JNEPHROL 2011; 24(02): 133-141

DOI:10.5301/JN.2011.6355

Emerging strategies to preserve renal function

Hélène Francois [1, 2], Antoine Jacquet [1, 2], Séverine Beaudreuil [1, 2], Alexandre Seidowsky [1, 2], Hadia Hebibi [1, 2], Bernard Charpentier [1, 2], Antoine Durrbach [1, 2]

[1] Department of Nephrology, Dialysis and Transplantation, Bicêtre Hospital, APHP, Paris - France

[2] University of Paris XI Sud, Le Kremlin-Bicêtre - France

Abstract

Although there has been tremendous improvement in managing chronic kidney disease (CKD) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in the last 15 years, CKD still progresses. Therefore, new emerging strategies are needed. The gold standard still lies with optimum renin-angiotensin-aldosterone system blockade, although many questions remain about how this is best achieved, such as regarding the efficacy of combinations of ACE inhibitor and ARBs, supramaximal doses of ARBs alone and combinations of either ACE inhibitor or ARBs with direct renin inhibitors, antialdosterone agents. Other promising molecules currently being tested are endothelin receptor antagonists and glitazones. Also, the role of other current therapies being used during CKD, including statins, vitamin D and erythropoiesis-stimulating agents, will be discussed, as these may also exert nephroprotective effects.

Key words: *Aldosterone blockers, Angiotensin-converting enzyme, Angiotensin receptor blockers, Direct renin inhibitors, Endothelin receptor blockers, Nephroprotection*

Introduction

In most countries, the incidence and prevalence of chronic kidney disease (CKD) and terminal kidney disease are increasing. This is mainly due to the aging of patients, who develop more nephroangiosclerosis and diabetic nephropathy. Specific therapies for the majority of renal diseases are scarce, and the therapeutic options available to clinicians for the best possible nephroprotection include achieving optimal blood pressure (BP) control, blockade of the renin-angiotensin-aldosterone system (RAAS), a low protein diet and correction of all cardiovascular risk factors. Reduction of proteinuria to the lowest possible level (<0.5 g/24 hours) is generally used as a surrogate marker for the efficacy of the RAAS blockade and progression of CKD. Therefore, the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in low proteinuric kidney diseases (especially during chronic tubulointerstitial nephritis) is not as well documented. However, in most nephropathies, and especially if hypertension is present, blockade of the RAAS by ACE inhibitor (1, 2) or ARBs (3) remains the primary objective for clinicians, although controversies are emerging on how blockade of the RAAS is best achieved.

Although some trials initially reported the benefit of an association of ACE inhibitor and ARBs for blood pressure (BP) control and proteinuria reduction (4, 5), the ONTARGET trial reported an increased incidence of dialysis, doubling of serum creatinine levels and death (primary end point) during a combination therapy of ACE inhibitor and ARBs compared with monotherapy, whereas albuminuria was best controlled by a dual therapy (6). Therefore, the optimal strategy to block the RAAS is not yet fully defined. Moreover, the question of whether statins, erythropoiesis-stimulating agents (ESAs) and vitamin D, which are prescribed to control cardiovascular risk factors and secondary hyperparathyroidism, should be given as nephroprotective agents still remains unanswered. In addition, some recently researched molecules may be able to preserve renal function (e.g., direct renin inhibitors, endothelin receptor blockers and glitazones).

In this review, we discuss the best strategies to block the RAAS, the place of statins, erythropoiesis-stimulating agents and vitamin D to preserve renal function, and the role of endothelin receptor blockers and glitazones.

Blockade of the RAAS

ACE inhibitor, ARBs and their combinations

Activation of the RAAS plays an important role in the progression of CKD regardless of the initial nephropathy, and its blockade remains the most important goal in achieving preservation of renal function. The benefit of ACE inhibitor therapy in reducing proteinuria and the progression of CKD was demonstrated in the 1990s (1, 2, 7), though the benefits of ACE inhibitor therapy cannot be fully accounted for solely by its control of BP. More recently, similar efficacy has been demonstrated with ARBs during diabetic nephropathy (3) and during nondiabetic nephropathies (8, 9). However, incomplete blockade can occur when treating patients with a monotherapy, i.e., either ACE inhibitor or ARBs. Other enzymes (mainly chymases), especially during diabetic nephropathy, can account for angiotensin II (Ang II) production (10). Moreover, high levels of renin and angiotensin I (Ang I) are detectable due to the absence of a negative feedback loop during treatment with both ACE inhibitor and ARBs, and this can lead to the direct pathological effects of renin (11) through it binding to its prorenin receptor (PRR) (12), along with the more classical consequences of Ang I and II production. Therefore, and due to dissatisfactory results with ACE inhibitor and ARBs monotherapies, the dual blockade of the RAAS has emerged as a new therapeutic strategy in both cardiovascular and kidney disease.

