cardiovascular risk, particularly so when both alterations are present.[19] As a result, the prevention of development of either microalbuminuria or renal dysfunction are two essential targets in patients with hypertension.[1,11]

Importance of BP control

Hypertension is related not only to the development but also to the progression of renal disease. Several studies have analyzed the factors influencing the progression to chronic renal disease. Although many factors such as age, male gender, HbA1c in diabetics, smoking, obesity or hypercholesterolemia have been involved, BP control and proteinuria are the most important.[20–22] In the Multiple Risk Factor Intervention Trial, which involved 332,544 men between the ages of 35 and 57 years who were screened between 1973 and 1975, after a 16-year follow-up 814 subjects had either died of end-stage renal disease or were being treated for that condition (15.6 cases per 100,000 person-years of observation). A strong, graded relationship between both systolic and diastolic BP and end-stage renal disease was identified. Moreover, as compared with men with an optimal level of BP (<120/80 mmHg), the relative risk of end-stage renal disease for those with higher BP values (≥210/120 mmHg) was 22.1 ($P < 0.001$).[23] In a US study performed in California, after 8,210,431 person-years of follow-up, and on 316,675 subjects with an estimated glomerular filtration rate ≥60 mL/minute per 1.73 m^2 of body surface area and negative dipstick urinalysis results for proteinuria or hematuria, 1149 cases of end-stage renal disease occurred. Compared with subjects with a BP <120/80 mmHg, the relative risks for developing end-stage renal disease were 1.62 for BP of 120–129/80–84 mmHg, 1.98 for BP of 130–139/85–89 mmHg, 2.59 for BP of 140–159/90–99 mmHg, 3.86 for BP of 160–179/100–109 mmHg, 3.88 for BP of 180–209/110–119 mmHg, and 4.25 for BP of ≥210/120 mmHg.[22] With regard to BP components, it has been observed that systolic BP is a stronger predictor of end-stage renal disease than diastolic BP or pulse pressure.[24]

The Modification of Diet in Renal Disease study examined the effects of dietary protein restriction and strict BP control on the decline in glomerular filtration rate in 840 patients with diverse renal diseases. In the multivariate analysis, six factors (greater urine protein excretion, diagnosis of polycystic kidney disease, lower serum transferrin, higher mean arterial pressure, black ethnicity, and lower serum high-density lipoprotein cholesterol) independently predicted a faster decline in glomerular filtration rate. A low BP intervention was found to have greater benefit in patients with higher levels of baseline urine protein.[20] Different meta-analyses have shown in diabetics and nondiabetics that BP control slows progression of renal disease.[25,26] A meta-analysis by Jafar et al[26] analyzed eleven randomized controlled trials comparing the efficacy of antihypertensive regimens with or without angiotensin-converting enzyme (ACE) inhibitors for patients with predominantly nondiabetic kidney disease. The paper reported that a systolic BP goal between 110 and 129 mmHg may be beneficial in patients with urine protein excretion levels greater than 1.0 g/day. However, a systolic BP <110 mmHg may be associated with a higher risk of kidney disease progression.[26]

All these data emphasize the importance of attaining BP goals in the hypertensive population to avoid or at least slow the development or progression of renal disease. The question of what the BP goals should be, not only in the overall hypertensive population but also in high-risk patients, should be considered. The 2007 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension established that BP should be reduced to at least <140/90 mmHg, and to lower values, if tolerated, in all hypertensive patients. Target BP should be at least <130/80 mmHg in diabetics and in high- or very-high-risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria).[1] The reappraisal of European guidelines, published in 2009, indicates that there is sufficient evidence to recommend a BP goal below 140/90 mmHg in each hypertensive patient. However, on the basis of current data, it may be prudent to recommend lowering BP to values within the range 130–139/80–85 mmHg, and possibly closer to the lower values in this range, in every hypertensive.[27] National Institute for Health and Clinical Excellence guidelines recommend a BP goal <140/90 mmHg in the overall hypertensive population and <140/80 mmHg in diabetics (or <130/80 mmHg if kidney, eye, or cerebrovascular damage is present).[28] The Canadian guidelines establish that in hypertensive patients without other compelling indications, the BP goal should be <140/90 mmHg, as well as in hypertensive patients with a history of cardiovascular disease (coronary artery disease, previous myocardial infarction, heart failure, left ventricular hypertrophy, past stroke/transient ischemic attack or peripheral arterial disease). In patients with diabetes with/without albuminuria, nondiabetic chronic kidney disease with proteinuria or renovascular disease, the target BP should be <130/80 mmHg.[29]

