Outcome Studies in Diabetic Nephropathy

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Outcome studies in diabetic nephropathy have focused on strategies to prevent progression of diabetic nephropathy, the leading cause of ESRD in the United States. Once diabetics develop overt nephropathy, prognosis is poor. Risk factors for diabetic nephropathy are discussed, and include hyperglycemia, hypertension, angiotensin II, proteinuria, dyslipidemia, smoking, and anemia. Major outcomes as well as outcome studies in diabetic nephropathy for patients with microalbuminuria and macroalbuminuria are reviewed. Furthermore, the role of therapy with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and mineralocorticoid receptor antagonists as well as selected combination therapy are discussed. Recommendations for therapy with ace inhibitors and angiotensin II receptor blockers are made based on this evidence.

DIABETES IS THE LEADING cause of end-stage renal disease (ESRD) in the United States. Clinical diabetic nephropathy is characterized by proteinuria (>300 mg albumin/g creatinine), elevated blood pressure (BP) and rapidly declining renal function.[1-5] Nephropathy afflicts 30% to 40% of diabetic patients causing ESRD at a median age of 50 in type 1 and 65 in type 2 diabetics.[6] Morbidity and mortality are increased sharply after onset of nephropathy[7-11] and 20% of diabetics die within 1 year of onset of ESRD.[6] Among type 2 diabetics, nephropathy disproportionately afflicts ethnic minorities.[12-17] This disease is now a public health crisis. Both the prevalence and incidence of diabetic nephropathy are increasing and there is no effective treatment to halt progression to ESRD once renal disease is established. Furthermore, a projected shortage of nephrologists could compromise the overall care of ESRD patients in general, especially diabetics with ESRD. Moreover, federal expenditure for managing ESRD alone exceeds $4 billion. Consequently, discovery and implementation of effective strategies to prevent progression of diabetic nephropathy is of utmost priority. This article reviews risk factors for diabetic nephropathy and recent outcome studies in diabetics with early and late nephropathy attributed to diabetes. These new studies represent an important advance in management of diabetic nephropathy. They also underscore the need for studies that test add-on therapies to block the renin-angiotensin-aldosterone (RAAS) system (eg, angiotensin converting enzyme inhibition and angiotensin II type 1 receptor blockade) at multiple sites and novel therapeutics that go beyond blockade of RAAS.

RISK FACTORS FOR NEPHROPATHY IN DIABETES

Many factors may be responsible for onset and progression of diabetic nephropathy. In this section we review modifiable risk factors shown to be associated with development and progression of human diabetic renal disease. For the purposes of this discussion, microalbuminuria is defined as a urine albumin/creatinine ratio of 30 or greater and less than 300 mg/g and macroalbuminuria (also referred to as overt nephropathy) as 300 mg/g or greater.[18] Renal function is usually within the normal range in microalbuminuric patients and remains in normal range. In contrast, although renal function, measured as glomerular filtration rate (GFR), may be normal at initial evaluation in macroalbuminuric patients, it is the harbinger of rapidly declining renal function that often leads to ESRD.

Glycemia

Elevated blood glucose level is a key risk factor for onset and progression of diabetic renal disease. Both in vitro and animal models of diabetic renal disease indicate that hyperglycemia plays an important role in onset and progression of nephropathy.[19] Elevated cytosolic glucose level increases protein kinase C and nuclear factor-κ B activities, which in turn lead to activation of cell growth and proliferation.[20-25] In addition, hexosamine pathways may result in excessive glycosylation of key proteins leading to renal glomerular and tubular cell dysfunction.[26,27] The Diabetes Complications and Control Trial (DCCT) included more than 5,000 type 1 diabetics followed-up for up to 6

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years and showed that tight glycemic control substantially reduced the risk for development of microalbuminuria in normoalbuminuric subjects.[28,29] In addition, tight glycemic control significantly decreased the risk for progression of microalbuminuria to macroalbuminuria. The United Kingdom Prospective Diabetes Study (UKPDS) included more than 4,000 type 2 diabetic patients followed-up for up to 8 years.[30] This study showed that tight glycemic control decreased the risk for progression from normoalbuminuria to microalbuminuria and progression from microalbuminuria to macroalbuminuria.

Hypertension

It is well established that overt hypertension is a key risk factor for progression of established diabetic nephropathy.[1,31-40] Recent evidence indicates that nocturnal BP elevation is associated with an increased risk for development of microalbuminuria in type 1 diabetics.[41] However, it is less clear that prevention or treatment of hypertension in diabetics without nephropathy slows onset of nephropathy.[42] Lowering BP in hypertensive type 1 and type 2 diabetics with proteinuria is associated with a slowing in the rate of decline in GFR.[43] In the UKPDS, rigid BP control at 145/85 mm Hg versus 155/90 mm Hg was associated with a 38% reduction in development of microvascular complications including onset of microalbuminuria and macroalbuminuria.[43] The optimal level of BP lowering for slowing progression of nephropathy in type 1 or type 2 diabetes is not entirely clear. In type 1 diabetics with overt nephropathy who were followed up long term with treatment by angiotensin-converting enzyme inhibitor (ACEi) therapy, those with a mean arterial BP treated to less than 92 mm Hg not only had a slower rate of progression as compared with those with higher pressure but also had a lower urinary protein excretion rate.[44] Several studies in type 2 diabetics with nephropathy also indicate that lowering BP slows disease progression regardless of class of antihypertensive agent.[43,45-54] Lowering BP to 130 or less systolic and 80 or less mm Hg diastolic currently is recommended by the National Kidney Foundation and the American Diabetes Association.[55,56]

