The Pathogenesis and Management of Hypertension in Diabetic Kidney Disease

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KEYWORDS

• Hypertension • Vasoconstriction • ACE inhibitor • RAAS therapy • Hyperkalemia

KEY POINTS

- Hypertension commonly coexists with diabetes, and its prevalence is even higher in the presence of diabetic kidney disease.
- The pathogenesis of hypertension in this population stems from increased extracellular volume and increased vasoconstriction that result from mechanisms that may be attributed to both diabetes and the eventual impairment of renal function.
- Antihypertensive therapy aimed at reducing blood pressure remains a primary goal in preventing the incidence of diabetic kidney and slowing its progression. Initial therapy should consist of an ACE inhibitor or ARB titrated to the maximally tolerated dose.
- Using combination RAAS therapy further reduces proteinuria, but the benefits of this strategy compared with the potential risks of hyperkalemia and acute deterioration of renal function are still unknown.
- Endothelin receptor antagonists also lower proteinuria, but these can be associated with volume overload and edema with no clear long-term benefit on renal function yet identified.

INTRODUCTION

Diabetic kidney disease is one of the potential microvascular complications that can occur in diabetic patients. It is the leading cause of end-stage renal disease (ESRD) in the United States that also carries an augmented risk for cardiovascular morbidity

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and mortality in patients who still have some preservation of renal function. Blood pressure control, along with glycemic control and inhibition of the renin-angiotensin-aldosterone system (RAAS), has been established as a primary goal to reduce the incidence of and slow the progression of diabetic kidney disease. As hypertension is a common comorbidity associated with diabetes that has a multifactorial origin, this task remains difficult to achieve in many diabetic patients. Furthermore, the specific blood pressure targets that offer optimal benefit from both a renal and cardiovascular standpoint remain uncertain. This review article focuses on some of the predominant mechanisms responsible for increased blood pressure in diabetic kidney disease and the current clinical evidence on the antihypertensive agents that are used to manage diabetic kidney disease.

DIABETIC KIDNEY DISEASE

When kidney disease presents in diabetic patients as albuminuria and/or renal impairment, specific clinical cues may further guide the determination of whether or not diabetes is the underlying cause. The presence of extrarenal microvascular disease (diabetic retinopathy, diabetic neuropathy) and a long duration of diabetes before the onset of albuminuria support the diagnosis of diabetic kidney disease.[1] The lack of these findings, the presence of hematuria, or evidence of another systemic disease warrant consideration of a renal biopsy to establish the diagnosis. As diabetic kidney disease may take many years to develop and progress in patients with either type 1 or type 2 diabetes, a diagnosis will often be made late in the course of the disease at a time when the disease is progressing at a faster rate. The first phase, hyperfiltration, has usually already passed even when the diagnosis is made early. During the hyperfiltration phase, which is marked by an increase in glomerular filtration rate, clinical symptoms of albuminuria and hypertension are typically absent. Subsequent phases of diabetic kidney disease involve microalbuminuria and then macroalbuminuria with progressive decreases in the glomerular filtration rate and increases in blood pressure. Once overt diabetic nephropathy is present, there is increased risk for both ESRD and cardiovascular mortality. Hypertension is a critical comorbidity that further increases the risk of these outcomes at this stage of the disease.

Hypertension in Diabetic Kidney Disease

For individuals in the general population, a blood pressure of 140/90 mm Hg marks the threshold of stage I hypertension and the point at which antihypertensive therapy is indicated.[2] For individuals with diabetes or kidney disease (regardless of the underlying etiology), the recommended treatment target is a blood pressure lower than 130/80 mm Hg.[3,4] As these recommendations reflect relatively recent guidelines for blood pressure targets, the reported prevalence of hypertension among patients with diabetes may vary depending on when a study was conducted and the specific definition for hypertension that was used.

The clinical context in which hypertension presents will differ between patients with type 1 and type 2 diabetes. In type 1 diabetic patients, hypertension most frequently presents after microalbuminuria develops. One large epidemiologic study showed the prevalence of hypertension among patients with type 1 diabetes without microalbuminuria to be 4% (similar to the age-matched control population),[5] whereas another study showed its prevalence in this population to be 19%.[6] Both studies defined hypertension at values higher than the currently recommended blood pressure targets, but they were consistent in showing that the prevalence of hypertension increases as the amount of proteinuria increases. This association between

hypertension and albuminuria in patients with type 1 diabetes has been further defined by evidence that the failure of blood pressure to decrease during the nighttime on ambulatory blood pressure monitoring occurs before the development of microalbuminuria.[7] In patients with type 2 diabetes, hypertension may be present well before any manifestation of microalbuminuria or renal disease, indicating that insulin resistance is associated with increased blood pressure.[8] In fact, the prevalence of hypertension has been estimated to be as high as 58% to 70% in patients with type 2 diabetes without microalbuminuria.[9,10] Similar to type 1 diabetic patients, hypertension becomes even more prevalent as renal disease progresses in patients with type 2 diabetes and further augments the risk for cardiovascular events in these patients.[11]

PATHOPHYSIOLOGY

The underlying mechanisms responsible for hypertension in diabetic kidney disease involve increased extracellular volume, increased vasoconstriction, and the general inability of these components to appropriately balance out each other. Increased renal reabsorption of sodium and/or impaired renal excretion of sodium mediate the increase in extracellular volume, whereas increased vasoconstriction is mediated by numerous systems including the RAAS, endothelin system, and sympathetic nervous system. Some of the mediators from these systems are directly involved in promoting local renal damage, but the overall increase in systemic blood pressure these mediators induce and the inherent hemodynamic autoregulatory impairment in the renal microvasculature of diabetics facilitate further renal injury if hypertension is inadequately treated.

Hyperfiltration and Sodium Reabsorption

One of the first changes in renal function that may occur in diabetes is an increase in the glomerular filtration rate, referred to as hyperfiltration.[12] Because serum creatinine will be low and blood pressure will be normal in this context, overall renal function may be inappropriately perceived as normal. However, both the underlying cause and subsequent consequences of hyperfiltration are associated with the development of an unfavorable hemodynamic state that permits the eventual deterioration of renal function.

Increased proximal tubular reabsorption of sodium may coexist with hyperfiltration in patients with insulin-dependent diabetes.[13] In fact, it is hypothesized that hyperfiltration is an appropriate response of the tubuloglomerular feedback reacting to an inappropriate increase in sodium reabsorption. An animal study showed lower concentrations of tubular sodium and chloride measured proximal to the macula densa in diabetic rats compared with control animals.[13] With pharmacologic inhibition of proximal tubule sodium/glucose transporters, there were increased concentrations of sodium and chloride downstream to these transporters, which subsequently resulted in a decreased single-nephron glomerular filtration rate (GFR). There is experimental evidence that hyperfiltration is nitric oxide dependent and that this process also prevents increases in blood pressure early in the course of diabetes.[14,15] Although the primary mechanisms contributing to the increase in sodium reabsorption remain incompletely understood, the ultimate consequence is an expansion of extracellular volume. Furthermore, patients with diabetes respond to salt loading with an inadequate inhibition of RAAS activity.[16] As RAAS activity promotes renal sodium reabsorption throughout the nephron, achieving euvolemia can become even more difficult if this system is not adequately suppressed in volume-overloaded individuals.

The implications of various interventions related to either dietary salt ingestion or the use of diuretics in the context of pharmacologic RAAS inhibition are discussed later in the management section.