If benefits are shown for dual RAAS blockade for congestive heart failure (13, 14), then it is less clear whether this strategy remains equally beneficial for patients with CKD. Several studies have reported a benefit of the dual blockade of the RAAS by ACE inhibitor and ARBs both in reducing proteinuria and hypertension (15, 16), but most of these studies included fewer then 50 patients. The first large-scale study to report benefits of this dual blockade during nondiabetic kidney disease was that of Nakao et al (5), which has recently been retracted (17). In addition, 2 meta-analyses have reported in favor of the combination therapy of ACE inhibitor and ARBs to reduce proteinuria and to slow the progression of CKD (4, 18).

In 2008, the results of the ONTARGET trial were reported (6), and an increased incidence of dialysis, doubling of serum creatinine and of death during the combined therapy of ACE inhibitor and ARBs compared with a monotherapy alone were found, whereas albuminuria was best controlled by the dual therapy. Both the results of the ONTARGET study and the very recent retraction of the COOPERATE study (17) due to inadequate patient randomization have stirred some controversy among nephrologists. In the ONTARGET (6) study, the enrolled patients were at very high risk for cardiovascular disease, and only 17% had either microalbuminuria or overt proteinuria. Also, in the ONTARGET trial, patients treated with a dual combination of ACE inhibitor and ARBs at an optimum dosage had better control of proteinuria, but, overall, a higher proportion of those patients reached the composite primary end points than patients treated with ACE inhibitor or ARBs alone. However, death accounted for almost 90% of these composite primary end points, whereas there was no difference in the doubling of serum creatinine between treatments, which more truly represents the progression of CKD. Acute renal failure that necessitated dialysis also occurred more frequently in the combined ACE inhibitor and ARBs group, but dialysis for end-stage renal failure was not more frequent in this combined group. Thus, doubling of serum creatinine level and end-stage renal failure did not occur more frequently in the combination group. Consequently, no definitive conclusion regarding the potential benefit or harm of a combination therapy of ACE inhibitor and ARBs can be drawn from the ONTARGET trial. Therefore, further trials that enroll patients with a lower cardiovascular risk and overt proteinuria are mandatory before concluding that the combination of ACE inhibitor and ARBs is detrimental during CKD. Two large-scale studies are underway that will compare dual blockade using ACE inhibitor and ARBs, with the use of monotherapies to treat diabetic nephropathy (19), and in patients with microalbuminuria and CKD (20).

Maximal ARB monotherapy

Only small short-term studies have examined this therapeutic strategy to reduce proteinuria during diabetic nephropathy: doses of 2 to 4 times higher than the maximal dosage recommended were well tolerated and reduced proteinuria further than lower doses (21-23). Therefore, this could be a promising strategy.

Indeed, to achieve optimal BP control, a low salt diet is mandatory, and the use of diuretics can never be avoided during CKD (24). Diuretic use could even be beneficial to obtain optimum RAAS blockade and may even be more efficient than the dual combination of ACE inhibitor and ARBs (25).

Direct renin inhibitors

Direct renin inhibitors (DRIs) represent a new, appealing approach to inhibiting the RAAS. DRIs are a new class of drugs that block the catalytic site of renin, which is the rate-limiting enzyme in the RAAS pathway. As a consequence, conversion of angiotensinogen to Ang I is reduced, in addition to the downstream synthesis of Ang II and its pathophysiological actions (11). DRIs block the production of Ang I without increasing renin activity, which is observed during ACE inhibitor and ARBs therapy (26), and seems to promote a more complete blockade of the RAAS than an ACE inhibitor alone (11, 27). DRIs, which are efficient antihypertensive medications (28, 29), are currently used as a second-intention treatment (30). However, DRIs may prove effective as nephroprotective agents by themselves, similarly to the other RAAS blockers, such as ACE inhibitors and ARBs.

In addition, renin may directly exert deleterious effects through its receptor (31), including profibrotic actions. However, it is not currently known if DRIs are able to inhibit renin binding to its receptor (32). DRIs have proven effective in several animal models of chronic renal disease (33-35). Two exploratory studies found that aliskiren reduces proteinuria during diabetic nephropathy, alone (36) or in combination with ARBs (37).