A recent systematic review analyzed what should be the optimal BP target in patients with chronic kidney disease. For this purpose, three trials with a total of 2272 participants were included. Overall, trials did not show that a BP target <125/75–130/80 mmHg was more beneficial than a target of <140/90 mmHg. Lower-quality evidence suggested that a lower target may be beneficial in subgroups with proteinuria >300–1000 mg/day.[30]

Although BP control rates have improved in recent years, there remains a lot of room for improvement. One of the most important reasons for the recent improvements shown is the higher use of combined therapy. On the other hand, as cardiovascular risk increases, a smaller proportion of patients attain BP goals, including those with renal dysfunction (Table 1).[31–33]

Renin-angiotensin system inhibition and renovascular protection

Although the renin-angiotensin-aldosterone system (RAS) plays a critical role in human physiology, and although angiotensin II, the RAS effector peptide, is essential for the homeostatic control of the cardiovascular system (including, among others, sodium and water balance, BP control, and cellular growth and replication), the excessive RAS activation is markedly associated with the establishment and progression of the cardiovascular continuum.[6,34,35] In fact, the excessive activation of the RAS has been implied in the progression of the entire cardiovascular disease continuum, from the early

Table 1 Percentage of patients who attain blood pressure (BP) goals according to cardiovascular risk and clinical profile

Hypertensive population attended daily by primary care physicians							
Clinical condition	**Low risk**	**Medium risk**	**High risk**	**Diabetes**	**Metabolic syndrome**	**Cardiovascular disease**	**Cardiac disease**
BP control rates	37.5%	30.2%	15.4%	6.3%	17.2%	25.3%	27.4%

Note: Data from the PRESCOT (Prevención Cardiovascular en España en Atención Primaria: Intervención Sobre el Colesterol en Hipertensión) study (adapted from Barrios[32]).

stages (hypertension and diabetes) to the middle (left ventricular hypertrophy and microalbuminuria) and late stages (coronary disease, stroke, heart failure, and renal disease).[6]

In the case of the kidneys, at the beginning, and through different mechanisms such as oxidative stress, angiotensin II promotes subclinical damage to glomerular endothelium that results in endothelial dysfunction. Thereafter, because of vascular sclerosis and the glomerulosclerosis, tubulointerstitial fibrosis, which implies a progressive deterioration of the glomerular capillary barrier and the hemodynamic abnormalities in the vasculature at the glomerular level, microalbuminuria appears. As a result, microalbuminuria is an early manifestation of renal damage in patients with hypertension, particularly in diabetics. If treatment is not applied, renal damage progresses to macroalbuminuria or proteinuria. In this context, the glomerular filtration rate progressively declines to the final stages of renal disease. This gradual decline in renal function is associated with an increased risk of cardiovascular disease. Therefore, excess angiotensin II production is responsible, at least in part, for the establishment and development of hypertension and renal damage.[6,35–37]

However, despite the knowledge about the importance of the RAS in the development of cardiovascular disease provided, at least in part, from experimental data, and despite the fact that high renin activity is associated with cardiovascular outcomes, the most robust evidence has come from clinical trials using ACE inhibitors, angiotensin receptor blockers (ARBs) and, in recent years, aliskiren – the first oral direct renin inhibitor.[6,38–40]

Some trials have analyzed the effects of RAS inhibition in the prevention of microalbuminuria in patients with hypertension and type 2 diabetes. The BENEDICT (Bergamo Nephrologic Diabetes Complications Trial) study reported that in subjects with type 2 diabetes and hypertension but with normoalbuminuria, the use of trandolapril plus verapamil (5.7%) and trandolapril alone (6.0%) decreased the incidence of microalbuminuria to a similar extent. However, the effect of verapamil alone (11.9%) was similar to that of placebo (10.0%).[41] In the ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) study, 4447 patients with type 2 diabetes and normoalbuminuria were randomized to receive olmesartan (at a dose of 40 mg once daily) or placebo for a median of 3.2 years. Additional antihypertensive drugs (except ACE inhibitors or ARBs) were used as needed to lower BP to <130/80 mmHg. The main results of this study showed that the target BP (<130/80 mmHg) was achieved in nearly 80% of the patients taking olmesartan and in 71% of those taking placebo (clinic BP was 3.1/1.9 mmHg lower in the olmesartan group than in the placebo group). Microalbuminuria developed in 8.2% of the patients in the olmesartan group and in 9.8% of those in the placebo group. Moreover, the time to the onset of microalbuminuria was increased by 23% with the ARB olmesartan (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.63–0.94; $P = 0.01$) (Table 2).[42]