Angiotensin II

Abundant evidence indicates that intrarenal angiotensin II (AII) production and/or (sensitivity to) action are increased in diabetic nephropathy.[22,57-59] All binding to type 1 (AT_1) receptors causes glomerular hypertension, renal hypertrophy, sclerosis, proteinuria, and accelerated decline in renal function by hemodynamic[57,60-71] and nonhemodynamic mechanisms.[2,72] These effects are mediated via multiple cascading pathways including growth-promoting factors,[57,73,74] profibrotic factors, prothrombotic cytokines such as plasminogen activator inhibitor-1 (PAI-1),[75-79] and increased oxidative state,[19,20] which conspire to cause progressive renal disease. Chronic inhibition of All production by ACEi or selective AT_1 receptor blockade by angiotensin receptor blockers (ARBs) dramatically attenuates glomerular and tubular damage, proteinuria, and renal failure in animal models[2,57,69,70,80,81] and slows progression of renal disease in humans with diabetic nephropathy.[7,10,82] As discussed later, ACEis and ARBs are recommended as first-line agents for the treatment of diabetes with nephropathy.[56]

Proteinuria

Proteinuria is the strongest and most consistent predictor of long-term renal survival in diabetic nephropathy.[10,83-87] It has been hypothesized that excessive protein filtration may cause further renal injury in proteinuric nephropathies, but this hypothesis has not been proven.[88-90] Therefore, treatment strategies that maximally reduce proteinuria in diabetic nephropathy would be predicted to improve outcome. In type 1 diabetics, up to 20% have overt nephropathy. In this population, ACEi in conjunction with intensive BP lowering dramatically attenuates proteinuria and stabilizes renal function.[44,91,92] For these reasons, the National Kidney Foundation has recommended BP lowering combined with an ACEi as first-line therapy for hypertensive diabetics with nephropathy.[55]

Dyslipidemia

Dyslipidemia is common in diabetes. Atherogenic dyslipidemia consisting of hypertriglyceridemia and low concentration of high-density lipoprotein (HDL) as well as hypercholesterolemia and increased small, dense, low-density lipoprotein (LDL) are common patterns of dyslipidemia in diabetes.[93] Atherogenic dyslipidemia is associated with onset and progression of nephropathy in type 2 diabetics and hypercholesterolemia is a risk factor for onset of nephropathy in both type 1 and type

2 diabetics.[94] Limited data suggest that lipid-lowering therapy slows progression of nephropathy in type 2 diabetics; however, there are no long-term large-scale trials evaluating lipid-lowering therapy.[95-97] LDL treatment goal in diabetics is less than 100 mg/dL. Dietary intervention and statin treatment are recommended to achieve this goal because diabetic patients have excessive cardiovascular diseases risk.[98] In addition, treatment of atherogenic dyslipidemia by weight reduction when appropriate, optimal glycemic control, and fibric acid or statin therapy is recommended. It should be noted that these recommendations are based on cardiovascular outcomes data. There are no outcome trials evaluating the long-term effects of lipid-lowering therapies in diabetics with chronic kidney disease.

Smoking

Chronic cigarette smoking is a major risk factor for cardiovascular and cancer morbidity and mortality.[99] Smoking accelerates decline in renal function in patients with overt nephropathy and is associated with increasing albuminuria in microalbuminuric patients.[100,101] The mechanism of accelerated decline in renal function is not known, but renal vasoconstriction and glomerular endothelial injury are factors that may be involved.[102-105] Increased production of superoxide and other free radicals as well as activation of endothelin release, sympathetic activation, and suppression of nitric oxide in the kidney also may play a role.[106] All diabetics should be advised to stop smoking regardless of associated kidney disease.[101,102]

Anemia

Anemia may be a novel risk factor for progression of established chronic kidney disease (CKD) in diabetics. However, this has not been established firmly yet. The diagnosis of anemia in diabetic nephropathy remains controversial in part owing to confusion regarding the definition of anemia. For example, Schnall et al[107] define anemia in adults by a hemoglobin concentration of less than 14 g/dL (12 g/dL for premenopausal women). However, The World Health Organization defines anemia by a hemoglobin concentration of 13 g/dL for men, and 12 g/dL for women.[108] The National Kidney Foundation (NKF) Kidney Disease Quality Initiative CKD guidelines do not define anemia, but do set targets for anemia therapy. The NKF hemoglobin target is 12.5 g/dL for men and postmenopausal women (11 g/dL for premenopausal women).[109]

Regardless of the cut-point of hemoglobin that may define anemia, there is also the question of whether anemia is more severe in patients with diabetes. The distribution of hemoglobin in patients with diabetes and CKD has been reported as both similar to, and lower than that of, nondiabetic patients with CKD. After adjustment for GFR, similar hemoglobin distributions in chronic kidney disease with and without diabetes have been reported. Pooled information from 2 European studies does not show lower hemoglobin levels for diabetic patients. In the retrospective Predialysis Survey of Anemia Management and the prospective Early Renal Insufficiency Referral Survey, diabetic and nondiabetic patients had a similar relationship between hemoglobin and creatinine clearance.[110] In contrast, National Health and Nutrition Examination Survey III participants with a GFR of less than 30 mL/min/1.73 m^2 and a coexistent diagnosis of diabetes had a lower distribution of hemoglobin as compared with nondiabetics.[111]

