Slowing Progression Along the Renal Disease Continuum

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Patients in whom nephropathy develops as a result of hypertension or diabetes mellitus are more likely to die of cardiovascular disease (CVD) than of kidney disease. An early sign of impending nephropathy is microalbuminuria, defined as urinary excretion of albumin at a rate of 28.8 mg/24 h to 288 mg/24 h. Microalbuminuria is a marker of endothelial dysfunction, vascular injury, and renal disease and CVD, and it is associated with increased risk for myocardial infarction. Oxidative stress and endothelial dysfunction are unifying factors mediated by the renin-angiotensin system in renal disease and CVD. Clinical trials show reduced cardiovascular risk and a reversal of microalbuminuria with the use of agents that affect the renin-angiotensin system: angiotensin-receptor blockers in patients with type 2 diabetes mellitus and nephropathy, or angiotensin-converting enzyme inhibitors in patients with type 1 diabetes mellitus.

Preventing renal impairment is an urgent challenge for the medical profession. No treatment modality other than kidney transplantation effectively restores renal function once end-stage renal disease (ESRD) develops, and cardiovascular disease (CVD) is the leading cause of death among patients with ESRD. Progression along the continuum from early renal impairment to ESRD involves interactions of risk factors and deleterious conditions with increasing cardiovascular and renal risk (Figure).

The excessive risk for CVD associated with nephropathy is due to a greater prevalence of cardiovascular risk factors—older age, hypertension, high blood cholesterol and lipid levels, diabetes mellitus, and physical inactivity—in patients with renal disease. Use of the glomerular filtration rate (GFR) as a reliable indicator of renal function (Table 1) indicates an estimated 8.3 million persons in the United States have chronic kidney disease (CKD); of these, 5.9 million have stage 1 renal disease, and 300,000 are in stage 5, or kidney failure. Age, hypertension, and diabetes mellitus are key predictors of CKD (stages 3 through 5), and 11% of individuals in the United States aged 65 years and older have stage 3 kidney disease or worse, even without hypertension or diabetes. Renal disease clearly increases the risk for premature CVD. Even after the stratification by age, gender, race, and presence of diabetes, CVD mortality in patients with ESRD is 10 to 20 times greater than in the general population, and in patients aged 45 years and younger, more than 100 times greater. Left ventricular hypertrophy (LVH) already is present in approximately 75% of patients who start dialysis. Other cardiovascular diseases that occur in patients with ESRD include coronary atherosclerosis, heart failure, ischemic heart disease (angina pectoris, myocardial infarction), and aortic and arterial stiffening.

Kidney impairment that leads to ESRD usually progresses through several well-defined stages: microalbuminuria, macroalbuminuria (dipstick-positive albuminuria), chronic renal insufficiency, chronic renal failure, and ESRD. This progression to ESRD collectively is called chronic kidney disease and is classified into five stages as defined in Table 1. Diabetes mellitus is the most common cause of ESRD. Among patients with type 2 diabetes, the annual transition rate from one stage of renal disease to the next is between 2% and 3%.

Microalbuminuria: A Marker for Cardiovascular Disease

Microalbuminuria (a slight elevation in urinary albumin excretion) is associated with cardiovascular risk factors and is considered an independent risk factor for morbidity. In the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of microalbuminuria varied with the number and type of risk factors: 28.1% in diabetic patients, 12.8% in nondiabetic patients with hypertension, and 4.8% in persons with neither diabetes nor hypertension.

Patients with microalbuminuria may progress along the renal continuum to CKD (indicated by macroalbuminuria or proteinuria), increased serum creatinine concentration, and decreased GFR. Serum creatinine levels are used to estimate the GFR. With progressive CKD, single nephron glomerular pressure increases, eventually leading to glomerulosclerosis. In patients with early nephropathy, serum creatinine concentration and creatinine clearance are within normal limits, but microalbuminuria—the earliest clinical sign of nephropathy—already is present. Microalbuminuria is measured through laboratory assessments of 24-hour urine collection, timed col-

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Kopyt • Review Article
Hypertension