Both ACE inhibitors and ARBs have been shown to reduce the incidence of overt diabetic nephropathy. Thus, in the 3577 people with diabetes included in the HOPE study, ramipril reduced the risk of overt nephropathy by 24% ($P = 0.027$) when compared with placebo, and this effect was greater than that attributable to the decrease in BP.[43] In the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study, irbesartan was shown to be renoprotective independently of its BP-lowering effect in patients with type 2 diabetes and microalbuminuria.[44] In the RENAAL (Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) trial, 1513 patients with type 2 diabetes and nephropathy were randomized to receive losartan (50–100 mg once daily) or placebo, both taken in addition to conventional antihypertensive treatment. Over a mean treatment period of 3.4 years, the composite primary end point of a doubling of serum creatinine concentration, end-stage renal disease, or death occurred in 327 and 359 patients assigned to losartan and placebo, respectively (risk reduction, 16%; 95% CI, 2%–28%; $P = 0.02$).[45] The Irbesartan in Diabetic Nephropathy Trial compared the renoprotective efficacy of irbesartan 300 mg, amlodipine 10 mg, and placebo in 1715 hypertensive patients with nephropathy caused by type 2 diabetes. Over the mean follow-up period of 2.6 years, irbesartan reduced the risk of the primary end point (doubling of serum creatinine concentration, end-stage renal disease, or death) by 20% when compared with placebo and by 23% when compared with amlodipine. The risk of a doubling of the serum creatinine concentration was 33% and 37% lower with irbesartan than with placebo and amlodipine, respectively, and irbesartan also reduced the risk of end-stage renal disease by 23% compared with either placebo or amlodipine.[46] More recently, the ORIENT (Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial) study examined the effects of olmesartan on the primary composite outcome of doubling serum creatinine concentration, end-stage renal disease, and death in type 2 diabetic patients with overt nephropathy. A total of 577 patients treated with antihypertensive therapy (73.5% received concomitant ACE inhibitors) were

Table 2 Relevant studies that have studied the effects of renin-angiotensin system inhibition on renal outcomes

Clinical setting	Study	Population	Commentary
Prevention of microalbuminuria in patients with hypertension and type 2 diabetes	BENEDICT[41]	Subjects with type 2 diabetes and hypertension but with normoalbuminuria	The use of trandolapril plus verapamil (5.7%) and trandolapril alone (6.0%) decreased the incidence of microalbuminuria to a similar extent The effect of verapamil alone (11.9%) was similar to that of placebo (10.0%)
	ROADMAP[42]	Patients with type 2 diabetes and normoalbuminuria	Microalbuminuria developed in 8.2% of the patients in the olmesartan group and 9.8% in the placebo group Time to the onset of microalbuminuria was increased by 23% with olmesartan (HR, 0.77; $P = 0.01$)
Reduction of overt diabetic nephropathy	HOPE[43]	Patients of HOPE with diabetes	Ramipril reduced the risk of overt nephropathy by 24% ($P = 0.027$) when compared with placebo
	IRMA2[44]	Patients with type 2 diabetes and microalbuminuria	Irbesartan was shown to be renoprotective independently of its BP-lowering effect
	RENAAL[45]	Patients with type 2 diabetes and nephropathy	The composite primary end point of doubling of serum creatinine concentration, end-stage renal disease, or death was reduced with losartan when compared with placebo (risk reduction, 16%; $P = 0.02$)
	IDNT[46]	Hypertensive patients with type 2 nephropathy diabetes	Irbesartan reduced the risk of the primary end point (doubling of serum creatinine concentration, end-stage renal disease, or death) by 20% and 23%, compared with placebo and amlodipine, respectively
	ORIENT[47]	Type 2 diabetic patients with overt nephropathy	Olmesartan did not improve renal outcome on top of ACE inhibitors
	AVOID[40]	Hypertensive patients with type 2 diabetic nephropathy	Despite a small, not statistically significant difference in BP between groups, aliskiren reduced the mean urinary albumin-to-creatinine ratio by 20% ($P < 0.001$)
Nondiabetic renal disease	ROAD[51]	Patients with nondiabetic chronic renal insufficiency	Optimal antiproteinuric dosages of benazepril and losartan, at comparable BP control, achieved a greater reduction in both proteinuria and the rate of decline in renal function than with their conventional dosages