In patients who develop diabetic kidney disease, hyperfiltration ceases and reductions in GFR take place as there is progression through the phases of microalbuminuria and macroalbuminuria. Renal excretion of sodium and water becomes more difficult with reduction in GFR, and this further contributes to the increased prevalence of extracellular volume expansion and hypertension at these later stages.

RAAS

The RAAS has the potential to influence diabetic kidney disease through several mechanisms. One of the systemic functions of this system is to restore euvolemia and maintain sufficient blood pressure in the context of volume depletion. Both angiotensin II (Ang II) and aldosterone have functions that (1) promote increased reabsorption of sodium by binding to various receptors on renal tubules and (2) increase vascular tone by binding to receptors on vascular smooth muscle cells in the peripheral circulation. Local tissue levels of the angiotensin-converting enzyme (ACE) and Ang II have been shown to be increased in the glomeruli and renal tubules of streptozocin-induced diabetic rats and diabetic patients with or without nephropathy.[17–20] On the systemic level, the plasma renin activity of diabetic patients and patients with diabetic nephropathy is frequently the same as or lower than that of healthy individuals.[21,22] However, these levels seen in diabetic patients are still higher than would be expected given the degree of extracellular volume overload that is present.[22] Thus, deregulation of this axis may contribute to increased blood pressure by creating a persistent state of volume overload and increased vasoconstriction.

Beyond the traditional RAAS mediators (Ang II and aldosterone), there is emerging evidence that other novel components of this system may be important mediators of hypertension and diabetic kidney disease (**Fig. 1**). ACE 2 is responsible for the enzymatic conversion of Ang II to Ang-(1–7), as well as the conversion of Ang I to Ang-(1–9). In Zucker diabetic rats, independent of Ang II levels, infusion of Ang-(1–7) (1) lowered blood pressure, (2) reduced oxidative stress and inflammation in the kidney, (3) reduced renal extracellular matrix expansion, (4) reduced proteinuria, and (5) increased GFR compared with saline infusion.[23] Conversely, in diabetic mice, pharmacologic inhibition of ACE 2 promoted an increase in extracellular matrix production and proteinuria.[24] The significance of these findings has yet to be confirmed in humans. Current studies in patients with diabetes or CKD are limited by variability in research methods and consequently variable results regarding the renal expression of ACE 2 or ACE 2 activity.[25–27] The full implications of how the ACE 2 fits into the management of hypertension and diabetic nephropathy remains yet to be determined. The use of pharmacologic agents to inhibit the traditional components of the RAAS is discussed in significant detail in the management section.

Endothelial Cell Dysfunction

Endothelial cells are involved in important interactions with vascular smooth muscle cells to facilitate the regulation of vasodilation and vasoconstriction. In CKD, blood pressure correlates with the severity of endothelial cell dysfunction.[28] Furthermore, diabetes is independently associated with a greater degree of endothelial cell dysfunction compared with healthy individuals, and the amount of proteinuria correlates with the severity of this dysfunction.[29,30] A unifying abnormality among CKD and diabetes is the potential disruption of the balance of vasoconstrictors and vasodilators that modify vascular tone and function. Under physiologic conditions, nitric

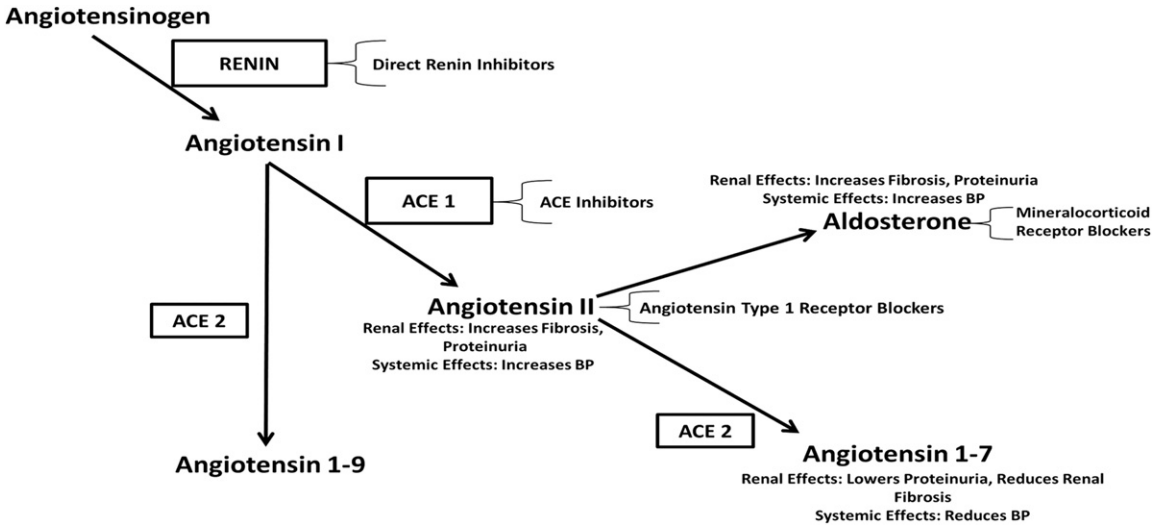

Fig. 1. The RAAS pathway is depicted along with the effects and potential therapeutic options for the individual mediators. Renin enzymatically converts angiotensinogen to angiotensin I. Direct renin inhibitors have been explored as an option to reduce renin activity, but the current clinical trial evidence does not support its use in combination with other RAAS inhibiting agents. ACE 1 converts Ang I to Ang II. ACE inhibitors are considered first-line antihypertensive therapies for patients with diabetic kidney disease. Ang II promotes renal fibrosis and proteinuria and also increases blood pressure systemically. Accordingly, ARBs are another consideration as first-line therapy. Ang II also promotes release of aldosterone, which can further promote fibrosis, proteinuria, and increased blood pressure. Mineralocorticoid receptor blockers inhibit the effects of aldosterone and can be effective in lowering proteinuria. A new concept that has emerged in this pathway is the role of the ACE 2 enzyme, which converts Ang II to a vasodilatory and potentially renoprotective mediator, Ang-(1–7). This enzyme may also prevent further production of Ang II by converting Ang I to Ang-(1–9).

oxide, which is synthesized in endothelial cells, binds to vascular smooth muscle cells to cause vasodilation. In vitro evidence from endothelial cells shows that increased glucose concentrations interfere with nitric oxide metabolism.[31] In animal models of diabetes, the significance of nitric oxide becomes evident from the exaggerated increase in blood pressure that inhibitors of nitric oxide synthase induce.[32] Beyond the potential role of hyperglycemia in inducing such dysfunction, CKD and diabetes are also both associated with an increased level of an endogenous inhibitor of nitric oxide synthase, asymmetric dimethylarginine (ADMA). Vascular resistance and blood pressure increase with infusion of ADMA into healthy individuals,[33] and ADMA levels in patients with diabetes or CKD are independently associated with increased risk for cardiovascular events.[34–37]

Alternatively, vascular tone could be influenced by increased activity of vasoconstrictive mediators related to endothelial cell dysfunction. Endothelin-1 (ET-1) is a vasoconstrictive peptide that exerts its actions through binding to tissue receptors throughout the body, including the glomerulus and vascular smooth muscle cells. Both animal and human studies show increased local renal tissue levels and plasma levels of ET-1,[38,39] and insulin resistance has been potentially implicated as playing a role.[40] Subsequently, increased ET-1 activity may have adverse effects on both systemic blood pressure and local renal hemodynamics and function. Pharmacologic inhibition of endothelin receptors can improve endothelial cell dysfunction in patients with diabetes,[41] and the application of such drugs in larger randomized trials is discussed in the management section.