RAS activity
Angiotensin II
Oxidative Stress/
Vasoconstriction

IGT
DM Risk
CVD Risk

Glomerular Pressure

Microalbuminuria
UAER

GFR
Serum Creatinine

Gomerular Sclerosis

Macroalbuminuria
Proteinuria

Predicts Stroke,
CHD, CVD Risk

Chronic Kidney
Disease

End-Stage
Renal Disease

Figure. The renal disease continuum. Ang II indicates angiotensin II; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; IGT, impaired glucose tolerance; RAS, renin-angiotensin system; UAER, urinary albumin excretion rate.
Men (P < .05; 74 men, 26 women) and older (P < .0001; 64.4 vs 61.4 y) and to have more severe systolic hypertension (P < .02) and a history of myocardial infarction (P < .0001), stroke (P < .0001), or diabetes (P = .046). Because of the increased prevalence of myocardial infarction, LVH, and heart failure in this group, the relative risk for cardiovascular death was 3.24 (95% confidence interval [CI], 2.13–4.94; P < .001) among patients with reduced renal function at baseline.

Of a cohort of 6223 patients enrolled in the Framingham Heart Study, 9% of men and 8% of women were found to have mild chronic renal impairment. In both men and women, the prevalence of CVD, coronary heart disease, heart failure, and LVH were greater in those with mild renal impairment than in those with normal serum creatinine values. The Framingham data—gathered during more than 11 years of follow-up—indicate that even mild renal impairment is associated with risk for adverse outcomes, especially in men, and is strongly associated with coexisting CVD and risk factors for CVD.

Research implicates the renin-angiotensin system as a cause of elevated blood pressure in patients with primary hypertension and with certain chronic renal diseases. Approximately 50% of patients with polycystic kidney disease and preserved renal function have hypertension. The early increase in blood pressure is a result of increased sympathetic nervous system activity, which appears secondary to increased activation of the renin-angiotensin system; in turn, this may increase cardiovascular risk independent of blood pressure. In a study of hypertensive patients with normal renal function and polycystic kidney disease, plasma renin activity was inappropriately high, given the level of blood pressure. In patients with polycystic kidney disease and chronic renal failure (cre

<table>
<thead>
<tr>
<th>Renal Function Category (GFR, mL/min/1.73 m²)</th>
<th>Overall (N = 15,600)</th>
<th>Population With Diabetes (n = 1211)</th>
<th>Hypertensive Population (n = 2553)</th>
<th>Untreated (n = 2340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: Normal (&gt;90)</td>
<td>64.3</td>
<td>44.5</td>
<td>35.6</td>
<td>48.5</td>
</tr>
<tr>
<td>Stage II: Mildly Decreased (60–89)</td>
<td>31.2</td>
<td>40.4</td>
<td>46.0</td>
<td>43.2</td>
</tr>
<tr>
<td>Stage III: Moderately Decreased (30–59)</td>
<td>4.3</td>
<td>14.2</td>
<td>17.5</td>
<td>7.9</td>
</tr>
<tr>
<td>Stage IV: Severely Decreased (15–29)</td>
<td>0.2</td>
<td>0.92</td>
<td>0.94</td>
<td>0.34</td>
</tr>
<tr>
<td>Stage V: Kidney Failure (ESRD)</td>
<td>0.2</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

† GFR indicates glomerular filtration rate; ESRD, end-stage renal disease; N/A, not available.
‡ GFR was calculated for adults aged ≥20 years who participated in the Third National Health and Nutrition Examination Survey.
Role of the Renin-Angiotensin System

Angiotensin II binds to the angiotensin II type 1 (AT₁) receptor on cell membrane surfaces of a wide variety of tissues, including vascular smooth muscle, the heart, and the kidneys. Increased plasma renin activity leads to increased levels of angiotensin II. Data from a variety of sources now point to the renin-angiotensin system’s central role in the pathophysiology of diabetic and hypertensive nephropathy and the relationship between nephropathy and CVD. The presence of microalbuminuria, an important marker of renal disease and CVD, appears to indicate that vascular injury—endothelial dysfunction—already has occurred. In turn, endothelial dysfunction appears to be a consequence of oxidative stress, and evidence from animal studies indicates oxidative stress is reduced or reversed by the action of either AT₁ receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors.