Abbreviations: ACE, angiotensin-converting enzyme; AVOID, Aliskiren in the Evaluation of Proteinuria in Diabetes; BENEDICT, Bergamo Nephrologic Diabetes Complications Trial; BP, blood pressure; HOPE, Heart Outcomes and Prevention Evaluation; HR, hazard ratio; IDNT, Irbesartan in Diabetic Nephropathy Trial; IRMA2, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria; ORIENT, Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial; RENAAL, Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; ROAD, Renoprotection of Optimal Antiproteinuric Doses; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

included. Although olmesartan was well tolerated, it did not improve renal outcome on top of ACE inhibitors.[47] Aliskiren, the last marketed RAS inhibitor, has also been tested in this context.[48] Thus, the AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes) trial was performed to assess the renoprotective effects of dual blockade of the RAS by adding treatment with aliskiren to the maximally recommended dose of losartan (100 mg daily) and optimal antihypertensive therapy in hypertensive patients with type 2 diabetic nephropathy. Despite a small, not statistically significant difference in BP between groups (–2/–1 mmHg lower in the aliskiren group), aliskiren reduced the mean urinary albumin-to-creatinine ratio by 20% ($P < 0.001$) (Table 2).[40]

Some studies have been developed in patients with nondiabetic renal disease. Thus, it has been observed that in microalbuminuric subjects, treatment with fosinopril has a significant effect on urinary albumin excretion.[49] In a study performed in patients with chronic nephropathies with proteinuria ≥3 g/day, ramipril safely reduced proteinuria and the rate of glomerular filtration rate decline to an extent that seemed to exceed the reduction expected for the degree of BP lowering.[50] The ROAD (Renoprotection of Optimal Antiproteinuric Doses) study was aimed to determine whether titration of benazepril or losartan to optimal antiproteinuric doses would safely improve the renal outcome in nondiabetic chronic renal insufficiency. The study showed that optimal antiproteinuric dosages of benazepril and losartan, at comparable BP control, achieved a greater reduction in both proteinuria and the rate of decline in renal function than their conventional dosages (Table 2).[51]

In the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) study, telmisartan was clinically equivalent to ramipril in patients

with vascular disease or high-risk diabetes.[52] In a substudy that specifically analyzed renal outcomes, the composite primary outcome (a composite of dialysis, doubling of serum creatinine concentration, and death) was similar for telmisartan and ramipril (13.4% versus 13.5%, respectively; HR, 1.00; 95% CI, 0.92–1.09). The secondary renal outcome, dialysis or doubling of serum creatinine concentration, was also similar for telmisartan and ramipril (2.21% versus 2.03%; HR, 1.09; 95% CI, 0.89–1.34). The estimated glomerular filtration rate declined least with ramipril compared with telmisartan, but the increase in urinary albumin excretion was smaller with telmisartan than with ramipril.[53]

Although there are unquestionable benefits of RAS inhibition in the prevention of renal complications in the hypertensive population (particularly in diabetics), the majority of patients with hypertension, especially those at highest risk, will need at least two antihypertensive drugs to attain BP goals.[1,33] So, since RAS inhibitors are an essential component of combined therapy, the next question to be considered is which antihypertensive drug should be associated with RAS inhibitors to better prevent or at least delay renal outcomes.

Combination of RAS inhibitors and diuretics

Diuretics (usually thiazides or thiazide-like indoline diuretics such as indapamide) have been shown to effectively reduce BP levels.[54] Moreover, in the 13,101 hypertensive patients with type 2 diabetes enrolled in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study, chlorthalidone, a thiazide-type diuretic, reduced cardiovascular outcomes to an extent similar to lisinopril or amlodipine.[55] However, diuretics may cause urinary electrolyte wasting and, secondary to this, hyponatremia, hypokalemia, and/or hypomagnesemia. Moreover, thiazide diuretics may cause metabolic disturbances, particularly at higher doses. Fortunately, the combination of RAS inhibitors with thiazide diuretics reduces both electrolyte and metabolic disturbances. Furthermore, when side effects are present they are generally mild to moderate in severity.[6] At low doses, thiazide diuretics usually do not cause changes in renal function, and they can be used when the estimated glomerular filtration rate is >30 mL/minute.[54,56]