Oxidative Stress

Increased oxidative stress is one mechanism that potentially unifies the role that the RAAS and endothelial cell function play in hypertension. Increased reactive oxidative species may be generated in the vasculature through the effects of Ang II on nicotinamide adenine dinucleotide hydrate/nicotinamide adenine dinucleotide phosphate oxidase.[42,43] Through interaction with free radicals, nitric oxide may (1) lose its capacity to properly induce vasodilation and (2) propagate further reactions to augment the overall level of oxidative stress in the vasculature. The inhibitor of nitric oxide synthase, ADMA, is also believed to be increased with levels of high oxidative stress secondary to decreased function of an inhibiting enzyme of ADMA, dimethylarginine dimethylaminohydrolase (DDAH). Consequently, oxidative stress has been implicated in part of the pathogenesis of hypertension. The high levels of oxidative stress seen in both diabetes and CKD are likely involved in the high prevalence of hypertension in these populations (**Fig. 2**).[44–46]

Sympathetic Nervous System Activity

Similar to the RAAS, the increased activity of the sympathetic nervous system (SNS) can affect blood pressure through multiple mechanisms. In addition to increasing renal sodium reabsorption, increased sympathetic nervous activity may influence blood pressure through centrally mediated processes in animal models of renal ablation.[47] In humans, increased SNS activity can be seen in CKD and ESRD caused by various etiologies.[48,49] As autonomic neuropathy is a potential microvascular complication of diabetes, it has been proposed that increased nocturnal blood pressure in patients with type 1 or type 2 diabetes may be explained by this phenomenon.[50–52] Thus, both diabetes and CKD may independently contribute to increased SNS activity. Given the previously described role of the RAAS in hypertension in diabetic kidney disease, it is of interest that the ACE inhibitor enalapril has been shown to reduce SNS activity compared with the effects of amlodipine in patients with CKD.[49]

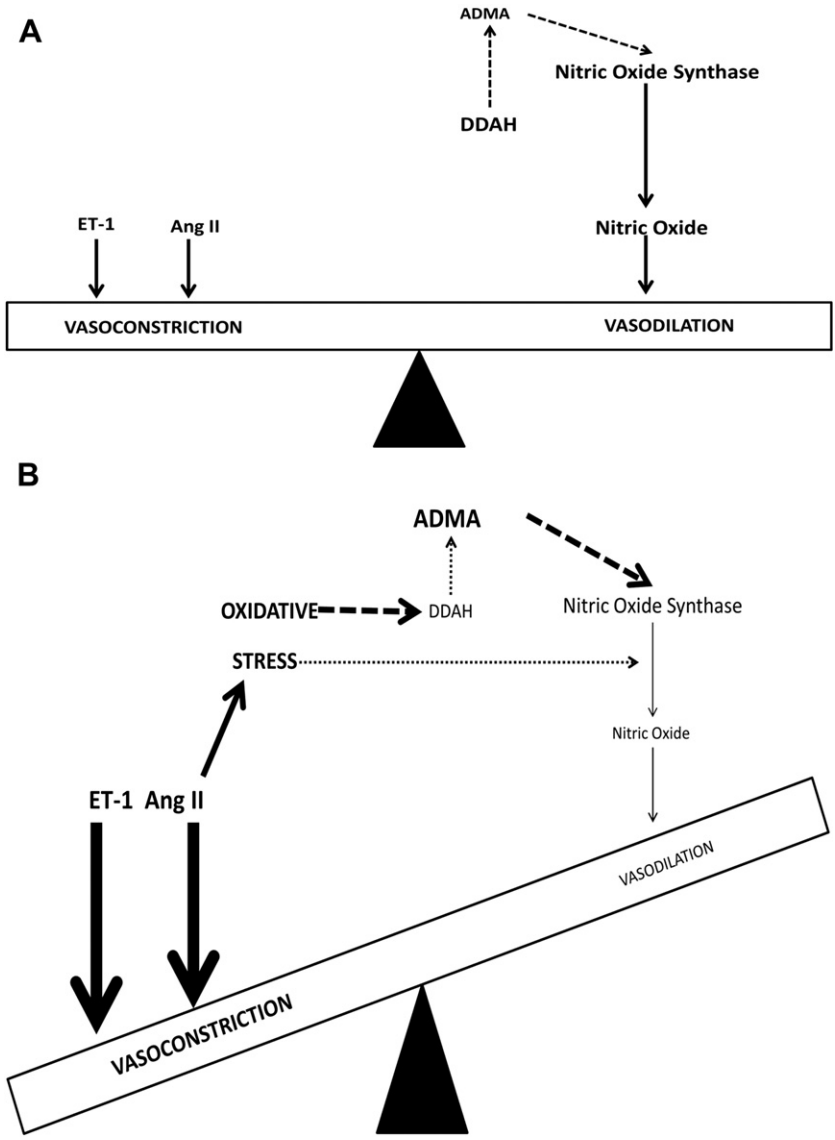

Fig. 2. The balance of various vasoconstrictors and the vasodilator nitric oxide on vascular smooth muscle tone is depicted in (*A*). Endothelial cell nitric oxide synthase should produce sufficient nitric oxide to balance out the effects of ET-1 and Ang II. Although ADMA can inhibit nitric oxide synthase activity, DDAH can sufficiently metabolize ADMA to restore balance. In the context of diabetic kidney disease (*B*), this entire balance can be disrupted owing in part to an increase level of oxidative stress. The RAAS system is inappropriately upregulated given the degree of extracellular volume overload, and Ang II can generate additional oxidative stress. This environment prevents adequate metabolism of ADMA by DDAH and promotes interaction of nitric oxide with free radicals. This ultimately results in inadequate nitric oxide production to counter the vasoconstriction caused by ET-1 and Ang II.

TREATMENT

Diabetic kidney disease develops and progresses over many years. In patients with type 2 diabetes, the presence of either albuminuria or microalbuminuria is the best predictor of rapid deterioration of GFR over the next several years.[53] The baseline GFR at the time of assessment is also an important predictor of ESRD.[54] Lowering blood pressure is one of the primary goals in the management of diabetic nephropathy. Blood pressure reduction slows decline in GFR in patients with type 1 diabetes and reduces the incidence of microalbuminuria in patients with type 2 diabetes.[55–58] The specific use of antihypertensive agents that offer additional renoprotective benefits, such as inhibitors of the RAAS, are considered to be the first-line antihypertensive agents in diabetic kidney disease.

RAAS Inhibition

The cardiovascular benefits of ACE inhibitors and angiotensin receptor blockers (ARBs) in diabetic patients have been extracted from clinical trials among more heterogeneous groups of high-risk patients.[59,60] One of these studies[59] further showed how ACE inhibitors may reduce the incidence of kidney disease. Appropriately, several large trials have been conducted to more specifically define the role RAAS inhibition in diabetic nephropathy.

Because of the potential for diabetic kidney disease to rapidly progress to ESRD once overt nephropathy is present, this stage of disease is expected to yield a large number of hard clinical end points that can be studied through clinical trials. The ACE inhibitor captopril, compared with placebo, reduced the risk for the primary end point doubling of serum creatinine among patients who are hypertensive with type 1 diabetes with more than 500 mg per day of proteinuria.[61] Therapy with captopril also resulted in a slower decline in creatinine clearance and a significant reduction in the composite end point of death and ESRD. Additionally, captopril therapy significantly attenuates the progression of albuminuria among patients with type 1 diabetes and overt nephropathy compared with standard antihypertensive therapy.[62] Inhibition of RAAS provides similar benefits for patients with type 2 diabetes and overt nephropathy. The Reduction in Endpoints in Non–insulin-dependent diabetes mellitus (RENAAL) trial and Irbesartan in Diabetic Nephropathy Trial (IDNT) both investigated the effects of ARBs versus placebo in this specific patient population.[63,64] The RENAAL trial showed the superior efficacy of losartan, and the IDNT showed superior efficacy of irbesartan.