The kidney is susceptible to oxidative stress; oxidative stress is associated with hyperglycemia and has a role in the development and progression of diabetic nephropathy. Oxidative stress represents discord in the dynamic equilibrium between antioxidants and prooxidants (reactive oxygen species such as free radicals, increased levels of which lead to tissue damage) and also in the equilibrium among prooxidants.

Nitric oxide, a free radical with a short half-life, mediates normal endothelial function. Nitric oxide deficiency is an important factor in endothelial dysfunction and atherogenesis. Nitric oxide deficiency secondary to inactivation by reactive oxygen species may have a central role in diabetic nephropathy. A potential source of reactive oxygen species, p47phox, is enhanced in the kidneys of diabetic rats, indicating oxidative stress. In diabetic rats treated with either the ACE inhibitor quinapril hydrochloride or the ARB candesartan cilexetil, however, expression of p47phox was suppressed significantly (p < .005 vs diabetic animals and p < .002 vs diabetic animals, respectively). Another manifestation of oxidative stress is increased production of nitrotyrosine. Nitrotyrosine production was significantly suppressed by treatment with either quinapril (p < .05) or candesartan (p < .01) versus untreated animals in this same study. In addition, treatment with either drug significantly reduced the renal excretion of albumin (p < .02 with quinapril and p < .05 with candesartan vs diabetic animals; which had increased substantially 4 weeks after induction of diabetes.

Data obtained from studies of diabetes in rats indicate the AT₁ receptor plays a critical role in the pathophysiology of oxidative stress in the diabetic kidney and, probably, in the hypertensive kidney. Angiotensin II type 1 receptor–dependent oxidative stress and the consequent adverse effects on endothelial function appear to be unifying factors in renal disease and CVD. The central role of the AT₁ receptor in oxidative stress also explains what has been observed in clinical trials: Either ARB treatment or ACE inhibition not only reverses or retards the progression of renal disease, but also reduces the risk of CVD in patients with nephropathy. The concept of AT₁-dependent oxidative stress also may explain why the beneficial effects of renin-angiotensin system antagonism on CVD and renal disease are independent of a reduction in blood pressure or changes in renal hemodynamics.

<table>
<thead>
<tr>
<th>Category</th>
<th>24-Hour Urine Excretion (mg/24 h)</th>
<th>Timed Collection (µg/min)</th>
<th>Spot Collection, Albumin-Creatinine Ratio (µg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
<td>&lt;20</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–299</td>
<td>20–199</td>
<td>30–299</td>
</tr>
<tr>
<td>Clinical Albuminuria (Overt Proteinuria)</td>
<td>≥300</td>
<td>≥200</td>
<td>≥300</td>
</tr>
</tbody>
</table>

ACE Inhibitors in Patients With Renal Disease
Since the 1993 publication of the first randomized clinical trial to demonstrate an antihypertensive-independent renoprotective effect of captopril in patients with type 1 diabetes mellitus and chronic renal insufficiency (proteinuria $\geq 500$ mg/24 h; serum creatinine $\leq 2.5$ mg/dL),32 other studies33-35 have confirmed the beneficial effects of ACE inhibition on diabetic nephropathy. Patients with microalbuminuria and normotensive, normoalbuminuric patients with type 2 diabetes mellitus have benefited from ACE inhibition. The benefits of this antagonism of the renin-angiotensin system also extend to patients with nondiabetes-associated renal disease.36

Among 3577 patients with diabetes and a high risk for CVD—who were enrolled in the Heart Outcomes Prevention Evaluation (HOPE) trial and received conventional therapy including $\beta$-blockers, diuretics, and calcium channel blockers—ramipril significantly decreased primary outcome (myocardial infarction, cardiovascular death, or stroke) ($P = 0.0004$), all-cause mortality ($P = 0.004$), and the development of overt nephropathy ($P = 0.027$) compared with either vitamin E or placebo.37,38 Ramipril also was significantly more effective than placebo in reducing the risk of death, myocardial infarction, and stroke in high-risk patients with and without diabetes and without left ventricular systolic dysfunction or heart failure ($P < 0.001$), independent of its antihypertensive effect.38 The HOPE trial showed that microalbuminuria predicted the onset of overt nephropathy and macroalbuminuria in patients with and without diabetes, and that treatment with ramipril reduced the risk for disease progression.39