The first available large clinical study involving DRIs during CKD was the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study (38), which compared the addition of aliskiren versus a placebo to losartan. This strategy resulted in a 20% reduction in albuminuria. Another large-scale study is still underway with a composite primary end point regarding long-term renal outcome (doubling of serum creatinine and end-stage renal disease) and death (the Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease End-points [ALTITUDE]) (39). Thus, it is still unknown whether DRIs should be used as nephroprotective agents in association with ACE inhibitors and/or ARBs when target levels of both hypertension and proteinuria are not reached. However, it seems logical to use DRIs in cases of intolerance to ACE inhibitor or ARBs.

Aldosterone blockers or mineralocorticoid receptor blockers

In CKD patients treated with an ACE inhibitor or ARBs, increased aldosterone levels are observed. Called "escape" or "breakthrough" (40), this phenomenon supports the use of mineralocorticoid receptor blockers (MRBs) in association with an ACE inhibitor or ARBs as nephroprotective agents. Recent meta-analyses (41, 42) have confirmed that the addition of MRBs to ACE inhibitor or ARBs reduces proteinuria, but without any effect on renal function and long-term renal outcomes and mortality. MRBs alone also reduce proteinuria (43, 44). However, only one of these 2 trials (44) seems to suggest that MRBs slow the progression of CKD. Nevertheless, the risk of hyperkalemia is the major drawback with the use of MRBs in CKD with a glomerular filtration rate (GFR) below 30 ml/min per 1.73 m^2 (as reported in both meta-analyses).

Caution should be used with MRBs during CKD as a nephroprotective agent: avoid their use when hyperkalemia is already present, monitor dietary KCl intake and use furosemide or thiazide to help control hyperkalemia. These measures are summed up in a recent review (45). So far, because of the lack of data on long-term renal function, the use of MRBs should only be considered when control of proteinuria is not obtained with optimum doses of ACE inhibitor or ARBs, or in cases of intolerance to one of these drugs. This strategy should be avoided when GFR is below 30 ml/min per 1.73 m^2; this, therefore, limits its use during CKD.

Endothelin receptor blockers

Endothelin-1 (ET-1) is a very potent vasoconstrictor peptide synthesized by endothelial cells (46). ET-1 synthesis is increased by Ang II and nitric oxide deficiency in both systemic and pulmonary hypertension. ET-1 alone can promote organ damage during systemic hypertension and is clearly involved in the progression of CKD (47). The mechanisms of ET-1-induced progression of CKD include regulation of BP, increased glomerular pressure, podocyte injury, increases in inflammation and reactive oxygen species and activation of the RAAS (48).

ET-1 binds to 2 types of receptors: ET-A and ET-B. ET-A is the most abundant and promotes vasoconstriction

and extracellular matrix-protein synthesis, and is also responsible for the progression of CKD (47). ET-B promotes both vasodilation and natriuresis in the distal part of the nephron, but can also lead to vasoconstriction to a lesser extent, as it is also expressed in vascular smooth muscle cells (49). Because natriuresis is promoted by ET-B receptors in collecting ducts (50-52) and plays an important role in BP regulation (51), ET-A selective receptor blockers should be used whenever possible to slow CKD. However, the first ET-1 blocker used to lower BP was the nonselective one bosentan, which efficiently reduced BP for hypertension within 4 weeks of treatment (53). Other clinical trials have confirmed the BP-lowering effect of selective ET-A blockers: darusentan reduced BP over a 6-week period. Darusentan is similar to an ACE inhibitor (54) and also effectively reduces hypertension (55). These results were confirmed during resistant hypertension, in a study that included patients with diabetes, heart disease and CKD, who also had a reduction in albuminuria (56). However, fluid retention occurred in about one third of patients, though it was manageable with increased diuretic doses: this suggests, however, that darusentan may lack selectivity (57).