Subsequent trials have investigated the effects of RAAS inhibition at earlier points in time including even before the onset of microalbuminuria. These studies have primarily used surrogate end points of disease progression, given the extended period that would be expected to generate hard clinical end points. Compared with placebo, irbesartan reduced the risk for incident diabetic nephropathy in a dose-dependent manner among patients who are hypertensive with type 2 diabetes and microalbuminuria.[65] Among patients with type 2 diabetes, trandolapril reduced the risk for developing microalbuminuria compared with both verapamil and placebo.[66] Most recently, olmesartan reduced the risk for microalbuminuria among a similar population compared with placebo.[67] These findings are in contrast to those from a study in patients who are normotensive with type 1 diabetes in which neither treatment with losartan nor enalapril resulted in any significant changes in mesangial fractional volume assessed on renal biopsy specimens compared with placebo.[68] Furthermore, in this study, more subjects receiving losartan developed microalbuminuria compared with those receiving placebo. Another analysis of studies including patients with type 1 and

type 2 diabetes failed to show any benefit of candesartan in preventing microalbuminuria, although this was not the original primary end point that these studies were powered to investigate.[69]

In summary, several landmark trials have specifically investigated the effects of RAAS inhibition in diabetic kidney disease. The findings from these studies fortify the evidence from subgroup analyses in clinical trials among more heterogeneous groups of diabetic patients. The cumulative evidence thus suggests that these drugs are beneficial to most patients with diabetes along a wide spectrum of renal disease.

Combined RAAS inhibition

Despite the findings from these trials and the common practice to implement RAAS inhibition in diabetic patients with any evidence of kidney disease, diabetic nephropathy continues to result in ESRD in a substantial number of patients. Because of the improvements in outcomes that have been proven with either an ACE inhibitor or ARB, there remains speculation that further inhibition of RAAS through combination therapy may extend the benefits experienced with the use of a single agent. Such a strategy theoretically offers the ability to target (1) incomplete inhibition of the production or effects of Ang II, (2) increases in renin that can occur with ACE inhibitor use, or (3) "aldosterone escape" that can occur with ACE inhibitor or ARB use. The effects of these strategies on BP and albuminuria in patients with diabetic nephropathy are summarized in **Table 1**.

There is conflicting evidence of the effect of combining an ACE inhibitor and ARB in diabetic patients. In studies that individually studied type 1 and type 2 diabetic patients alone, combination therapy showed greater proteinuria reduction compared with single-agent RAAS blockade.[70,71] In a study that included both type 1 and type 2 diabetic patients, such an effect was not seen.[72] Given that this latter study followed patients for up to 1 year, the paucity of studies that are of sufficient duration to detect hard clinical end points must be emphasized in considering this option of therapy.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) provides counterpoint evidence for combination RAAS inhibition in diabetes.[73] This trial used a composite of cardiovascular end points to compare ramipril, telmisartan, or combination therapy among a large population of subjects (with or without diabetes) considered at high risk for such events. Hyperkalemia and renal failure occurred more often in the combination therapy group despite both groups having similar results regarding the primary composite end point. A limitation in generalizing these findings to diabetic kidney disease is that (1) this study had relatively few subjects with diabetic kidney disease at baseline and (2) those with diabetic kidney disease were not found to be the subjects with the highest risk for renal outcomes in post hoc analysis.[74] Ultimately, the Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy VA NEPHRON-D Study: Nephropathy in Diabetes Study (VA NEPHRON) should answer the question of what role ACE inhibitor plus ARB therapy has in this population.[75] This active study includes patients with type 2 diabetes with overt nephropathy and is using a composite of renal outcomes and mortality as the primary end point in comparing lisinopril plus losartan therapy with losartan alone.

Addition of a mineralocorticoid receptor antagonist (MRA) to baseline therapy, including an ACE inhibitor or ARB, is another potential consideration that targets the specific renal and extrarenal effects of aldosterone. Two brief studies (one in patients with type 1 diabetes only) and a 1-year study in patients with type 1 and type 2 diabetes demonstrated that this strategy reduces proteinuria compared with single-agent therapy.[76–78] The long-term effects of combination therapy, including an MRA

Table 1
Clinical trials in diabetic nephropathy comparing dual RAAS inhibition to single-agent RAAS inhibition

Population/Baseline Medication Use	Intervention Groups	Renal End Point	BP Effect
ACE Inhibitor + ARB			
Type 2 DM Receiving maximum dose of ACE Inhibitor[71]	1. Candesartan 16 mg 2. Placebo	Albuminuria (mg/24 h) 1. Candesartan 706 2. Placebo 508 (28% reduction, $P<.001$)	24 h SBP (mm Hg): 1. Candesartan 135 vs 2. Placebo 138 ($P = .21$)
Type 1 DM[70]	1. Benazepril 20 mg 2. Valsartan 80 mg 3. Benazepril + Valsartan 4. Placebo	Albuminuria (mg/24 h) 1. Benazepril: 239 2. Valsartan: 225 3. Combination: 138 4. Placebo: 701 All $P<.001$ vs placebo; combination <.01 vs monotherapy	24 h SBP vs placebo: 1. Benazepril: –15 mm Hg 2. Valsartan: –15 mm Hg 3. Combination Therapy: –22 mm Hg
Type 1 or 2 DM[72]	1. Lisinopril 40 mg 2. Candesartan 16 mg + Lisinopril 20 mg	UACR change (mg/mmol) 1. Lisinopril: –0.16 2. Combination therapy: –0.42 ($P = .38$ vs lisinopril)	Mean difference between 24 h SBP: 3.9 mm Hg ($P = .16$)
Type 2 DM[75]	1. Losartan 2. Losartan + Lisinopril	ONGOING TRIAL (VA-NEPHRON)	

ACE Inhibitor or ARB + Mineralocorticoid Receptor Antagonist			
Type 1 DM ACE Inhibitor or ARB[76]	1. Spironolactone 25 mg 2. Placebo	Albuminuria (mg/d) 1. Spironolactone: 584 2. Placebo: 831 (P<.001)	24 h BP (mm Hg) 1. Spironolactone:136 2. Placebo: 144 (P = .08)
Type 1 and 2 DM Nephrotic Syndrome ACE Inhibitor or ARB[77]	1. Spironolactone 25 mg 2. Placebo	Albuminuria (g/d) 1. Spironolactone: 2.5 2. Placebo: 3.7 (P<.001)	24 h SBP (mm Hg) 1. Spironolactone:137 2. Placebo: 143 (P = .004)
Type 1 and 2 DM Lisinopril 80 mg[78]	1. Spironolactone 25 mg 2. Losartan 100 mg 3. Placebo	Albuminuria Reduction 1. Spironolactone: –51.6% (–38.2% vs placebo, P = .007) 2. Losartan –38.2% (–16.8% vs placebo, P = .2)	SBP (mm Hg) 1. Spironolactone: 132 2. Losartan: 134 3. Placebo: 136 (NS between groups)
ACE Inhibitor or ARB + Direct Renin Inhibitor			
Type 2 DM Losartan 100 mg[80]	1. Aliskiren 300 mg 2. Placebo	UACR 1. Aliskiren: –20% vs placebo (P<.001)	SBP (mm Hg) 1. Aliskiren: –2 vs placebo (P<.07)
Type 2 DM[81]	1. Aliskiren 300 mg 2. Irbesartan 300 mg 3. Aliskiren + Irbesartan 4. Placebo	Albuminuria reduction vs placebo: 1. Aliskiren: –48% (P<.001) 2. Irbesartan –58% (P<.001) 3. Combination therapy: –71% (P<.00 compared with placebo and this was significant compared with either monotherapy: P<.001 and P = .028)	24 h SBP reduction (mm Hg) 1. Aliskiren: –3 (NS) 2. Irbesartan –12 (P<.001) 3. Combination therapy: –10 (P = .001 vs placebo, NS vs Irbesartan)
Type 2 DM[82]	1. Aliskiren 300 mg 2. Placebo	TERMINATED secondary to adverse events in Aliskiren group	