A HOPE substudy—Microalbuminuria, Cardiovascular, and Renal Outcomes in the HOPE Study (MICRO-HOPE)—examined the relationships among microalbuminuria and other renal and cardiovascular risk factors and between microalbuminuria and cardiovascular outcomes in patients at high risk for CVD.40 Microalbuminuria was associated independently with several risk factors for CVD, including increased age, hypertension, history of a cardiovascular event, abdominal obesity, and LVH.40 Treatment with ramipril reduced the relative risk of myocardial infarction, stroke, and death by 25% and overt nephropathy by 24%, compared with placebo.37

The Captopril Primary Prevention Project (CAPP)—a randomized, open-label, blinded endpoint trial of 10,985 patients—demonstrated that captopril was equivalent to conventional therapy (diuretics and $\beta$-blockers) in preventing cardiovascular morbidity and mortality in hypertensive patients.41 During the 6-year course of the study, captopril significantly reduced the risk of new-onset diabetes by 14% ($P = 0.039$) and significantly decreased cardiovascular risk in patients with diabetes mellitus with a relative risk of 0.59 (95% CI, 0.38-0.91; $P = 0.019$), independent of blood pressure.41,42

Hypertension and nephropathy pose a greater risk for ESRD in African Americans than in Caucasians, and African Americans represent 32% of treated patients with ESRD.4 The African American Study of Kidney Disease and Hypertension (AASK) trial evaluated the efficacy of two levels of blood pressure control in African American patients with hypertensive renal disease (GFR, 20 mL/min/1.73 m$^2$ to 65 mL/min/1.73 m$^2$) but without diabetes. Ramipril appeared more effective in slowing the progression of hypertensive nephropathy than metoprolol or amlodipine.43-45 A somewhat surprising finding was that achieving the goal of lower blood pressure (mean arterial pressure $< 92$ mm Hg) provided no additional benefit in terms of slowing the progression of nephropathy than achieving the usual blood pressure goal (mean arterial pressure, 102-107 mm Hg).44

ARBs in Patients With Renal Disease
In patients with type 2 diabetes mellitus, ARBs are especially effective for decreasing nephropathy progression rate, independent of their blood pressure–lowering effect (Table 3). The randomized, double-blind, active-controlled, parallel-group MicroAlbuminuria Reduction with VALsartan (MARVAL) trial investigated the renoprotective effects of valsartan and amlodipine in patients with diabetes, with or without hypertension.31 During the 24-week course of the MARVAL trial, valsartan was significantly more effective than amlodipine in reducing the urinary albumin excretion rate in the entire population with diabetes ($P < 0.001$), in patients with diabetes and hypertension at study entry ($P < 0.001$), and in normotensive patients with diabetes at study entry ($P < 0.001$) with equivalent effects on blood pressure.31

In the Reduction of Endpoints in NIDDM (non-insulin–dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (RENAAL) study, 1513 patients were assigned at random to receive losartan or placebo in addition to conventional antihypertensive therapy (excluding ACE inhibitors or another ARB).46 Losartan reduced the risk of the doubling of serum creatinine concentration by 25% ($P = 0.006$) and of ESRD by 28% ($P = 0.002$).46 The decreased risks of ESRD (26%; $P = 0.007$) and of ESRD or death (19%; $P = 0.02$) remained unchanged after adjustment for blood pressure, indicating renoprotection was independent of blood pressure reduction.46

The Losartan Intervention For Endpoint reduction in hypertension study (LIFE) found that losartan was more effective than atenolol in preventing cardiovascular morbidity or death in hypertensive patients with and without diabetes ($P = 0.021$),47,48 with a 25% lower incidence of new-onset diabetes and stroke (both $P = 0.001$) and a lower adverse event rate ($P = 0.001$).47 Throughout the mean 4.8 years of follow-up, blood pressure responses (systolic, diastolic, and mean arterial pressure) were virtually identical in patients randomly assigned to either drug, indicating the reduced risk for cardiovascular events with losartan was independent of its blood pressure–lowering effect.47,48 In contrast, in a community-based
Table 3
Trials of Angiotensin-Receptor Blockers in Patients
With Type 2 Diabetes Mellitus and Nephropathy*