Several studies have analyzed the effects of the combination of RAS inhibitors and diuretics on renal outcomes. Thus, it has been shown that in hypertensive patients with stage 3–4 chronic kidney disease, the combination of losartan and hydrochlorothiazide significantly reduced the urinary protein-to-creatinine ratio, without significant changes in the serum creatinine levels and estimated glomerular filtration rates. Notably, none of the patients exhibited a significant increase in the occurrence of adverse effects.[57] Similarly, in hypertensive patients with stage 3 chronic kidney disease, combination therapy with the maximum recommended daily dose of losartan of 100 mg and a low dose of hydrochlorothiazide of 12.5 mg ameliorated proteinuria and reduced BP more effectively than treatment with losartan 100 mg alone, irrespective of whether the patients had diabetes.[58] In a study that evaluated the changes in BP and urinary protein excretion in poorly controlled hypertensive and proteinuric patients with mild to moderate chronic kidney disease, patients were evaluated after switching from the high-dose ARBs to a combination of normal-dose telmisartan (40 mg) and low-dose hydrochlorothiazide (12.5 mg). The combination of telmisartan and hydrochlorothiazide appeared to be more efficacious than a monotherapy of high-dose ARBs in reducing BP and urinary protein excretion.[59]

The PREMIER (Preterax in Albuminuria Regression) study compared the effects of the combination of perindopril 2 mg and indapamide 0.625 mg with the effects of enalapril monotherapy on albumin excretion rates in patients with type 2 diabetes, albuminuria, and hypertension in a 12-month, international, multicenter, randomized, double-blind, parallel-group study. Although both treatments reduced BP, the fixed combination of perindopril and indapamide resulted in a greater, statistically significant fall in both BP (Δsystolic BP −3.0 mmHg, $P = 0.012$; Δdiastolic BP −1.5 mmHg, $P = 0.019$) and albumin excretion rate (−42% versus −27%) than enalapril. Remarkably, the greater albumin excretion rate reduction remained significant after adjustment for mean BP (Table 3).[60]

The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation) trial was performed to assess the effects of the fixed combination of perindopril and indapamide on serious vascular events in patients with diabetes, irrespective of initial BP levels or the use of other BP-lowering drugs. A total of 11,140 patients with type 2 diabetes were randomized to treatment with the fixed combination or matching placebo, in addition to current therapy. Compared with the patients assigned placebo, after a mean of 4.3 years of follow-up, those assigned to active therapy had a mean reduction in systolic BP of 5.6 mmHg and diastolic BP of 2.2 mmHg. The relative risk of a major macrovascular or microvascular event was reduced by 9% (HR, 0.91; 95% CI, 0.83–1.00; $P = 0.04$). Active treatment was associated with a significant 21% reduction in all renal

Table 3 Relevant studies of the effects of combining diuretics or calcium channel blockers with renin-angiotensin system inhibitors on renal outcomes

Clinical setting	Study	Population	Commentary
Diuretics	PREMIER[60]	Patients with type 2 diabetes, albuminuria, and hypertension	The combination of perindopril and indapamide, when compared with enalapril, resulted in a greater, statistically significant fall in both BP (Δsystolic BP −3.0 mmHg, $P = 0.012$; Δdiastolic BP −1.5 mmHg, $P = 0.019$) and albumin excretion rate (−42% vs −27%)
	ADVANCE[61]	Patients with type 2 diabetes	Those patients assigned to active treatment (perindopril-indapamide) were associated with a significant reduction (21%) in all renal events ($P < 0.0001$), with a trend in the reduction in new or worsening nephropathy ($P = 0.055$) and a significant reduction in the development of microalbuminuria (relative risk reduction, 21%; $P < 0.0001$)
Calcium channel blockers	AMANDHA[66]	Type 2 diabetic patients with hypertension and microalbuminuria uncontrolled with renin-angiotensin system blockers	Although manidipine and amlodipine decreased BP values to a similar extent, urinary albumin excretion was more greatly reduced with manidipine than with amlodipine (65.5% vs 20%, respectively, $P < 0.01$ at 6 months; 62.7% vs 16.6%, respectively, $P < 0.01$ at the end of the extension phase of 18 months)
	CARTER[70]	Hypertensive patients with kidney disease	After 1 year of treatment, despite a similar BP reduction, the urinary protein-to-creatinine ratio significantly decreased in the cilnidipine group compared with the amlodipine group
	DIAL[75]	Hypertensive patients with type 2 diabetes	After 9–12 months of follow-up, both lercanidipine and ramipril treatments resulted in a significant reduction in albumin excretion rate without a statistically significant difference between the two treatments
	ACCOMPLISH[78]	Patients with hypertension and at high risk for cardiovascular events	2.0% of the benazepril plus amlodipine group vs 3.7% of patients treated with the benazepril plus hydrochlorothiazide showed chronic kidney disease progression (HR, 0.52; $P < 0.0001$)