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; DM, diabetes mellitus; RAAS, renin angiotensin aldosterone system; SBP, systolic blood pressure; UACR, urine albumin creatinine ratio.

on hard clinical end points remain unknown. Hyperkalemia is also a potential risk to be aware of with this strategy.

One final RAAS-inhibiting combination therapy that has been explored is the addition of a direct renin inhibitor (DRI) to either an ACE inhibitor or an ARB. Direct renin inhibitors are antihypertensive drugs that lower albuminuria in diabetic nephropathy compared with placebo, and they further reduce albuminuria when combined with an ARB[79–81]; however, there have been recent safety concerns for this strategy following the early termination of the Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints (ALTITUDE) trial. Inclusion criteria for this study were (1) type 2 diabetes, (2) current use of either an ACE inhibitor or ARB, and (3) either macroalbuminuria or reduced kidney function plus 1 additional cardiovascular risk factor.[82] The subjects were randomized to either aliskiren 300 mg daily or placebo. Early termination from the trial resulted from excessive incidents of hyperkalemia, renal failure, and hypotension in the aliskiren group.[83] There were not reported to be any beneficial effects of aliskiren on the primary outcome, and this combination strategy is currently contraindicated in patients with diabetes.

The role of dietary sodium in RAAS inhibition

Although the role of combination RAAS therapy continues to be explored, it is important to acknowledge RAAS inhibition can be optimized with judicious management of extracellular volume. Recently, a retrospective analysis of IDNT and RENAAL investigated the association of urinary sodium/creatinine ratio on renal and cardiovascular outcomes.[84] Among subjects who were randomized to an ARB, there were fewer renal events and fewer cardiovascular events among those with lower amounts of sodium excretion. This effect was not seen in the subjects who were not randomized to an ARB. Furthermore, the beneficial effects seen in subjects randomized to ARB compared with those not randomized to ARB were amplified in the subjects with the lowest sodium excretion. Dietary sodium ingestion has similarly been shown to influence outcomes in a retrospective analysis of nondiabetic patients with CKD. Among subjects from the Ramipril Efficacy in Nephropathy (REIN) studies receiving ramipril, the risk for ESRD increased with increases in urinary sodium excretion and appeared to be influenced by proteinuria.[85] Although these findings remain limited by the retrospective nature of the studies, dietary sodium restriction and judicious use of diuretics remain recommended strategies to enhance the effects of ACE inhibitors and ARB.

Vitamin D therapy

Vitamin D has also been identified as a potential mediator of RAAS activity in animal studies.[86,87] In animal models of diabetes, knockout of the vitamin D receptor resulted in more proteinuria and glomerulosclerosis.[88] Vitamin D is widely prescribed for patients with CKD and ESRD with secondary hyperparathyroidism. Recent evidence suggests that vitamin D may have additional therapeutic benefits among patients with diabetic nephropathy.[89] In a randomized clinical trial, paracalcitiol, 2 μg daily, significantly reduced both systolic blood pressure and urinary albumin excretion compared with placebo. Among subjects receiving either 1 or 2 μg daily, there remained a positive trend toward albuminuria reduction compared with placebo. The overall cardiovascular and renal effects of vitamin D remain to be further explored.

Mediators of Endothelial Cell Dysfunction

Inhibition of the RAAS does not completely eliminate proteinuria in all patients with diabetic kidney disease. Consequently, therapies that target other potential mechanisms

for hypertension and renal disease progression offer alternative strategies to improve outcomes in these patients. Endothelial cell dysfunction plays a role in hypertension in this population, but likely also has an independent effect on kidney disease.[90] Several clinical trials have investigated the effects of various endothelin receptor antagonists on diabetic kidney disease.[41,91–93] Some of these medications differ in their specificity for inhibiting either the ET-A receptor or the ET-B receptor. On vascular smooth muscle cells, the ET-A receptor is responsible for vasoconstriction, whereas the ET-B receptor is more responsible for vasodilation and removal of circulating ET-1. Although these studies consistently show reduction in proteinuria regardless of the study medication, the different receptor specificities may be responsible for differences in adverse effects that have been noted among them.

Bosentan is an ET-1 receptor antagonist that binds to both ET-A and ET-B receptors. One small randomized trial in subjects with type 2 diabetes and microalbuminuria showed that 4 weeks of bosentan improved peripheral endothelial cell function compared with placebo. This short study failed to show improvement in macrovascular endothelial cell function assessed by brachial artery flow-mediated vasodilation or in microalbuminuria (not a specified end point) so that the clinical relevance of these results remains unclear.[41]

Larger studies with other endothelin receptor antagonists have overall shown positive results regarding proteinuria reduction in (**Table 2**), but have been limited by concurrent adverse events. Compared with placebo, avosentan achieved significant reductions in the primary end point of albuminuria reduction but resulted in peripheral edema in a dose-dependent manner.[91] A larger placebo-controlled trial with this drug in diabetic nephropathy was terminated early because of an increased incidence of congestive heart failure with avosentan, despite the proteinuria reduction.[92] A trial investigating the effects of a more ET-A–specific drug, atrasentan, showed a lower incidence of peripheral edema compared with those reported with avosentan while preserving the proteinuria-reducing effects of this drug class.[93] As this trial was of brief duration, further investigation is warranted to establish the efficacy and safety of this drug.

Other Novel Applications of Antihypertensives in Diabetic Kidney Disease

Lowering blood pressure with antihypertensive drugs has clearly been demonstrated to improve outcomes in diabetic kidney disease. As we have learned about the mechanisms responsible for not only hypertension, but also kidney disease progression itself, certain antihypertensive drugs, such as RAAS inhibitors, have stood out as offering renoprotection independent of their blood pressure–lowering effect. As the clinical research arena follows the basic science advancements in understanding diabetic kidney disease, there are likely to be more novel approaches to treating this disease.