<table>
<thead>
<tr>
<th>Study†</th>
<th>Patients (N)</th>
<th>Treatment</th>
<th>Mean Duration</th>
<th>Endpoints</th>
<th>Results (P)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RENAAL</strong></td>
<td>Type 2 diabetes mellitus, nephropathy (1513)</td>
<td>Losartan vs placebo</td>
<td>3.4 y</td>
<td>Composite of doubling serum creatinine concentration, ESRD, death</td>
<td>15% risk reduction of composite endpoint (.03)</td>
</tr>
<tr>
<td><strong>IDNT</strong></td>
<td>Hypertension, type 2 diabetes mellitus, nephropathy (1715)</td>
<td>Irbesartan vs amlodipine vs placebo</td>
<td>2.6 y</td>
<td>Composite of doubling serum creatinine concentration, ESRD, death</td>
<td>24% risk reduction of composite endpoint vs amlodipine (.005); 19% risk reduction of composite endpoint vs placebo (.03)</td>
</tr>
<tr>
<td><strong>IRMA-2</strong></td>
<td>Hypertension, type 2 diabetes mellitus, microalbuminuria (590)</td>
<td>Irbesartan vs placebo</td>
<td>2 y</td>
<td>Time to new-onset diabetic nephropathy</td>
<td>39% risk reduction in 150-mg group (.08); 70% risk reduction in 300-mg group (&lt;.001)</td>
</tr>
<tr>
<td><strong>MARVAL</strong></td>
<td>Type 2 diabetes mellitus, microalbuminuria (332)</td>
<td>Valsartan vs amlodipine</td>
<td>24 wk</td>
<td>Percent change in urinary baseline albumin excretion rate</td>
<td>44% risk reduction from baseline with valsartan (&lt;.001); 8% risk reduction from baseline with amlodipine; treatment effect, valsartan vs amlodipine (&lt;.001)</td>
</tr>
<tr>
<td><strong>LIFE</strong></td>
<td>&gt;55 years with hypertension, left ventricular hypertrophy (1913)</td>
<td>Losartan vs atenolol (with or without other medications)</td>
<td>4.8 y</td>
<td>Cardiovascular death, myocardial infarction, or stroke (composite); stroke; diabetes mellitus</td>
<td>13% risk reduction of endpoint (.021); 25% risk reduction of stroke (.001); 25% risk reduction of diabetes mellitus (.001)</td>
</tr>
</tbody>
</table>

* ESRD indicates end-stage renal disease.
† Sources:
‡ Adjusted values.
study of 12,550 adults, type 2 diabetes mellitus was almost 2.5 times more likely to develop in patients with hypertension, and 28% more likely to develop in patients taking β-blockers than in those receiving no medication (relative hazard, 1.28; 95% CI, 1.04–1.57).60 This increased risk was not seen in patients receiving thiazide diuretics, calcium channel blockers, or ACE inhibitors. In addition, risk was not influenced by the presence or absence of hypertension, weight gain, health-related behavior, level of education, or a variety of diabetes-related clinical traits and coexisting conditions.60 Potential mechanisms for the increased incidence of diabetes with β-blockers include an attenuation of the β-receptor-mediated release of insulin from pancreatic β cells and decreased blood flow through the microcirculation in skeletal muscle tissue leading to decreased insulin sensitivity.50

Among patients with echocardiographic evidence of LVH at entry into the LIFE study, the urinary albumin-creatinine ratio was significantly higher in those with both eccentric and concentric LVH than in hypertensive patients with normal left ventricular geometry.51 The correlation between urinary albumin-creatinine ratio and LVH was independent of age, race, systolic blood pressure, and presence of diabetes.51