Few studies have evaluated anemia and outcomes in patients with diabetes and nephropathy. Brown et al[112] followed-up 17 patients with diabetes, anemia, and CKD prospectively for the period of 1 year. One group was treated with erythropoietin and the other group was treated with placebo. Both groups had a similar increase in serum creatinine level. Patients treated with erythropoietin to higher hematocrits had a delay in uremic symptomatology. An evaluation of patients selected for a diagnosis of type 2 diabetes with proteinuria and elevated serum creatinine levels followed-up for 26 months showed that hemoglobin and proteinuria were identified as independent predictors of nephropathy.[113]

Recently, a risk score was developed from the baseline characteristics of the patients in the Reduction of Endpoints in NIDDM with the Angiotensin II Type 1 Receptor Antagonist Losartan (RENAAL) study. Anemia was one of 4 baseline risk factors identified for progression of kidney disease. In this analysis, CKD progression was measured as doubling of serum creatinine level or ESRD.[114] In this analysis, baseline hemoglobin level below 13.8 g/dL was associated independently with progression of nephropathy. At this time, no specific anemia treatment guidelines exist

for anemic patients with type 2 diabetes and nephropathy. Outcome studies examining this issue are needed urgently.

DEFINING AND MEASURING OUTCOMES IN DIABETIC NEPHROPATHY

Clinical trials of patients with renal disease have used 2 types of outcomes or endpoints to measure efficacy of interventions in diabetic nephropathy: (1) single primary renal outcome, and (2) combined renal and nonrenal (death) outcomes.

Single Endpoints

Renal outcomes include estimates of decline in GFR, surrogate markers such as proteinuria, and ESRD. The rate of decline in GFR has been estimated by direct measurement, slope of the reciprocal of serum creatinine level, measurement or calculation of creatinine clearance, and rate of doubling of serum creatinine level. Because of cost, technical aspects, variability in measurement, statistical problems, and logistical aspects, rate of decline in GFR is not a practical method to estimate progression in large trials or in practice. Doubling of serum creatinine level as a primary outcome in diabetic nephropathy was established as a surrogate marker for ESRD in 1993 in the Collaborative Study Group evaluation of the effect of captopril in type 1 diabetics with overt nephropathy.[115]

Primary endpoints using proteinuria include development of macroalbuminuria in microalbuminuric patients, reversion of microalbumnuria to normoalbuminuria, and significant reduction in albuminuria or proteinuria. Albuminuria is measured by a 24-hour urine, as well as by spot urine albumin to creatinine ratio. Although proteinuria endpoints are well accepted in the literature, they are not established as surrogates for ESRD by the Food and Drug Administration (FDA).

There are problems related to the use of laboratory measures alone as outcomes. For example, serum creatinine may be different between laboratories, and may be different in different groups of people, such as men and women. Furthermore, because different studies use different creatinine endpoints, such as serum creatinine versus doubling of serum creatinine, it is challenging to compare studies. Another important point is that patients who are lost to follow-up can no longer be assessed by laboratory samples.

ESRD is widely accepted as the most convincing measure of renal outcome. The definition of ESRD varies among clinical trials and includes the need for dialysis or transplantation and the surrogate of a cut-off serum creatinine value.[7,115-117] However, thus far no uniform definition of ESRD has been applied to clinical trials.

Combined Endpoints

Combined endpoints include doubling of serum creatinine level, time to ESRD, and death. Some trials and meta-analysis of trials use both types of endpoints.[118] Combined primary endpoints are used in large-scale trials to increase power, to reduce ambiguity of outcomes, and because the endpoints are clinically relevant. The combined endpoint of doubling serum creatinine levels or ESRD or death has been used as a primary endpoint and secondary endpoint in large-scale trials of CKD and has gained acceptance in the medical community as a valid outcome. Also, the individual endpoints of doubling serum creatinine levels, ESRD, and death were accepted outcomes in these trials.[7,115-117,119] Death is further divided into 2 categories in the renal literature: (1) renal death, defined as the need for chronic renal replacement therapy, and (2) death of the patient. With hard outcomes, vital statistics are available even if patients are no longer followed-up in the study. It is possible to track ESRD and death vital statistics in the United States and to compare these endpoints across studies. In patients with diabetic nephropathy, death is now coming to the forefront as a hard outcome. Time to death and time to ESRD were included as secondary endpoints in the captopril study in patients with type 1 diabetes and nephropathy.[120] Similarly, both time to death and time to ESRD were part of the primary outcome for 2 trials published in 2001 in patients with type 2 diabetes and nephropathy (see next section).