Losartan established the role of ARBs in diabetic kidney disease in the RENAAL trial. Subsequent analysis of that study now demonstrates a significant reduction in serum uric acid in patients randomized to losartan compared with placebo and that the reduction in uric acid was independently associated with a reduction in the risk for renal end points.[94] At present, the adverse effects of endothelin receptor antagonists have hindered their acceptance as a safe option to treat diabetic nephropathy. However, therapeutic interventions that improve endothelial cell dysfunction are still sought after. One drug, nicorandil, is a nitrogen donor and is also believed to inhibit the production of free radicals within endothelial cells. When administered to rats with streptozocin-induced diabetes, there is a reduction in proteinuria that coincides with preservation of podocyte structure, although there was no evidence of systemic benefits on endothelial cell dysfunction.[95] There are currently available “third-generation”

Table 2
Clinical trials studying the effects of endothelin receptor antagonists in diabetic nephropathy

Population/Baseline Medication	Intervention Group	Renal End Point	BP End Point
Type 1 and 2 DM ACE inhibitor or ARB therapy[91]	1. Avosentan 5 mg 2. Avosentan 10 mg 3. Avosentan 25 mg 4. Avosentan 50 mg 5. Placebo	Mean relative percent change in UAER from baseline: 1. Avosentan 5 mg: –20.9% 2. Avosentan 10 mg: –16.3% 3. Avosentan 25 mg: –25% 4. Avosentan 50 mg: –29.9% 5. Placebo: +35.5 (P<.01 for all doses vs placebo)	SBP (mm Hg) (baseline, week 12 follow up): 1. Avosentan 5 mg: 146, 142 2. Avosentan 10 mg: 147, 144 3. Avosentan 25 mg: 140, 141 4. Avosentan 50 mg: 146, 144 5. Placebo: 144, 147 (P<.01 for all doses vs placebo)
Type 2 DM ACE Inhibitor or ARB[92]	1. Avosentan 25 mg 2. Avosentan 50 mg 3. Placebo	No effect seen on primary outcome of doubling serum creatinine, ESRD or death. terminated early albuminuria reduced with avosentan Median UACR −40%−50% in Avosentan Groups vs –8%–10% in placebo (P<.0001) Change in sitting SBP at 3 months and 6 months: Avosentan 25 mg: –4.1 and –4.3 mm Hg (P = .09, .09) Avosentan 50 mg: –4.4 and –6.1 mm Hg (P = .02 and .02); Placebo: 0.5, –0.5	
Type 2 DM ACE Inhibitor or ARB[93]	1. Atresentan 0.25 mg 2. Atresentan 0.75 mg 3. Atresentan 1.75 mg 4. Placebo	UACR Reduction 1. Atresentan 0.25 mg: 21% (P = .03 vs placebo) 2. Atresentan 0.75 mg: 42% (P = .02 vs placebo) 3. Atresentan 1.75 mg: 35% (P = .07 vs placebo) 4. Placebo: –11%	SBP Reduction (mm Hg) 1. Atresentan 0.25 mg: –0.3 (P = .8 vs placebo) 2. Atresentan 0.75 mg: –8.8 (P = .05 vs placebo) 3. Atresentan 1.75 mg: –7.6 (P = .09 vs placebo) 4. Placebo+ 0.7

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; DM, diabetes mellitus; ESRD, end stage renal disease; SBP, systolic blood pressure; UACR, urine albumin creatinine ratio; UAER, urinary albumin excretion ratio.

beta adrenergic receptor antagonists that possess properties that are believed to improve endothelial cell dysfunction.[96–98]

Blood Pressure Targets

Despite the Kidney Disease Outcomes Quality Initiative recommendations to target a blood pressure of 130/80[4], there is no randomized clinical trial that establishes this target for patients with diabetic kidney disease. In subgroup analysis of the Hypertension Optimal Treatment (HOT) trial, the 1500 subjects with diabetes had significant reductions in a composite of major cardiovascular events with randomization to lower diastolic blood pressure levels (80 vs 85 vs 90 mm Hg)[99]; however, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study did not show any benefit of lowering systolic blood pressure to lower than 120 mm Hg compared with lower than 140 mm Hg among patients with type 2 diabetes without significant proteinuria or renal impairment.[100] Among patients with diabetic nephropathy in retrospective analysis of IDNT, there was increased risk for all-cause and cardiovascular mortality with systolic blood pressure lower than 120 mm Hg and diastolic blood pressure lower than 85 mm Hg, respectively.[101] This is in contrast to analyses showing that lower blood pressure invariably improves renal outcomes in patients with diabetes, including those with diabetic nephropathy at baseline.[102,103] The potential cardiovascular risk of achieving too low of a blood pressure must be weighed against the apparent renal benefits of such a strategy, and thus some uncertainty remains as to what the absolute ideal blood pressure target should be for patients with diabetic kidney disease.

RECOMMENDATIONS

Regardless of the stage of kidney disease, an ACE inhibitor or ARB should be used as a first-line antihypertensive drug in all diabetic patients. This strategy offers cardioprotective effects in those with preserved kidney function and renoprotective effects in those with varying degrees of renal impairment. Blood pressure should be lowered to a target of 130/80, but further prospective research is required to further delineate more specific goals beyond that. Patients should be instructed to limit their dietary sodium ingestion and diuretics should be used in patients who remain hypertensive despite the use of a RAAS inhibitor or for patients susceptible to hyperkalemia. It is likely that many patients will require even further antihypertensive therapy, which should include beta blockers, calcium channel blockers, vasodilators, and centrally acting agents as guided by the underlying comorbidities of an individual patient. Regarding combination RAAS therapy, the use of an ACE inhibitor plus ARB requires completion of the VA NEPHRON study. Direct renin inhibitors should not be used with an ACE inhibitor or ARB in patients with diabetic nephropathy, but adding a mineralocorticoid receptor blocker remains a potentially viable strategy that requires further investigation.

SUMMARY

Hypertension commonly coexists with diabetes, and its prevalence is even higher in the presence of diabetic kidney disease. The pathogenesis of hypertension in this population stems from increased extracellular volume and increased vasoconstriction that results from mechanisms that may be attributed to both diabetes and the eventual impairment of renal function. Antihypertensive therapy aimed at reducing blood pressure remains a primary goal in preventing the incidence of diabetic kidney and slowing its progression. Initial therapy should consist of an ACE inhibitor or ARB titrated to the maximally tolerated dose. Using combination RAAS therapy further reduces proteinuria, but the benefits of this strategy compared with the potential risks of hyperkalemia

and acute deterioration of renal function are still unknown. Endothelin receptor antagonists also lower proteinuria, but these can be associated with volume overload and edema with no clear long-term benefit on renal function yet identified. Further large clinical trials are needed to better understand how progression to ESRD can be slowed or halted in patients with diabetic kidney disease.

REFERENCES

1. Parving H, Gall M, Skott P, et al. Prevalence and causes of albuminuria in non insulin-dependent diabetic patients. Kidney Int 1992;4:758–62.
2. Chobanian A, Bakris G, Black H, et al. The Seventh Report of the Joint National Committee on Prevention, detection, evaluation, and treatment of high blood pressure. J Am Med Assoc 2003;289:2560–72.
3. American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care 2003;26:S80–2.
4. National Kidney Foundation. KDOQI Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49(Suppl 2):S1–180.
5. Norgaard K, Feldt-Rasmussen B, Johnsen K, et al. Prevalence of hypertension in type 1 (insulin dependent) diabetes mellitus. Diabetologia 1990;33:407–10.
6. Parving H, Hommel E, Mathiesen E, et al. Prevalence of microalbuminuria, arterial hypertension, retinopathy, and neuropathy in patients with insulin dependent diabetes. Br Med J (Clin Res Ed) 1988;296:156–60.
7. Lurbe E, Redon J, Kesani A. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N Engl J Med 2002;347:797–805.
8. Haffner S, Mykkanen L, Festa A, et al. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. Circulation 2000;101:975–80.
9. Keller C, Bergis K, Filser D, et al. Renal findings in patients with short term type 2 diabetes. J Am Soc Nephrol 1996;7:2627–35.
10. Ismail N, Becker B, Strzelczyk P, et al. Renal disease and hypertension in non-insulin dependent diabetes mellitus. Kidney Int 1999;55:1–28.
11. Hypertension in Diabetes Study Investigators. Hypertension in Diabetes Study (HDS): II, increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. J Hypertens 1993;11:319–25.
12. Mogensen C. Glomerular filtration rate and renal plasma flow in short-term and long-term juvenile diabetes mellitus. Scand J Clin Lab Invest 1971;28:91–100.
13. Vallon V, Richter K, Blantz R, et al. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. J Am Soc Nephrol 1999;10: 2569–76.
14. Brands M, Bell T, Gibson B. Nitric oxide may prevent hypertension early in diabetes by counteracting renal actions of superoxide. Hypertension 2004;43: 57–63.
15. Veelken R, Hilgers K, Hartner A, et al. Nitric oxide synthase isoforms and glomerular hyperfiltration in early diabetic nephropathy. J Am Soc Nephrol 2000;11:71–9.
16. Tuck M, Corry D, Trujillo A. Salt-sensitive blood pressure and exaggerated vascular reactivity in the hypertension of diabetes mellitus. Am J Hypertens 1990;88:210–6.