Abbreviations: ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation; AMANDHA, Efficacy and Tolerance Assessment of Manidipine in Type 2 Diabetic Patients with Hypertension and Microalbuminuria Uncontrolled with Renin-Angiotensin System Blockers; BP, blood pressure; CARTER, Cilnidipine versus Amlodipine Randomised Trial for Evaluation in Renal Desease; DIAL, Diabete, Ipertensione, Albuminuria, Lercanidipina; HR, hazard ratio; PREMIER, Preterax in Albuminuria Regression; vs, versus.

outcomes ($P < 0.0001$), with a trend in the reduction in new or worsening nephropathy (3.3% versus 3.9%; relative risk reduction, 18%; $P = 0.055$), and a significant reduction in the development of microalbuminuria (19.6% versus 23.6%; relative risk reduction, 21%; $P < 0.0001$) (Table 3).[61]

In summary, volume excess has been shown to blunt the BP and albuminuria response to RAS inhibitors. Thus, acting on volume status by means of diuretic therapy effectively reduces BP and albuminuria.[62] As a result, the combination of RAS inhibitors and diuretics seems to be particularly beneficial in hypertensive patients with renal disease.

Combination of RAS inhibitors and calcium channel blockers

Combining RAS inhibitors with a calcium channel blocker has been shown to effectively reduce BP values.[1] Dihydropyridines are potent vasodilators that induce reflex activation of the RAS. As a result, the concomitant use of ACE inhibitors or ARBs may buffer this excessive activation. Furthermore, as calcium channel blockers raise angiotensin II levels, the antihypertensive effect of RAS inhibitors increases.[63] Notably, the combination of calcium channel blockers with RAS inhibitors decreases the presence of drug-related side effects, particularly peripheral edema.[64]

Although through the reduction of BP levels calcium channel blockers may reduce urinary albumin excretion, not all calcium channel blockers are equal, as they differ in their effect on glomerular hemodynamics and urinary albumin excretion.[54] Conventional dihydropyridines block only L-type calcium channels. This promotes peripheral vasodilatation, including afferent renal arterioles with little change in the efferent arteriole diameter, as the efferent arterioles lack L-type receptors. Consequently, there is an increase of intraglomerular pressure and, secondary to this, proteinuria. On the other hand, T-type calcium channel blockers are present in both afferent and efferent arterioles. Newer calcium channel blockers such as manidipine block both L- and T-type receptors, inducing vasodilatation not only

in the glomerular afferent arteriole but also in the efferent arteriole, resulting in a reduction of proteinuria.[54,65–67]

Different studies have tested the effects of combining calcium channel blockers with RAS inhibitors.[65,66,68–79] In a 12-week, double-blind study conducted in patients with hypertension and type 2 diabetes, patients were randomized either to a fixed-dose combination of amlodipine besylate and benazepril or to enalapril monotherapy. Although both treatments were similarly effective in lowering BP, reducing systemic vascular resistance, and decreasing urinary albumin excretion, those patients treated with combined therapy exhibited a significantly greater improvement in large-vessel compliance (52% versus 32%; $P < 0.05$).[68] In a study comparing the long-term effect of amlodipine and fosinopril, either in monotherapy or in combination, on urinary albumin excretion, 453 hypertensive patients with type 2 diabetes and microalbuminuria were randomized to amlodipine (5–15 mg/day), fosinopril (10–30 mg/day), or amlodipine plus fosinopril (from 5/10 to 15/30 mg/day) for a 3-month titration period. The nonresponder patients or those complaining of side effects during the titration period were discontinued (n = 144); the remaining 309 patients were enrolled in the trial and were treated with the same therapy for 4 years. The combination therapy was more effective in reducing BP than either drug in monotherapy at any time of the study without affecting glucose homeostasis. Although the three treatment arms significantly reduced urinary albumin excretion during the 48-month study period, this effect was more pronounced and became evident earlier with fosinopril than with amlodipine monotherapy. Notably, the amlodipine-fosinopril combination provided a greater antialbuminuric effect than any of the monotherapies, but this could be because of the greater antihypertensive effects.[69] The AMANDHA (Efficacy and Tolerance Assessment of Manidipine in Type 2 Diabetic Patients with Hypertension and Microalbuminuria Uncontrolled with Renin-Angiotensin System Blockers) study compared the efficacy and safety of adding manidipine 20 mg versus amlodipine 10 mg to the treatment of diabetic patients with uncontrolled hypertension and microalbuminuria despite full-dose treatment with a RAS blocker for at least 6 months. Although manidipine and amlodipine decreased BP values to a similar extent, urinary albumin excretion was more significantly reduced with manidipine than with amlodipine (65.5% versus 20%, respectively, $P < 0.01$ at 6 months; 62.7% versus 16.6%, respectively, $P < 0.01$ at the end of the extension phase of 18 months) (Table 3).[66] Cilnidipine is a dual L- and N-type calcium channel blocker that dilates both efferent and afferent arterioles. In the CARTER (Cilnidipine versus Amlodipine Randomised Trial for Evaluation in Renal Desease) study, nearly 340 patients with hypertension and kidney disease already receiving RAS inhibitor treatment were randomly assigned to cilnidipine or amlodipine. After 1 year of treatment, despite a similar BP reduction, the urinary protein-to-creatinine ratio significantly decreased in the cilnidipine group compared with the amlodipine group (Table 3).[70]