The Irbesartan Diabetic Nephropathy Trial (IDNT) compared irbesartan with amlodipine and placebo in diabetic hypertensive patients with macroalbuminuria (urinary protein excretion ≥900 mg/24 h).52 Over the mean 2.6 years of follow-up, irbesartan was associated with a significantly slower increase in serum creatinine concentration compared with placebo (P = .008) and with amlodipine (P = .02).52 Although the degree of blood pressure control in the irbesartan and amlodipine groups was the same, patients receiving amlodipine had worse renal outcomes (primary renal endpoint, doubling of baseline serum creatinine concentration).52 This observation supports the concept that renoprotection provided by angiotensin-receptor blockade in patients with type 2 diabetes mellitus and nephropathy is a result of suppression of angiotensin II activity.52

The randomized, double-blind, placebo-controlled trial IRBesartan in patients with type 2 diabetes and MicroAlbu-

Therapeutic Options

 Tight blood pressure control reduces the risk of microvascular and macrovascular complications in patients with type 2 diabetes,53 and intensive blood glucose control delays the onset and slows the progression of diabetic vascular complications.54 Based on results of clinical trials and basic research data implicating the renin-angiotensin system in the etiology of endothelial dysfunction, renal disease, and CVD, the JNC 7 report recommends ARBs or ACE inhibitors as first-line treatment in patients with diabetic hypertension and in patients with hypertension and microalbuminuria, often in combination with another medication, to achieve target blood pressure.16

American Diabetes Association guidelines emphasize the necessity of reducing risk factors for CVD and delaying the onset of nephropathy or slowing progression along the renal continuum from microalbuminuria to macroalbuminuria.55 An important strategy to reduce CVD risk in patients with diabetes is blood pressure control, with a target of 130/80 mm Hg or lower.55 In patients with hypertension, diabetes mellitus prompts consideration of an ARB or ACE inhibitor as first-line therapy because both classes of medication reduce proteinuria and slow progression of diabetic nephropathy. In addition, ARBs reduce progression to macroalbuminuria,10,16,55 as indicated by the 44% reduction from baseline urinary albumin excretion rate in patients taking valsartan in the MARVAL trial.31

In patients with type 1 diabetes mellitus, with or without hypertension and with any degree of albuminuria, ACE inhibition delays the progression to nephropathy; in patients with type 2 diabetes mellitus, hypertension, and microalbuminuria, ARBs delay progression to macroalbuminuria and nephropathy; and in patients with type 2 diabetes mellitus, hypertension, and nephropathy (macroalbuminuria and serum creatinine >1.5 mg/dL), ARBs slow progression of nephropathy and are the initial agent of choice.55

The randomized, double-blind, placebo-controlled Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial60 is investigating associations among the renin-angiotensin system, cardiovascular risk, and diabetes progression in a large, high-risk population (N = 7500 to 11,000 patients) with impaired glucose tolerance that has been treated with valsartan, the antidiabetic agent nateglinide, a combination of both, or neither. Results are expected in 2007.

Comment

Microalbuminuria, an early indication of nephropathy, appears to indicate widespread endothelial dysfunction. Experimental evidence shows endothelial dysfunction is a consequence of AT1-dependent oxidative stress, an early step in the progression along the renal continuum. Microalbuminuria is a risk factor for both CVD and renal disease progression in patients.
with diabetes or hypertension or both, and patients with reduced renal function have an increased risk of cardiovascular death. Multiple randomized clinical trials have demonstrated that medications can: suppress the renin-angiotensin system, either through ACE inhibition or blocking the AT1 receptor; improve vascular and renal function as evidenced by reduced microalbuminuria; slow the progression of nephropathy in patients with diabetes and in hypertensive patients with and without diabetes; and reduce the risk for CVD.

Medications that slow the progression along the renal continuum include ACE inhibitors in type 1 diabetes mellitus and ARBs in type 2 diabetes mellitus. ARBs are effective antihypertensive agents with a better tolerability profile that may lead to improved patient care. Their actions independent of blood pressure effects improve cardiovascular and renal function. ARBs are a reasonable choice as initial therapy for patients with microalbuminuria, particularly when both hypertension and microalbuminuria are present.

References