17. Anderson F, Jung F, Ingelfinger J. Renal rennin-angiotensin system in diabetes: functional, immunohistochemical, and molecular biologic correlations. Am J Physiol 1993;265(4 Pt 2):F477–86.
18. Konoshita T, Wakahara S, Mizuno EA. Tissue gene expression of rennin-angiotensin system in human type 2 diabetic nephropathy. Diabetes Care 2006;29:848–52.
19. Mizuiri S, Yoshikawa H, Tanegashima M, et al. Renal ACE immunohistochemical localization in NIDDM patients with nephropathy. Am J Kidney Dis 1998;31:301–7.
20. Mezzano S, Droguett A, Burgos M, et al. Renin-angiotensin system activation and interstitial inflammation in human diabetic nephropathy. Kidney Int Suppl 2003;86:S64–70.
21. Price D, Porter L, Gordon M. The paradox of the low renin state in diabetic nephropathy. J Am Soc Nephrol 1999;10:2382.
22. Price D, De'Oliveira J, Fisher N, et al. The state and responsiveness of the renin-angiotensin-aldosterone system in patients with type 2 diabetes mellitus. Am J Hypertens 1999;12:348.
23. Giani J, Burghi V, Veiras L, et al. Angiotensin-(1-7) attenuates diabetic nephropathy in Zucker diabetic fatty rats. Am J Physiol Renal Physiol 2012;302: F1606–15.
24. Ye M, Wysocki J, William J, et al. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. J Am Soc Nephrol 2006;17:3067–75.
25. Lely A, Hamming I, van Goor H, et al. Renal ACE2 expression in human kidney disease. J Pathol 2004;204:587–93.
26. Mizuiri S, Hemmi H, Arita M, et al. Expressio of ACE and ACE2 in individuals with diabetic kidney disease and healthy controls. Am J Kidney Dis 2008;51:613–23.
27. Soro-Paavonen A, Gordin D, Forsblom C, et al. Circulating ACE2 activity is increased in patients with type 1 diabetes and vascular complications. J Hypertens 2012;30:375–83.
28. Dogra G, Irish A, Chan D, et al. Insulin resistance, inflammation, and blood pressure determine vascular function in CKD. Am J Kidney Dis 2006;48:926–34.
29. Makino H, Doi K, Hiuge A, et al. Impaired flow-mediated vasodilation and insulin resistance in type 2 diabetic patients with albuminuria. Diabetes Res Clin Pract 2008;79:177–82.
30. Chan W, Chan N, Lai C, et al. Vascular defect beyond the endothelium in type II diabetic patients with overt nephropathy and moderate renal insufficiency. Kidney Int 2006;70:711–6.
31. Giugliano D, Marfella R, Coppola L, et al. Vascular effects of acute hyperglycemia in humans are reversed by L-arginine: evidence for reduced availability of nitric oxide during hyperglycemia. Circulation 1997;95:1783–90.
32. Fitzgerald S, Brands M. Nitric oxide may be required to prevent hypertension at the onset of diabetes. Am J Phys 2000;279:E762–8.
33. Achan V, Broadhead M, Malaki M, et al. Asymetric dimethylarginine causes hypertension and cardiac dysfunction in humans and is actively metabolized by dimethyl dimethylaminohydrolase. Arterioscler Thromb Vasc Biol 2003;23: 1455–9.
34. Kielstein J, Boger R, Bode-Boger S. Asymetric dimethylarginine concentrations differ in patients with end stage renal disease: relationship to treatment method and atherosclerotic disease. J Am Soc Nephrol 1999;10:594–600.
35. Zoccali C, Bode-Boger S, Mallamaci F, et al. Plasma concentrations of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. Lancet 2001;358:2113–7.

36. Tarnow L, Hovind P, Teerlink T, et al. Elevated plasma asymetric dimethylarginine as a marker of cardiovascular morbidity in early diabetic nephropathy in type 1 diabetes. Diabetes Care 2004;27:765–9.
37. Abbasi F, Asagmi T, Cooke J, et al. Plasma concentrations of asymetric dimethylarginine are increased in patients with type 2 diabetes mellitus. Am J Cardiol 2001;88:1201–3.
38. Kakizawa H, Itoh M, Itoh Y, et al. The relationship between glycemic control and plasma vascular endothelial growth factor and endothelin-1 concentration in diabetic patients. Metabolism 2004;53:550–6.
39. Minchenko A, Stevens M, White L, et al. Diabetes-induced overexpression of endothelin-1 and endothelin receptors in the rat renal cortex is mediated via poly (ADP-ribose) polymerase activation. FASEB 2003;17:1514–6.
40. Muniyappa R, Quon M. Insulin action and insulin resistance in vascular endothelium. Curr Opin Clin Nutr Metab Care 2007;10:523.
41. Rafnsson A, Bohm F, Settergren M, et al. The endothelin receptor antagonist bosentan improves peripheral endothelial cell function in patients with type 2 diabetes mellitus and microalbuminuria: a randomised trial. Diabetologia 2012;55:600–7.
42. Rajagopalan S, Kurz S, Munzel T, et al. Angiotensin II-mediated hypertension in the rate increases vascular superoxide production via membrane NADH/NADPH oxidase activation. J Clin Invest 1996;97:1916–23.
43. Griendling K, Ollernenshaw J, Minieri C, et al. Angiotensin II stimulates NADH and NADPH activity in cultured vascular smooth muscle cells. Circ Res 1994;74:1141–8.
44. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813–20.
45. Spittle M, Hoenich N, Handelman G, et al. Oxidative stress and inflammation in hemodialysis patients. Am J Kidney Dis 2001;38:1408–13.
46. Ceballos-Picot I, Wtiko-Sarsat V, Merad-Boudia M, et al. Glutathione antioxidant system as a marker of oxidative stress in chronic renal failure. Free Radic Biol Med 1996;21:845–53.
47. Campese V, Kogosove E. Renal afferent denervation prevents hypertension in rats with chronic renal failure. Hypertension 1995;25:878–82.
48. Converse R, Jacobsen T, Toto R, et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med 1992;327:1912–8.
49. Ligtenberg G, Blankestijn P, Oey P, et al. Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. N Engl J Med 1999;340:1321–8.
50. Spallone V, Gambardella S, Maiello M, et al. Relationship between autonomic neuropathy, 24-h blood pressure profile, and nephropathy in normotensive IDDM patients. Diabetes Care 1994;17:578–84.
51. Liniger C, Favre L, Assal J. Twenty-four hour blood pressure and heart rate profiles of diabetic patients with abnormal cardiovascular reflexes. Diabet Med 1991;8:420–7.
52. Nielsen F, Hansen H, Jacobsen P. Increased sympathetic activity during sleep and nocturnal hypertension in Type 2 diabetic patients with diabetic nephropathy. Diabet Med 1999;16:555–62.
53. Zoppini G, Targher G, Choncol M, et al. Predictors of estimated GFR decline in patients with type 2 diabetes and preserved kidney function. Clin J Am Soc Nephrol 2012;7:401–8.
54. Berhane A, Weil E, Knowler W, et al. Albuminuria and estimated glomerular filtration rate as predictors of diabetic end-stage renal disease and death. Clin J Am Soc Nephrol 2011;6:2444–51.