Death is recognized as an important competing event for patients with CKD. Death and ESRD are 2 individual primary outcomes evaluated in the recent Medicare 5% study data matched with Medicare ESRD patients.[121] This study evaluated the ratio of death to ESRD for patients with and without CKD, and also with and without the comorbidities of anemia and congestive heart failure. The study showed that death was a more common outcome for patients with CKD, compared with ESRD as an outcome, especially when comorbidi-

ties were present.[121] Another study evaluated the outcome of death for patients with CKD in a health maintenance organization to identify modifiable risk factors for death. The study stratified patients by stage of CKD, and found that patients in all stages had a greater chance of dying before ESRD, compared with patients who reached ESRD. In a substudy of these patients, diabetes was found to be one of the important predictors of dying before ESRD.[122] Death before ESRD also has been identified as important in studies of patients with type 2 diabetes and nephropathy. Death and ESRD were 2 of the endpoints evaluated in studying development and progression of nephropathy in 5,097 patients from the UKPDS. Once patients developed macroalbuminuria, their risk for death exceeded their risk for ESRD.[123] This study again underscores the point that both ESRD and death are important hard outcomes that are meaningful for patients with diabetic nephropathy.

Taken together, we believe the combined outcome of ESRD or death (owing to any cause) is the most important and relevant endpoint for future clinical trials for diabetics with nephropathy. Future outcome trials in diabetic nephropathy should be designed with the primary endpoint as the combination of ESRD and death.

OUTCOME TRIALS IN DIABETICS WITH MICROALBUMINURIA AND OVERT NEPHROPATHY

Type 1 Diabetes

Microalbuminuria

Clinical trials in microalbuminuric patients with type 1 diabetes have shown that ACEis can significantly reduce the risk for development of overt nephropathy.[124-132] The primary outcome in all of these studies was a change in albuminuria level. An increasing albuminuria level is considered a surrogate marker for progression of disease. However, the bulk of these studies indicated that ACEis induce remission of microalbuminuria to normalbuminuria, or slow progression of microalbuminuria. A meta-analysis of many studies in which ACEis were compared with placebo or comparator drug (eg, calcium channel blocker, β blocker) in normotensive and hypertensive type 1 diabetics with microalbuminuria concluded that the beneficial effects of ACEi treatment outweighed their potential adverse side effects (eg, cough, angioedema, hyperkalemia).[124] A caveat to this conclusion is that progression to macroalbuminuria is not an accepted clinical endpoint by the FDA. Thus, there is no FDA indication for use of an ACEi (or ARB) to slow progression of diabetic nephropathy in microalbuminuric patients.

Macroalbuminuria (Overt Nephropathy)

Several small studies have shown that ACEi therapy as compared with non-ACEi therapy slows progression of kidney disease in type 1 diabetics with nephropathy.[131,133-141] All of these studies showed that ACEis consistently reduced proteinuria to a greater extent as compared with non-ACEi drugs and BP control was similar between treatment arms. Only one large-scale clinical trial in diabetic nephropathy evaluated progression of nephropathy estimated by doubling of serum creatinine level or ESRD or death as the endpoints. In this trial, 409 type 1 diabetics with overt nephropathy were administered either captopril 25 mg 3 times daily or placebo. Captopril reduced the risk for doubling of serum creatinine level and the combined endpoints of ESRD or death by 50%.[116] This trial led to an FDA indication for the use of captopril in type 1 diabetics with nephropathy. It is important to note that the reduction in events was observed in those patients with baseline serum creatinine levels of less than 1.5 mg/dL. Moreover, those with the highest degree of proteinuria derived the greatest benefit in preservation of renal function. Furthermore, captopril, but not placebo, significantly lowered urine protein excretion despite the fact that reduction in mean BP was on average only 4 mm Hg lower in the captopril group.

Recently angiotensin II receptor antagonists also have been shown to lower proteinuria in type 1 diabetics with overt nephropathy.[142] In this crossover study, the effect of losartan was compared with enalapril on BP reduction and albuminuria. Losartan reduced BP and proteinuria to a similar extent compared with enalapril. This is one of few studies in which these agents have been compared directly. There are no long-term studies in which ARBs have been shown to slow decline in GFR or reduce the risk for ESRD.

Type 2 Diabetes

Type 2 diabetes rapidly is becoming the number one cause of ESRD. Despite this fact, there are no

Table 1. Effect of ACE Inhibitors and Irbesartan on Development of Overt Nephropathy in Microalbuminuric Type 2 Diabetics

Study	Ref	N	ACEi/ARB	Dose (mg/d)	Risk Reduction (%)	*P* Value
IRMA 2	147	590	Irbesartan	150	39	<.05
			Irbesartan	300	71	<.001
MicroHOPE	144	1140	Ramipril	2.5-10	24	<.05
UKPDS	94	299	Captopril	50-100	−20	.09
Ravid	145	94	Enalapiril	10	30	<.001

N = total number of patients in study.

large-scale trials using ACEis in an attempt to prevent renal failure. Nevertheless, ACEis have been applied to type 2 diabetics with established or suspected diabetic nephropathy through extrapolation from studies performed in type 1 diabetics with nephropathy. Several clinical trials in patients with microalbuminuria and type 2 diabetes showed significant reduction in albuminuria.[51,53,144] In 2 studies, onset of macroalbuminuria was shown to be delayed or prevented during ACEi therapy with risk reduction ranging from 24% to 30%.[45,145-147]