Moreover, in addition to lowering BP in CKD patients, ET-A blockers increase renal blood flow and decrease renal vascular resistance (58). Consistent with these results, a significant reduction in proteinuria has been found when treating diabetic nephropathy with avosentan (59, 60), though the last 1 of these randomized control trials was terminated because of an excess number of cardiovascular events and fluid retention (59, 60). However, in the ASCEND trial, during the 6-month treatment period, there was a trend toward slowing the progression of CKD (59, 60). It seems likely though that these findings may also be due to a lack of ET-A selectivity, and that the use of a lower dosage will permit proteinuria reduction as well as less fluid retention (61). A reduction in proteinuria was also observed with an ET-A-selective blocker during nondiabetic CKD and was also accompanied with a reduction in arterial stiffness (62). These results are indeed encouraging, even though the data regarding long-term renal outcome and mortality are still lacking. However, compared with MRBs, ET blockers do not have any effect on kaliemia, and therefore, clinical trials using more selective ET-A blockers are needed and should then offer another therapeutic strategy to clinicians in the future. Moreover, increasing diuretic use and close monitoring of patients should permit consideration of the use of ET-A blockers for CKD, provided patients have stable cardiac function.

Statins

Despite their well-known lipid-lowering effects, statins are also widely used because they decrease cardiovascular mortality through their antiinflammatory properties and their protective effect on endothelial cells. They also inhibit vascular smooth muscle cell proliferation and, therefore, are key players in cardiovascular protection (63). They may also exert renoprotective effects (63), which is mainly supported by experimental data from animals (64, 65). The clinical data were reviewed in a meta-analysis by Sandhu et al (66), which found that statins slow the decrease of renal function during CKD in patients with cardiovascular disease, but not in patients with nephroangiosclerosis or diabetic nephropathy. There was also a trend for statins to reduce albuminuria. Other meta-analyses have found a significant reduction in albuminuria or proteinuria during CKD, but no beneficial reduction in the decline of renal function was found (67-69).

In a recent randomized trial, add-on fluvastatin failed to reduce residual proteinuria in patients with combined ACE inhibitor and ARBs therapy, and had no effect on GFR over a 6-month treatment period (70). A subanalysis of the LIVALO Effectiveness and Safety (LIVES) study found increased GFR after 2 years of treatment during CKD (71). The ongoing Study of Heart and Renal Protection (SHARP) trial should provide reliable information on the effects of statins with regard to both vascular and renal risks in CKD patients (72).

To sum up, it appears reasonable to consider statins as a therapeutic strategy to help reduce proteinuria when both the control of BP and blockade of the RAAS seem optimum. Moreover, most patients with CKD are patients with a high cardiovascular risk and should be treated with statins for cardiovascular protection before dialysis (73, 74) because during end-stage renal disease, statins do not lower cardiovascular events, as 2 large randomized trials have reported (75, 76).

Erythropoiesis-stimulating agents

The rationale for using ESAs during CKD is both the correction of tissue hypoxemia and the protective role of ESAs on endothelial cells (77). Although anemia during CKD is clearly associated with increased cardiovascular mortality, and its correction (but not its normalization) results in improved survival (78), its role in the progression of CKD is less clear. A few trials have reported a slowing

of the progression of CKD, plus correction of anemia, with ESAs (77, 79). However, 2 large randomized studies (80, 81), designed to examine the cardiovascular benefits of correcting anemia with ESAs in the CKD population, did not find any benefit to renal function when comparing 2 different target hemoglobin levels (i.e., complete correction versus partial correction for both trials). In fact, no clear benefits have been found for the complete correction of anemia, for slowing the progression of CKD, and data are still lacking for outcomes if only partial correction of anemia is performed.

More recently, a large placebo-controlled double-blind randomized study that was neutral for primary end points found that the use of darbepoetin alfa in patients with CKD with a target level of 13 g/dL did not reduce the risk of either of the 2 primary composite outcomes (either death or a cardiovascular event, or death or a renal event) (82). Thus, a renoprotective effect of ESAs seems very unlikely. Moreover, the last randomized study raised safety concerns as there were significantly more incidences of stroke in the ESA-treated group compared with the placebo group, as found in a secondary analysis of the results, and also a trend toward an increased risk of cancer, which was significant when analyzing patients with a past medical history of malignancies (82).