55. Mogensen C. Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. Br Med J 1982;285:685–8.
56. Parving H, Smidt U, Andersen A, et al. Early aggressive anithypertensive treatment reduces rate of decline of kidney function in diabetic nephropathy. Lancet 1983;321:1175–9.
57. Parving H, Andersen A, Smidt U, et al. Effect of antihypertensive treatment on kidney function in diabetic nephropathy. Br Med J 1987;294:1443–7.
58. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–13.
59. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; 355:253–9.
60. Lindholm L, Ibsen H, Dahlof B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359:1004–10.
61. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993;329(20):1456–62.
62. Parving HH, Hommel E, Jensen BR, et al. Long-term beneficial effect of ACE inhibition on diabetic nephropathy in normotensive type 1 diabetic patients. Kidney Int 2001;60(1):228–34.
63. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345(12):851–60.
64. 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(12):861–9.
65. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345(12):870–8.
66. Ruggenenti P, Fassi A, Ilieva A, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941–51.
67. Haller H, Ito S, Izzo J, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–17.
68. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40–51.
69. Bilous R, Chaturvedi N, Sjolie A, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes. Ann Intern Med 2009;151: 11–20.
70. Jacobsen P, Andersen S, Jensen B, et al. Additive effect of ACE inhibition and angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. J Am Soc Nephrol 2003;14:992–9.
71. Rossing K, Jacobsen P, Pietraszek L, et al. Renoprotective effects of adding angiotensin II receptor blocker to maximal recommended doses of ACE inhibitor in diabetic nephropathy. Diabetes Care 2003;26:2268–74.
72. Andersen N, Poulsen P, Knudson S, et al. Long-term dual blockade with candesartan and lisinopril in hypertensive patients with diabetes. Diabetes Care 2005; 28:273–7.

73. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–59.
74. Mann J, Schmieder R, McQueen EA. Renal outcomes with telmisartan, ramipril, or both in people at high vascular risk (the ONTARGET study): a multicentre, randomized, double-blind, controlled trial. Lancet 2008;372:547–53.
75. Department of Veteran Affairs; Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy; VA NEPHRON-D Study: Nephropathy iN Diabetes Study. In: Clinical Trials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000-[cited 2012 March 26]. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00555217. Accessed on 26th March 2012.
76. Schjoedt K, Rossing K, Juhl T, et al. Beneficial impact of spironolactone in diabetic nephropathy. Kidney Int 2005;68:2829–36.
77. Schjoedt KJ, Rossing K, Juhl TR, et al. Beneficial impact of spironolactone on nephrotic range albuminuria in diabetic nephropathy. Kidney Int 2006;70(3): 536–42.
78. Mehdi U, Adams-Huet B, Raskin P, et al. Addition of angiotensin receptor blockade or a mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. J Am Soc Nephrol 2009;20:2641–50.
79. Persson F, Rossing P, Schjoedt K, et al. Time course of the antiproteinuric and anithypertensive effects of the direct rennin inhibition in type 2 diabetes. Kidney Int 2008;73:1419–25.
80. Parving H, Persson F, Lewis J, et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008;358:2433–46.
81. Persson F, Rossing P, Reinhard H. Renal effects of aliskiren compared with and in combination with irbesartan in patients with type 2 diabetes, hypertension, and albuminuria. Diabetes Care 2009;32:1873–9.
82. Parving H, Brenner B, McMurray J, et al. Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design. Nephrol Dial Transplant 2009;24:1663–71.
83. Aliskiren-containing medications: drug safety communication—new warning and contraindication. 2012. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm301120.htm?source=govdelivery. Accessed May 4, 2012.
84. Heerspink H, Holtkamp F, Parving H, et al. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. Kidney Int 2012;82:330–7.
85. Vegter S, Perna A, Postma M, et al. Sodium intake, ACE inhibition, and progression to ESRD. J Am Soc Nephrol 2012;23:165–73.
86. Li Y, Kong J, Wei M, et al. 1,25-Dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002;110:229–38.
87. Zhou C, Lu F, Cao K, et al. Calcium-independent and $1,25(OH)_2D_3$-dependent regulation of the renin-angiotensin system in 1 alpha-hydroxylase knockout mice. Kidney Int 2008;74:170–9.
88. Zhang Z, Sun L, Wang Y, et al. Renoprotective role of the vitamin D receptor in diabetic nephropathy. Kidney Int 2008;73:163–71.
89. de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet 2010;376:1543–51.
90. Jawa A, Nachimuthu M, Pendergrass M, et al. Impaired vascular reactivity in African American patients wtih type 2 diabetes mellitus and microalbuminuria

or proteinuria despite angiotensin converting enzyme inhibitor therapy. J Clin Endocrinol Metab 2006;91:31–5.
91. Wenzel R, Littke T, Kuranoff S, et al. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. J Am Soc Nephrol 2009;20:655–64.
92. Mann J, Green D, Jamerson K, et al. Avosentan for overt diabetic nephropathy. J Am Soc Nephrol 2010;21:527–35.
93. Kohan D, Pritchett Y, Molitch M, et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. J Am Soc Nephrol 2011;22:763–72.
94. Miao Y, Ottenbros S, Laverman G, et al. Effect of a reduction in uric acid on renal outcomes during losartan treatment. Hypertension 2011;58:2–7.
95. Tanabe K, Lanaspa M, Kitagawa W, et al. Nicorandil as a novel therapy for advanced diabetic nephropathy in the e-NOS deficient mouse. Am J Physiol Renal Physiol 2012;302:F1151–60.
96. Saijonmaa O, Metsarinne K, Fyhrquist F. Carvedilol and its metabolites suprress endothelin-1 production in endothelial cell culture. Blood Press 1997;6:24–8.
97. Inrig J, Van Buren P, Kim C, et al. Probing the mechanisms of intradialytic hypertension: a pilot study targeting endothelial cell dysfunction. Clin J Am Soc Nephrol 2012;7:1300–9.
98. Zepeda R, Castillo R, Rodrigo R, et al. Effect of Carvedilol and Nebivolol on Oxidative Stress-related Parameters and Endothelial Function in Patients with Essential Hypertension. Basic Clin Pharmacol Toxicol 2012;111:309–16.
99. Hansson L, Zanchetti A, Carruthers S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351: 1755–62.
100. The ACCORD Study Group. Effects of intensive blood pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–85.
101. Berl T, Hunsicker LG, Lewis J, et al. Impact of achieved blood pressure on cardiovascular outcomes in the irbesartan diabetic nephropathy trial. J Am Soc Nephrol 2005;16:2170–9.
102. Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Arch Intern Med 2003;163(13):1555–65.
103. de Galan B, Perkovic V, Ninomiya T, et al. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol 2009;20:883–92.