Microalbuminuria

The Irbesartan in Type 2 Diabetics with Microalbuminuria trial. This study compared the effects of the ARB irbesartan at a dose of either 150 mg or 300 mg once daily with non-ACE, non-ARB, non–calcium channel blocker antihypertensives in microalbuminuric hypertensive type 2 diabetics.[147] The study population consisted of 590 patients with hypertension, type 2 diabetes, and microalbuminuria who were followed-up for an average of 2 years. As in some studies in type 2 diabetics using ACEis (Table 1), the primary outcome was the development of macroalbuminuria defined as 300 mg or greater every 24 hours/and at least a 30% decrease from baseline, an endpoint used in several type 2 diabetic nephropathy studies. Approximately 6% of 194 patients in the 300-mg irbesartan group and 9.7% of 195 patients in the 150-mg irbesartan group reached the primary endpoint, as compared with 14.9% of the 201 patients in the placebo group during 2 years of follow-up evaluation. Overall there was a 71% risk reduction for the primary endpoint in those treated with 300 mg of irbesartan as compared with placebo. Average BP during the study was 144/83 mm Hg in the placebo group as compared with 143/83 mm Hg in the irbesartan 150-mg group and 141/83 mm Hg in the irbesartan 300-mg group. The results of the Irbesartan in Type 2 Diabetics with Microalbuminuria (IRMA 2) trial are compared with trials in type 2 diabetics in which an ACEi was tested against a placebo or comparator group. As shown in Table 1, risk reduction for onset of overt nephropathy was greatest in the IRMA 2 trial. In this regard, recall that development of overt proteinuria was the primary outcome of the trial, whereas in UKPDS and Heart Outcomes Prevention Evaluation (HOPE), proteinuria was a secondary outcome. Also, it is noteworthy that there were no direct comparisons of ACEi and ARB in any of these studies. Comparison of the effects of candesartan with lisinopril in type 2 diabetics with microalbuminuria followed-up for 2 years revealed comparable effects on BP and proteinuria.[148] Proteinuria was reduced about 40% from baseline with either class of agents. Combining these agents resulted in a further reduction in both BP and microalbuminuria as compared with either agent alone.

Macroalbuminuria

Recently, 2 large multicenter clinical trials using ARBs to treat patients with overt nephropathy in type 2 diabetes have been completed and published. Table 2 summarizes the outcomes of the Irbesartan on the Development of Diabetic Nephropathy in Patients with Type 2 diabetes (IDNT) and RENAAL trials.

The RENAAL trial. This trial was based on lack of evidence that ACEi were renoprotective in type 2 diabetics with nephropathy and the advent of the angiotensin II antagonists. It was a multinational, double-blind, randomized, placebo-controlled trial evaluating the renal protective effects of losartan in 1,513 patients with type 2 diabetes and nephropathy at 250 centers in 29 countries.[7] It was initiated in 1996 and enrollment was com-

Table 2. Summary of Outcomes in RENAAL and IDNT

Outcome	IDNT (% Risk Reduction or Reduction in Proteinuria Favoring Irbesartan)	RENAAL (% Risk Reduction or Reduction in Proteinuria Favoring Losartan)
DSCr or ESRD or death	20% *v* placebo 23% *v* amlodipine	16% *v* placebo
DSCr	33% *v* placebo 37% *v* amlodipine	25% losartan *v* placebo
ESRD	NS irbesartan *v* placebo NS irbesartan *v* amlodipine 23% Irbesartan *v* placebo + amlodipine	28% losartan *v* placebo
ESRD + death	—	20% losartan *v* placebo
Congestive heart failure	—	32% *v* placebo
Proteinuria	30% *v* placebo or amlodipine	35% *v* placebo
Hyperkalemia necessitating discontinuation of study drug*	Irbesartan 1.9% Amlodipine 0.5% Placebo 0.4%	Losartan 1.1% Placebo 0.5%

NOTE. All comparisons shown are statistically significant. DSCr, doubling of serum creatinine.
*Percent incidence of hyperkalemia by randomized group.

pleted in 1998. The study was closed early in March of 2001 with an average of 3.4 years of follow-up evaluation. Participants were included if they had type 2 diabetes, urine protein albumin to creatinine ratio of greater than 300 mg/g, serum creatinine level of 1.5 mg/dL or greater (1.3 mg/dL in women) to 3.0 mg/dL. They were excluded if they had type 1 diabetes, known nondiabetic renal disease, HgbA1c greater than 12 mg %, history of myocardial infarction, coronary artery bypass graft within the past month, cerebrovascular accident, percutaneous coronary angioplasty within the past 6 months, or transient ischemic attack within the past 12 months, history of heart failure, known renal artery stenosis, primary aldosteronism, or pheochromocytoma. After completing a baseline evaluation, participants were maintained on conventional therapy at baseline and then randomized to either placebo or losartan 50 mg administered once daily. The dose of losartan was titrated to 100 mg/d and conventional, non-ACEi/non-ARB therapies were added as needed to achieve a target systolic BP goal of less than 140 mm Hg and a target diastolic BP goal of less that 90 mm Hg (remember this study was designed in 1996 when BP goal for renal disease was not defined as stringently as today). The primary composite endpoint of the trial was time to first event of doubling serum creatinine level, ESRD, or death. Secondary endpoints were the time to first cardiovascular event including myocardial infarction, congestive heart failure, unstable angina, cerebrovascular accident, reduction in proteinuria, and decrease in the rate of decline in GFR estimated by 1/serum creatinine versus time. The results showed that losartan treatment reduced the risk for the primary composite outcome by 16% ($P = .024$). The risk reduction for doubling serum creatinine level was 25% ($P = .006$) and ESRD was 28% ($P = .002$), and the risk reduction for the combination of ESRD or death was 20% ($P = .10$). This is the first and only clinical trial in any form of renal disease ever to show a significant risk reduction for an end-stage renal disease endpoint. There was no significant difference in all-cause mortality in losartan-treated patients. In the secondary outcomes analysis, the losartan-treated group had a 32% risk reduction for first hospitalization for heart failure. Furthermore, median proteinuria decreased by 35% in the losartan group as compared with a slight increase in the placebo group ($P = .0001$). The rate of decline in GFR also was attenuated significantly with losartan as compared with placebo ($P = .01$). Importantly, there was no difference in average BP level between groups during follow-up evaluation: 140/74 mm Hg for losartan and 142/74 mm Hg for placebo (P = NS). An additional important finding was a 32% risk reduction in subsequent development of ESRD in those patients who reached a doubling of serum creatinine level endpoint but continued on blinded study medication. This finding indicates that continuing