Lercanidipine is a dihydropyridine characterized by its high lipophilicity and selectivity for vascular smooth muscle, with a gradual and prolonged antihypertensive effect, as well as good tolerability, compared with other dihydropyridines.[71–74] In the DIAL (Diabete, Ipertensione, Albuminuria, Lercanidipina) study, hypertensive patients with type 2 diabetes were treated with lercanidipine (10–20 mg/day) or ramipril (5–10 mg/day). After 9–12 months of follow-up, both lercanidipine and ramipril treatments resulted in a significant reduction in the albumin excretion rate without a statistically significant difference between the two treatment groups (Table 3).[75] In a study that included 203 patients with chronic renal failure (creatinine >1.4 mg/dL for males, creatinine >1.2 mg/dL for females, or creatinine clearance <70 mL/minute) who were all treated with RAS inhibitors (63.4% with ACE inhibitors, 36.6% with ARBs), lercanidipine showed a high antihypertensive effect, with a good tolerability profile. Notably, creatinine clearance improved from 41.8 to 45.8 mL/minute and proteinuria significantly decreased from 3.5 to 2.8 g/day.[76] In a study that included 68 proteinuric (>500 mg/day) patients, receiving ACE inhibitors (51.4%) or ARBs (48.6%) but with high BP, the addition of lercanidipine 20 mg/day showed a high antihypertensive and antiproteinuric effect. This antiproteinuric effect seemed to be dose dependent and proportionally higher than BP reduction.[77]

However, the most important trial performed in this context has been a substudy of the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial. This study showed that initial antihypertensive therapy with benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in reducing cardiovascular morbidity and mortality in 11,506 patients with hypertension who were at high risk for cardiovascular events. The effects of these drug combinations on progression of chronic kidney disease were assessed in this substudy. Progression of chronic kidney disease, a prespecified end point, was defined as the doubling of serum creatinine concentration or end-stage renal disease (estimated glomerular filtration

rate <15 mL/minute per 1.73 m^2 of body surface area or the need for dialysis). The trial was prematurely stopped (mean follow-up of 2.9 years) because of the superior efficacy of benazepril plus amlodipine compared with benazepril plus hydrochlorothiazide. With regard to renal end points, 2.0% of the benazepril plus amlodipine group versus 3.7% of patients treated with benazepril plus hydrochlorothiazide showed chronic kidney disease progression (HR, 0.52; 95% CI, 0.41–0.65; $P < 0.0001$). With regard to side effects in patients with chronic kidney disease, while peripheral edema (33.7% versus 16.0%, for the benazepril plus amlodipine group and the benazepril plus hydrochlorothiazide group, respectively) and angioedema were more frequent in the benazepril plus amlodipine group, dizziness, hypokalemia, and hypotension were more frequent in the benazepril plus hydrochlorothiazide group (Table 3).[78,79]

Dual blockade of the RAS

Despite a complete RAS inhibition with ARBs or ACE inhibitors, a number of patients develop or experience progression of renal disease.[1] As a result, several studies have investigated the effects of dual blockade of the RAS in renal outcomes. The CALM (Candesartan and Lisinopril Microalbuminuria) study aimed to assess and compare the effects of candesartan or lisinopril, or both, on BP and urinary albumin excretion in patients with microalbuminuria, hypertension, and type 2 diabetes. At 24 weeks the mean reduction in diastolic BP was significantly greater with combination treatment than with candesartan or lisinopril alone. Moreover, the reduction in urinary albumin-to-creatinine ratio was also greater with combination treatment, with a good tolerability profile.[80] In a 12-month follow-up randomized, clinical trial, lisinopril 40 mg once daily was compared with dual-blockade treatment with candesartan 16 mg once daily and lisinopril 20 mg once daily in diabetic patients aged 35–74 years. Reductions in systolic BP were similar in both groups (6 mmHg with dual blockade versus 2 mmHg with lisinopril; $P = 0.10$), with similar low rates of side effects.[81]