Vitamin D

It is now well recognized that the benefits of vitamin D extend far beyond its role on bone metabolism and the control of calcium and phosphate balance. Vitamin D is involved in slowing tumor progression, in immune modulation and also in BP regulation and cardiovascular functions. A lack of vitamin D has been associated with a poor cardiovascular outcome, poor control of BP and a higher risk of cancer (83). Moreover, lack of vitamin D is associated with increased renin levels in both animal models (84, 85) and hypertensive patients (86, 87). Moreover, in several trials that have examined RAAS activity, vitamin D supplementation promoted a decrease in renin and Ang II (88-90). Therefore, lack of vitamin D should be avoided in CKD patients, as they have a high cardiovascular risk. However, the role of vitamin D in the progression of renal failure still remains to be established. A few trials seem to suggest a possible benefit during CKD: Szeto et al reported 1 uncontrolled trial that involved 10 patients with IgA nephropathy who were treated with calcitriol: this reduced their proteinuria despite optimum RAAS blockade (91). In addition, 4 randomized double-blind trials found a reduction in proteinuria or albuminuria during paricalcitol treatment (88, 92). Another randomized trial found that calcitriol treatment was associated with a reduction in mortality and also a reduction in dialysis need (93). However, although treating vitamin D deficiency is strongly recommended to reduce morbidity and mortality in CKD patients, and to better control secondary hyperparathyroidism, evidence-based data are too scarce to recommend its use solely as a nephroprotective agent in the absence of vitamin D deficiency.

Glitazones

Glitazones are ligands for the gamma peroxisome proliferator-activated receptors (PPARs) and are potent insulin sensitizers that are currently used as antidiabetic agents. There is now a wide body of evidence, both from animal and human studies, that thiazolidinediones exert several other beneficial metabolic and vascular effects, in addition to improved glycemic control, improvement in lipid profiles, lowering of BP, reduction of Ang II, antiinflammatory effects and improvement in endothelial function (94, 95). Therefore, they could be useful to prevent progression of CKD. Several trials have found a reduction in microalbuminuria or proteinuria in randomized studies of type 2 diabetes nephropathy (96, 97) and slower progression of CKD based on measured GFR and serum creatinine (97). A reduction in proteinuria in obese nondiabetic CKD patients (98) has been also reported in a randomized study. However, because glitazones may increase the risk of myocardial infarction (99, 100), as well as promote fluid retention and heart failure (101), their use is problematic in CKD patients. Although pioglitazone could be safer than rosiglitazone, meta-analyses and current safety data suggest that, at the very least, elderly patients with a high cardiovascular risk should avoid this medication (102). Therefore, its use in CKD patients, most of whom are over 65 and at high risk for cardiovascular disease, will be limited.

Conclusions

Although the optimum treatment to prevent the progression of CKD is not yet known, several promising molecules have emerged as future therapies. The most promising to date are DRIs, which have a good safety profile, and endothelin-A selective receptor antagonists (although they may promote fluid retention in cases of low selectivity). Statins may help reduce proteinuria, but there is insufficient data on their role in the progression of CKD to consider them for nephroprotection purposes.

Glitazones could be promising, but some may increase the risk of myocardial infarction and heart failure. MRBs may also slow CKD progression, but can only be used during moderate renal failure due to the serious risk of increasing kalemia. There are also insufficient data for ESAs and vitamin D as renoprotective agents in CKD. Thus, the best option to obtain the greatest BP control and reduction of proteinuria is the combination of ACE inhibitor and ARBs, as, to date, they both remain the gold standards for treating CKD.

Financial support: No financial support.

Conflict of interest statement: None declared.

Address for correspondence:
Hélène Francois, MD, PhD
Service de Néphrologie
Dialyse et Transplantation
Hôpital Bicêtre
78 rue du général Leclerc
FR-94270 Le Kremlin-Bicêtre, France
helene.francois@bct.aphp.fr

References

1. 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. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet. 1997;349:1857-1863.
2. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329:1456-1462.
3. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861-869.
4. Catapano F, Chiodini P, De Nicola L, et al. Antiproteinuric response to dual blockade of the renin-angiotensin system in primary glomerulonephritis: meta-analysis and metaregression. Am J Kidney Dis. 2008;52:475-485.
5. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet. 2003;361:117-124.
6. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008;372:547-553.
7. Maschio G, Alberti D, Janin G, et al. 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. 1996;334:939-945.
8. Li PK, Leung CB, Chow KM, et al. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. Am J Kidney Dis. 2006;47:751-760.
9. Praga M, Andrade CF, Luno J, et al. Antiproteinuric efficacy of losartan in comparison with amlodipine in non-diabetic proteinuric renal diseases: a double-blind, randomized clinical trial. Nephrol Dial Transplant. 2003;18:1806-1813.
10. Brewster UC, Setaro JF, Perazella MA. The renin-angiotensin-aldosterone system: cardiorenal effects and implications for renal and cardiovascular disease states. Am J Med Sci. 2003;326:15-24.
11. Hollenberg NK. Direct renin inhibition and the kidney. Nat Rev Nephrol. 2010;6:49-55.
12. Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. J Clin Invest. 2002;109:1417-1427.
13. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362:767-771.
14. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667-1675.
15. Berger ED, Bader BD, Ebert C, Risler T, Erley CM. Reduction of proteinuria; combined effects of receptor blockade and low dose angiotensin-converting enzyme inhibition. J Hypertens. 2002;20:739-743.
16. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in

patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ. 2000;321:1440-1444.
17. Retraction: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet. 2009;374:1226.
18. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med. 2008;148:30-48.
19. Fried LF, Duckworth W, Zhang JH, et al. Design of combination angiotensin receptor blocker and angiotensin-converting enzyme inhibitor for treatment of diabetic nephropathy (VA NEPHRON-D). Clin J Am Soc Nephrol. 2009;4:361-368.
20. Maione A, Nicolucci A, Craig JC, et al. Protocol of the Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) randomized trial. J Nephrol. 2007;20:646-655.
21. Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving HH. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. Kidney Int. 2005;68:1190-1198.
22. Burgess E, Muirhead N, Rene de Cotret P, Chiu A, Pichette V, Tobe S. Supramaximal dose of candesartan in proteinuric renal disease. J Am Soc Nephrol. 2009;20:893-900.
23. Hollenberg NK, Parving HH, Viberti G, et al. Albuminuria response to very high-dose valsartan in type 2 diabetes mellitus. J Hypertens. 2007;25:1921-1926.
24. Ernst ME, Gordon JA. Diuretic therapy: key aspects in hypertension and renal disease. J Nephrol. 2010;23:487-493.
25. Esnault VL, Ekhlas A, Nguyen JM, Moranne O. Diuretic uptitration with half dose combined ACEI + ARB better decreases proteinuria than combined ACEI + ARB uptitration. Nephrol Dial Transplant. 2010;25:2218-2224.
26. Nussberger J, Wuerzner G, Jensen C, Brunner HR. Angiotensin II suppression in humans by the orally active renin inhibitor Aliskiren (SPP100): comparison with enalapril. Hypertension. 2002;39:E1-E8.
27. Fisher ND, Jan Danser AH, Nussberger J, Dole WP, Hollenberg NK. Renal and hormonal responses to direct renin inhibition with aliskiren in healthy humans. Circulation. 2008;117:3199-3205.
28. O'Brien E, Barton J, Nussberger J, et al. 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. 2007;49:276-284.
29. Andersen K, Weinberger MH, Egan B, et al. Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. J Hypertens. 2008;26:589-599.
30. Israili ZH, Velasco M, Bermudez V. Direct renin inhibitors as antihypertensive agents. Am J Ther. 2010;17:237-254.
31. Nguyen M, Solle M, Audoly LP, et al. Receptors and signaling mechanisms required for prostaglandin E2-mediated regulation of mast cell degranulation and IL-6 production. J Immunol. 2002;169:4586-4593.
32. Bracquart D, Cousin C, Contrepas A, Nguyen G. [The prorenin receptor] [article in French]. J Soc Biol. 2009;203:303-310.
33. Feldman DL, Jin L, Xuan H, et al. Effects of aliskiren on blood pressure, albuminuria, and (pro)renin receptor expression in diabetic TG(mRen-2)27 rats. Hypertension. 2008;52:130-136.
34. Pilz B, Shagdarsuren E, Wellner M, et al. Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. Hypertension. 2005;46:569-576.
35. Muller DN, Luft FC. Direct renin inhibition with aliskiren in hypertension and target organ damage. Clin J Am Soc Nephrol. 2006;1:221-228.
36. Persson F, Rossing P, Schjoedt KJ, et al. Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. Kidney Int. 2008;73:1419-1425.
37. Persson F, Rossing P, Reinhard H, et al. Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. Diabetes Care. 2009;32:1873-1879.
38. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med. 2008;358:2433-2446.
39. Parving HH, Brenner BM, McMurray JJ, et al. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. Nephrol Dial Transplant. 2009;24:1663-1671.
40. Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. Nat Clin Pract Nephrol. 2007;3:486-492.
41. Navaneethan SD, Nigwekar SU, Sehgal AR, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2009;4:542-551.
42. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis. 2008;51:199-211.
43. Nagase M, Fujita T. Aldosterone and glomerular podocyte injury. Clin Exp Nephrol. 2008;12:233-242.
44. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int. 2006;70:2116-2123.
45. Jain G, Campbell RC, Warnock DG. Mineralocorticoid receptor blockers and chronic kidney disease. Clin J Am Soc Nephrol. 2009;4:1685-1691.
46. Karet FE, Davenport AP. Localization of endothelin peptides in human kidney. Kidney Int. 1996;49:382-387.
47. Dhaun N, Goddard J, Webb DJ. The endothelin system and its antagonism in chronic kidney disease. J Am Soc Nephrol. 2006;17:943-955.
48. Barton M. Reversal of proteinuric renal disease and the