losartan therapy slows renal disease progression. The reported incidence of clinical and laboratory adverse events was similar between losartan and placebo.

In summary, the RENAAL trial showed that treatment of type 2 diabetic nephropathy with losartan (alone or in combination with conventional antihypertenisve therapy) delayed the progression to ESRD, reduced proteinuria, and reduced the incidence of hospitalization for heart failure. Moreover, these benefits were beyond achieved BP. Because there was no head-to-head comparison with ACEis, it is not known whether similar results would be obtained with this class of agents.

IDNT. The IDNT was a major clinical trial in type 2 diabetes with overt nephropathy performed contemporaneously with the RENAAL study.[116] The IDNT study population was similar to that of the RENAAL trial and the primary endpoint was identical, that is, time to first event of doubling of serum creatinine level, ESRD, or death. Secondary endpoints included a composite of death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for heart failure, cerebrovascular accident, or above-ankle amputation. The IDNT is unique in that it studied 1,715 patients randomized in double-blind fashion to 1 of 3 arms: (1) irbesartan; (2) amlodipine; and (3) placebo. Participants were included if they had seated BP greater than 135/85 mm Hg, age between 30 and 70 years, a documented diagnosis of type 2 diabetes mellitus, documented treatment with antihypertensive agents, and urinary protein excretion of at least 900 mg per 24 hours. Serum creatinine concentration was required to be between 1.0 and 3.0 mg/dL in women, and 1.2 and 3.0 mg/dL in men. All groups received conventional antihypertensive therapy excluding ACEis, all types of calcium channel blockers, and other ARBs. The goal BP was systolic BP less than 135 mm Hg and diastolic BP less than 85 mm Hg, similar to but lower than that in RENAAL. The average follow-up period was 2.6 years.

Irbesartan treatment resulted in a risk reduction of 20% ($P < .02$) compared with placebo, and 23% ($P < .006$) compared with amlodipine for the primary composite endpoint. The risk for a doubling of serum creatinine level endpoint was 33% lower in the irbesartan group than in the placebo group ($P = .003$), and 37% lower in the irbesartan group than in the amlodipine group ($P < .001$). The relative risk reduction for development of ESRD was 23% lower with irbesartan than both other groups ($P = .07$). As in the RENAAL trial, the differences in outcome could not be explained by differences in achieved BP. Also, serum creatinine level increased about 24% more slowly in irbesartan-treated as compared with placebo-treated ($P = .008$) and 21% more slowly than amlodipine-treated ($P = .02$) groups. No difference in cardiovascular composite endpoint was observed. There was also a reduction in proteinuria in the irbesartan but not the other groups. BP control was similar among groups, indicating that the beneficial effects of irbesartan on renal outcomes were independent of the BP-lowering effects. The main message from this trial is that the AII receptor antagonist irbesartan is preferable to amlodipine or conventional antihypertensive therapy alone because of its superior renoprotective effect in type 2 diabetic nephropathy.

It is noteworthy that neither RENAAL nor IDNT were powered sufficiently to detect differences in death among treated groups. This is an important point in view of the results from the HOPE trial in which the ACEi ramipril was shown to lower mortality in more than 3,000 patients with type 2 diabetes.[144] However, it is important to point out that the diabetic population included in the HOPE study was dramatically different from the populations studies in RENAAL and IDNT. There are several reasons that come to mind. First, the HOPE trial was not designed to study patients with renal disease or to evaluate renal outcomes. Thus, only 275 diabetic patients in the HOPE study had microalbuminuria whereas all 3,230 of the RENAAL and IDNT patients had overt proteinuria. Second, few HOPE study patients had advanced renal disease and only 956 of the total HOPE trial cohort had a serum creatinine level greater than 1.4 mg/dL. Third, the diabetic patients were not severely hypertensive and had few cardiovascular complications before onset of the trial.

In summary, we now have 2 completed, large, multicenter, clinical trials in type 2 diabetics involving more than 3,000 type 2 diabetics with nephropathy that both showed risk reduction for progression of renal disease. These 2 trials represent unparalleled advances in the management of type 2 diabetic nephropathy.