In a study comparing the efficacy of enalapril 5 mg, losartan 50 mg, or both in normotensive type 2 diabetic patients with microalbuminuria, the percentages of reduction in urinary albumin excretion rates at the end of 12 months were 58%, 59%, and 60%, respectively ($P = 0.0001$, $P = 0.0002$, $P = 0.0003$, respectively; $P = 0.346$ between groups).[82] In a meta-analysis that studied the effects of dual blockade in the prevention of the progression of diabetic nephropathy, dual blockade was associated with a more marked proteinuria reduction ($P = 0.01$), a trend towards an increase in serum creatinine concentration (6.86 μmol/L; $P = 0.09$), and an increase in potassium levels by 0.2 mmol/L ($P < 0.01$).[83]

More recently, the ONTARGET study showed that the combination of telmisartan and ramipril, despite reducing BP by a few millimeters of mercury more than therapy with either ramipril or telmisartan, was associated with more adverse events without an increase in benefit.[52] With regard to renal outcomes, the number of events for the composite primary outcome (dialysis, doubling of serum creatinine concentration, and death) was increased with combination therapy (HR, 1.09; 95% CI, 1.01–1.18; $P = 0.037$). The secondary renal outcome (dialysis or doubling of serum creatinine concentration) was also more frequent with combination therapy (HR, 1.24; 95% CI, 1.01–1.51; $P = 0.038$).[53] However, only approximately 4% of patients had overt proteinuria at baseline, and worsening of renal outcomes mostly occurred in the patients without baseline microproteinuria or frank proteinuria. As a result, these data can extend to patients with vascular disease or high-risk diabetes without heart failure, but they can hardly extend to patients with severe renal disease.[27] A recent meta-analysis reported that there is a lack of evidence at present to support the use of combination therapy.[84] As reported in the AVOID trial, the dual blockade of RAS by aliskiren and losartan in hypertensive patients with type 2 diabetic nephropathy reduced the mean urinary albumin-to-creatinine ratio beyond BP control.[40]

Conclusion

To effectively reduce or at least slow the establishment and progression of renal disease in the hypertensive population it is crucial to attain BP goals. Although BP control rates have improved in recent years, mainly because of the increase in use of combined therapy, the fact is that many patients do not reach BP targets.[33]

As European guidelines indicate, all major antihypertensive drug classes (ACE inhibitors, ARBs, diuretics, calcium channel blockers, and beta-blockers) can be considered for treatment, including for diabetic patients.[27] However, a number of studies have shown that treatment with ACE inhibitors, ARBs, and, more recently, aliskiren may provide beneficial effects beyond BP control, particularly in those with diabetes, microalbuminuria, or chronic kidney disease. As the majority of these patients will need at least two antihypertensive drugs to reach BP goals, the use of RAS inhibitors is a mandatory part of antihypertensive therapy in this population.

The best antihypertensive drugs to combine in this setting are diuretics and calcium channel blockers. Various studies have shown the benefits of combining RAS inhibitors with

diuretics or calcium channel blockers in patients with renal disease. Canadian guidelines recommend the use of ACE inhibitors or ARBs as initial therapy in patients with diabetes and albuminuria and, when necessary to attain BP goals, thiazide diuretics (a loop diuretic should be considered if creatinine level is >150 µmol/L), cardioselective beta-blockers, or long-acting calcium channel blockers can be added.[29] In diabetic patients without albuminuria, Canadian guidelines indicate that ACE inhibitors, ARBs, dihydropyridine calcium channel blockers, or thiazide diuretics are adequate options for starting treatment; if the BP target is not achieved, these drugs can be combined, except ACE inhibitors and ARBs together.[29] Finally, in subjects with nondiabetic chronic kidney disease with proteinuria, ACE inhibitors (ARBs if not tolerated) should be used as initial therapy, and diuretics as additive therapy.[29]

However, it is likely that new studies or new post hoc analyses may at least partly change these recommendations, clarifying the subgroups of patients who will benefit more from a combination with a diuretic or from a combination with a calcium channel blocker. To date, the RAS inhibitors recommended in this context are ACE inhibitors and ARBs. Aliskiren, the first available oral direct renin inhibitor, has shown promising results. Nonetheless, until the final results of the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) study (expected in 2012) are known, aliskiren could be used in hypertension, particularly in combination with other agents.[27]

Disclosure

The authors report no conflicts of interest in this work.

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