emerging role of endothelin. Nat Clin Pract Nephrol. 2008;4:490-501.
49. de Nucci G, Thomas R, D'Orleans-Juste P, et al. Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. Proc Natl Acad Sci U S A. 1988;85:9797-9800.
50. Ahn D, Ge Y, Stricklett PK, et al. Collecting duct-specific knockout of endothelin-1 causes hypertension and sodium retention. J Clin Invest. 2004;114:504-511.
51. Ge Y, Bagnall A, Stricklett PK, et al. Collecting duct-specific knockout of the endothelin B receptor causes hypertension and sodium retention. Am J Physiol Renal Physiol. 2006;291:F1274-F1280.
52. Ge Y, Stricklett PK, Hughes AK, Yanagisawa M, Kohan DE. Collecting duct-specific knockout of the endothelin A receptor alters renal vasopressin responsiveness, but not sodium excretion or blood pressure. Am J Physiol Renal Physiol. 2005;289:F692-F698.
53. Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan Hypertension Investigators. N Engl J Med. 1998;338:784-790.
54. Nakov R, Pfarr E, Eberle S. Darusentan: an effective endothelinA receptor antagonist for treatment of hypertension. Am J Hypertens. 2002;15:583-589.
55. Black HR, Bakris GL, Weber MA, et al. Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo-controlled dose-ranging study. J Clin Hypertens (Greenwich). 2007;9:760-769.
56. Weber MA, Black H, Bakris G, et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;374:1423-1431.
57. Dhaun N, Goddard J, Webb DJ. An endothelin antagonist for resistant hypertension. Lancet. 2010;375:635; author reply 636-7.
58. Goddard J, Johnston NR, Hand MF, et al. Endothelin-A receptor antagonism reduces blood pressure and increases renal blood flow in hypertensive patients with chronic renal failure: a comparison of selective and combined endothelin receptor blockade. Circulation. 2004;109:1186-1193.
59. Mann JF, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol. 2010;21:527-535.
60. Wenzel RR, Littke T, Kuranoff S, et al. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. J Am Soc Nephrol. 2009;20:655-664.
61. Ritz E, Wenzel R. Endothelin receptor antagonists in proteinuric renal disease: every rose has its thorn. J Am Soc Nephrol. 2010;21:392-394.
62. Dhaun N, Macintyre IM, Melville V, et al. Blood pressure-independent reduction in proteinuria and arterial stiffness after acute endothelin-a receptor antagonism in chronic kidney disease. Hypertension. 2009;54:113-119.
63. Campese VM, Nadim MK, Epstein M. Are 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors renoprotective? J Am Soc Nephrol. 2005;16(Suppl 1):S11-S17.
64. Zoja C, Corna D, Camozzi D, et al. How to fully protect the kidney in a severe model of progressive nephropathy: a multidrug approach. J Am Soc Nephrol. 2002;13:2898-2908.
65. Vazquez-Perez S, Aragoncillo P, de Las Heras N, et al. Atorvastatin prevents glomerulosclerosis and renal endothelial dysfunction in hypercholesterolaemic rabbits. Nephrol Dial Transplant. 2001;16(Suppl 1):40-44.
66. Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol. 2006;17:2006-2016.
67. Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria. Ann Intern Med. 2006;145:117-124.
68. Strippoli GF, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ. 2008;336:645-651.
69. Navaneethan SD, Pansini F, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2009;CD007784.
70. Ruggenenti P, Perna A, Tonelli M, et al. Effects of add-on fluvastatin therapy in patients with chronic proteinuric nephropathy on dual renin-angiotensin system blockade: the ESPLANADE Trial. Clin J Am Soc Nephrol. 2010;5:1928-1938.
71. Kimura K, Shimano H, Yokote K, Urashima M, Teramoto T. Effects of pitavastatin (LIVALO tablet) on the estimated glomerular filtration rate (eGFR) in hypercholesterolemic patients with chronic kidney disease: sub-analysis of the LIVALO Effectiveness and Safety (LIVES) Study. J Atheroscler Thromb. 2010;17:601-609.
72. Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). Kidney Int Suppl. 2003;84:S207-10.
73. Kendrick J, Shlipak MG, Targher G, Cook T, Lindenfeld J, Chonchol M. Effect of lovastatin on primary prevention of cardiovascular events in mild CKD and kidney function loss: a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study. Am J Kidney Dis. 2010;55:42-49.
74. Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. J Am Coll Cardiol. 2010;55:1266-1273.
75. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238-248.
76. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin

and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395-1407.
77. Carlini RG, Alonzo EJ, Dominguez J, et al. Effect of recombinant human erythropoietin on endothelial cell apoptosis. Kidney Int. 1999;55:546-553.
78. Paoletti E, Cannella G. Update on erythropoietin treatment: should hemoglobin be normalized in patients with chronic kidney disease? J Am Soc Nephrol. 2006;17:S74-S77.
79. Kuriyama S, Tomonari H, Yoshida H, Hashimoto T, Kawaguchi Y, Sakai O. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in nondiabetic patients. Nephron. 1997;77:176-185.
80. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085-2098.
81. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006;355:2071-2084.
82. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019-2032.
83. Gal-Moscovici A, Sprague SM. Use of vitamin D in chronic kidney disease patients. Kidney Int. 2010;78:146-151.
84. Zhou C, Lu F, Cao K, Xu D, Goltzman D, Miao D. Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. Kidney Int. 2008;74:170-179.
85. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002;110:229-238.
86. Burgess ED, Hawkins RG, Watanabe M. Interaction of 1,25-dihydroxyvitamin D and plasma renin activity in high renin essential hypertension. Am J Hypertens. 1990;3:903-905.
87. Resnick LM, Muller FB, Laragh JH. Calcium-regulating hormones in essential hypertension: relation to plasma renin activity and sodium metabolism. Ann Intern Med. 1986;105:649-654.
88. Agarwal R, Acharya M, Tian J, et al. Antiproteinuric effect of oral paricalcitol in chronic kidney disease. Kidney Int. 2005;68:2823-2828.
89. Lind L, Wengle B, Wide L, Ljunghall S. Reduction of blood pressure during long-term treatment with active vitamin D (alphacalcidol) is dependent on plasma renin activity and calcium status: a double-blind, placebo-controlled study. Am J Hypertens. 1989;2:20-25.
90. Freundlich M, Quiroz Y, Zhang Z, et al. Suppression of renin-angiotensin gene expression in the kidney by paricalcitol. Kidney Int. 2008;74:1394-1402.
91. Szeto CC, Chow KM, Kwan BC, Chung KY, Leung CB, Li PK. Oral calcitriol for the treatment of persistent proteinuria in immunoglobulin A nephropathy: an uncontrolled trial. Am J Kidney Dis. 2008;51:724-731.
92. Alborzi P, Patel NA, Peterson C, et al. Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized double-blind pilot trial. Hypertension. 2008;52:249-255.
93. Shoben AB, Rudser KD, de Boer IH, Young B, Kestenbaum B. Association of oral calcitriol with improved survival in nondialyzed CKD. J Am Soc Nephrol. 2008;19:1613-1619.
94. Vasudevan AR, Balasubramanyam A. Thiazolidinediones: a review of their mechanisms of insulin sensitization, therapeutic potential, clinical efficacy, and tolerability. Diabetes Technol Ther. 2004;6:850-863.
95. Diep QN, El Mabrouk M, Cohn JS, et al. Structure, endothelial function, cell growth, and inflammation in blood vessels of angiotensin II-infused rats: role of peroxisome proliferator-activated receptor-gamma. Circulation. 2002;105:2296-2302.
96. Agarwal R, Saha C, Battiwala M, et al. A pilot randomized controlled trial of renal protection with pioglitazone in diabetic nephropathy. Kidney Int. 2005;68:285-292.
97. Jin HM, Pan Y. Renoprotection provided by losartan in combination with pioglitazone is superior to renoprotection provided by losartan alone in patients with type 2 diabetic nephropathy. Kidney Blood Press Res. 2007;30:203-211.
98. Bakris GL, Ruilope LM, McMorn SO, et al. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. J Hypertens. 2006;24:2047-2055.
99. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457-2471.
100. Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010 Jun 28 [Epub ahead of print].
101. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007;298:1180-1188.
102. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010;304:411-418.

Received: August 18, 2010
Revised: October 29, 2010
Accepted: November 12, 2010