Role of Calcium Channel Blockers

Calcium channel blockers were included as part of the treatment regimen in about 80% of patients in the RENAAL trial as part of their regimen to lower BP. In contrast, calcium channel blockers were excluded in patients in the IDNT trial unless patients were in the amlodipine arm. An important clinical question is: What is the role of calcium channel blockers in the management of diabetic nephropathy? Nondihydropyridine calcium channel blockers lower BP and in some studies slow progression of renal failure in type 2 diabetics with nephropathy.[45] In addition, these agents are recommended as third-line agents after ACEis and diuretics for diabetics with hypertension by the NKF.[55] However, clinical trials using calcium channel blockers to lower BP and preserve renal function in diabetics and nondiabetics with renal disease reveal conflicting results. In a controlled trial of hypertensive, proteinuric type 2 diabetics with mild renal insufficiency, Bakris et al[45] showed that nondihydropyridine calcium channel blockers (CCB) or ACEis reduced proteinuria and slowed decline in creatinine clearance to a greater extent than β blockers despite similar BP in all groups. In addition, long-term BP lowering to about 135/85 mm Hg in type 2 diabetics with nephropathy by using a nondihydropyridine calcium channel blockers significantly reduced proteinuria, whereas similar BP lowering with a dihydropyridine CCB did not.[47] In hypertensive type 2 diabetic African Americans with nephropathy, ACEis decreased and dihydropyridine calcium channel blockers increased proteinuria at similar levels of BP control.[149] In nondiabetic African Americans with hypertensive nephrosclerosis, decreased baseline GFR, and proteinuria, long-term administration of ramipril-based treatment was superior to amlodipine-based treatment for slowing the decline in renal function and reducing proteinuria despite similar BP control.[150] In contrast to the African American Study of Kidney Disease and Hypertension, in the Renal Endpoints in Nephropathy (REIN) trial, hypertensive proteinuric patients with primary glomerular disease treated with dihydropyridine calcium channel blockers had worsening proteinuria and renal function when mean arterial BP was 110 mm Hg or greater but decreasing proteinuria and preservation of renal function when mean arterial pressure was lowered to less than 95 mm Hg.[151] The reduction in proteinuria and preservation in renal function in the latter group occurred regardless of whether patients were treated concomitantly with an ACEi.

Thus, the role of dihydropyridine calcium channel blockers remains controversial in both diabetics and nondiabetics with renal disease. Yet the use of dihydropyridine calcium channel blockers for lowering BP in hypertensive, proteinuric type 2 diabetics is widely practiced. Bakris et al[152] showed that in hypertensive, proteinuric type 2 diabetics, combination therapy with an ACEi and nondihydropyridine calcium channel blocker reduced proteinuria to a greater extent then either agent alone, despite similar degrees of BP lowering. Unfortunately, in this study combination therapy with a dihydropyridine calcium channel blocker and an ACEi was not examined. It remains uncertain whether lowering BP to an appropriate level by adding a dihydropyridine calcium channel blocker to an ACEi and diuretic in type 2 diabetics with persistent hypertension and proteinuria is effective in reducing proteinuria. Given overall inadequate rates of achieving adequate BP control in patients with proteinuric renal disease, there is a need for studies to determine the efficacy, tolearability, and safety of combining dihydropyridine CCBs and ACEis, particularly in hypertensive type 2 diabetics with nephropathy. However, as noted earlier, 80% of losartan and placebo participants in RENAAL were treated with a calcium channel blocker at some point during the trial. In practice it seems reasonable to infer that in the presence of ACE inhibition or angiotensin II type 1 receptor blockade, addition of a calcium channel blocker is reasonable and beneficial to the extent that this class of agents helps to achieve BP control.

Multisite Blockade of the RAAS May Provide Added Benefit in Diabetic Nephropathy

Despite recent improvements in diagnosis, prevention, and management of diabetes mellitus, the prevalence and incidence of diabetic ESRD are increasing.[21,153] Chronic ACEi treatment does not completely block AII production,[57,154,155] plasma AII levels may return to normal[156,157] and plasma aldosterone concentration may increase in hypertensives.[158] Similarly, chronic ARB administration does not completely block AT_1 receptors.[57,159] ACEi and ARB combination decreases tissue AII to a greater extent than with either agent alone in rats with chronic renal disease.[160] Moreover,

plasma aldosterone levels are unchanged or slightly reduced by ACEi or ARB treatment in humans with chronic renal disease.[161] In most patients renal function continues to decline at an accelerated rate (>5 mL/min/y) despite treatment with either an ACEi (type 1 diabetes) or an ARB (type 2 diabetes), and ESRD is not prevented.[116] In fact, these treatments increase time to ESRD by 1 year at best.[7,116] Therefore, the beneficial effect of agents that block the RAAS at only one site (ACEi or ARB) fall far short of the goal of preventing ESRD. Possible reasons for this shortfall include insufficient BP lowering and incomplete RAAS blockade.

ACEi and ARB Combination

Short-term (1-6 mo) studies have examined the effect of combined ACEi and ARB treatment on proteinuria and hypertension in diabetic,[148,162,163] nondiabetic,[164,165] and mixed (diabetic and nondiabetic) nephropathies.[13-17,20,21,120] In nondiabetics some,[13,16,17,19-21] but not all,[15,82] studies showed an additive antiproteinuric effect of ACEi and ARB. In an encouraging preliminary report from Japan, long-term treatment with an ACEi and ARB versus either agent alone combined with strict BP control (120/70 mm Hg) reduced the risk for doubling of serum creatinine level or ESRD in a cohort of 245 patients with nondiabetic renal disease.[21] However, published studies of ACEi and ARB combinations have important shortcomings, including small numbers of study subjects, short-term follow-up (1-6 mo), mixed renal diseases, lack of control of sodium intake, variable doses of both classes of agents, low doses of ACEi or ARB, variation in proteinuria measurements, and lack of safety data reporting. Furthermore, no study has examined the effect of ACEi and ARB combination on progression of renal disease or systematically investigated the effect of such therapy on plasma renin activity, plasma AII, and aldosterone levels.

ACEi and Mineralocorticoid Receptor Antagonist Combination

Experimental animal studies suggest that aldosterone acts independently of AII to cause proteinuria and renal fibrosis[166,167] and reducing aldosterone level or blocking its receptor are renoprotective.[67,168-171] Plasma aldosterone is increased in some patients with diabetic nephropathy.[168,172-173] Plasma AII levels are elevated in some patients with type 2 diabetes and early nephropathy[175] and chronic ACEi treatment in hypertensive patients may increase plasma aldosterone levels despite persistent hypotensive effect of ACEi.[159] However, no study has correlated plasma aldosterone, AII, or plasma renin activity with progression of renal disease and there are no well-controlled trials of the effect of mineralocorticoid receptor antagonists (MRAs) on proteinuria in diabetic nephropathy. In patients with congestive heart failure, long-term MRA treatment provides additional survival benefit when added to an ACEi-based regimen.[175] Taken together, these findings suggest that combining an MRA with an ACEi could provide additive beneficial effects in patients with diabetic nephropathy. In one report of 8 proteinuric patients (5 patients with type 2 diabetes), addition of sprironolactone 25 mg once daily to an ACEi-based regimen for 6 months reduced baseline proteinuria by 50%, suggesting a BP-independent effect of multisite RAAS blockade. However, one should note that BP was decreased significantly by addition of spironolactone, dietary sodium intake was not monitored, and plasma potassium was not reported.[177]

Special Effects Versus BP Lowering

Despite claims that blockade of the RAAS provides renoprotection beyond BP lowering, questions remain. In rats with renal ablation, original studies showing BP-independent renoprotection of ACEi treatment used only tail cuff BP measurement.[177] Repeat experiments in this model using continuous, radiotelemetric BP monitoring found no BP-independent renoprotection of ACEi over noncalcium channel blocker antihypertensives.[178] In large-scale clinical trials of diabetic nephropathy, renoprotection beyond BP control afforded by ACEi and ARB treatment is based solely on clinic BP measurements. But even clinic BP goals were not achieved in either the IDNT or the RENAAL trials.[7,116,139] Furthermore, it is well established that nighttime BP burden is increased consistently,[179-181] and ambulatory blood pressure monitoring (ABPM) is a better indicator of cardiovascular injury and correlate of proteinuria than office BP in patients with chronic renal diseases, including diabetic nephropathy.[182-186] Therefore, significant differences in 24-hour ABPM between placebo and active drug treatment groups in clini-

cal diabetic nephropathy could have been missed as it was in the HOPE substudy.[187] Hence, outcome differences between placebo and experimental groups could be explained largely, if not entirely, on the basis of differences in time-averaged BP burden. There are no prospective clinical trials involving a multiethnic cohort, including minorities at highest risk for ESRD owing to diabetic nephropathy, in which ABPM has been used to document time-averaged (especially nighttime) BP burden. It is tempting to speculate that the superiority of ACEis and ARBs in diabetic renal disease may be attributed to their superior effects on time-averaged BP burden. Future studies designed to show BP-independent effects of test agents should use ABPM to effectively monitor adequacy of BP control.

Economics

Cost effectiveness of interventions in diabetic nephropathy has not been evaluated extensively. However, it is important to consider the potential benefits of interventions that prolong survival and reduce dialysis or transplantation resources. Several studies indicated that treatment of overt diabetic nephropathy with ACEis and ARBs was cost effective. Rodby et al[188] calculated cost savings by slowing progression of nephropathy in type 1 diabetics with nephropathy. Several preliminary analyses of the RENAAL and IDNT studies have indicated that ARBs also are cost effective in the treatment of overt diabetic nephropathy.[189-191] Projected savings to the US population from the IDNT trial comparing irbesartan with placebo and amlodipine indicate a savings of about $7 billion. Similar savings were calculated from the RENAAL trial. Cost savings from these analyses are those incurred over time for dialysis care. The cost savings are very substantial, particularly with ACEis as compared with ARBs because ARBs are considerably more expensive than ACEis. Nevertheless, the cost savings with ARBs remain important. Validation and confirmation of these preliminary reports are anticipated.

SUMMARY AND RECOMMENDATIONS

Based on the evidence, it is recommended that patients with type 1 diabetes with either microalbuminuria or overt nephropathy should be treated with an ACEi to slow progression or renal disease. In patients with type 2 diabetes, and one other cardiovascular risk factor but without albuminuria, the HOPE trial data provide compelling evidence to treat with an ACEi to reduce the risk for major cardiovascular events. In type 2 diabetics with microalbuminuria, use of an ACEi or an ARB is reasonable to reduce the risk for onset of nephropathy. Until a long-term clinical trial is conducted comparing an ACEi with an ARB in patients with diabetic nephropathy, it is not possible to know whether these agents are equivalent for reducing the risk for progression of nephropathy. Therefore, based on current evidence, type 2 diabetics with overt nephropathy should be treated with an ARB as first-line therapy for reducing risk for progression of renal disease. Future outcome trials in diabetics with nephropathy should be designed with the primary combined endpoint of ESRD or death.

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