

Prevention and Treatment of Diabetic Renal Disease in Type 2 Diabetes: The BENEDICT Study

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Diabetic nephropathy (DN) is the leading cause of end-stage renal failure in Western countries and carries an increased risk for cardiovascular mortality. Studies have identified a number of factors that play a part in the development of DN. Among them, hypertension and proteinuria are the most important. In the early stages of DN, when albumin is present in the urine in very low quantities (microalbuminuria) and an increase is seen in BP, there is no loss of filtrate and patients respond well to prophylactic measures. Microalbuminuria is considered an early marker of DN. Prevention of the onset of microalbuminuria, therefore, could be considered as the primary means of preventing DN. The Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) was a prospective, randomized, double-blind, parallel-group study that was organized in two phases. Phase A included 1204 patients and was aimed at assessing the efficacy of the angiotensin-converting enzyme (ACE) inhibitor trandolapril, the non-dihydropyridine calcium channel blocker verapamil, and the trandolapril plus verapamil combination as compared with placebo in prevention of microalbuminuria in hypertensive patients with type 2 diabetes and normal urinary albumin excretion rate. Phase B was aimed at assessing the efficacy of the combination as compared with trandolapril alone in prevention of macroalbuminuria in patients with microalbuminuria. The BENEDICT Phase A study showed that DN can be prevented by ACE inhibitor therapy. The beneficial effect of ACE inhibition is not enhanced by combined non-dihydropyridine calcium channel blocker therapy. The apparent advantage of ACE inhibitors over other agents includes a protective effect on the kidney against the development of microalbuminuria, which is a major risk factor for cardiovascular events and death in this population.

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Diabetic nephropathy (DN) is the leading cause of end-stage renal failure in Western countries and carries a 20- to 40-fold increased risk for cardiovascular (CV) mortality. In the past 2 decades, there has been a continual increase in the incidence of ESRD among patients with diabetes, predominantly those with type 2 diabetes (1,2).

Until recently, the risk for renal complications was thought to be considerably lower among patients with type 2 diabetes than in those with type 1 diabetes (3); however, it now has been shown that the risk for nephropathy with progression to ESRD is similar for the two groups (4). The incidence of type 2 diabetes (and, hence, the related incidence of ESRD) is greater than that of type 1 diabetes. In addition, the incidence of ESRD within the type 2 diabetes population has increased dramatically in the past few years. This is thought to be due partly to improved treatments for hypertension and coronary heart disease, allowing more patients with type 2 diabetes to live long enough for nephropathy and ESRD to develop (5). Another, perhaps more important, factor may be that patients are not being treated correctly and, therefore, the BP target ($\geq 130/80$ mmHg) is not being achieved, resulting in increased genesis of

renal failure. Also, proteinuria may not be treated as a risk factor. Numerous studies have demonstrated that attenuated increases in proteinuria or its reduction from baseline levels by at least 30% provide greater slowing of renal disease progression (6–12).

Increased urinary albumin and protein excretion are associated with CV disease mortality independent of other CV risk factors in both patients without diabetes and patients with type 2 diabetes (8,13). However, the presence of type 2 diabetes independently increases the risk for atherosclerotic vascular and CV disease events, regardless of the proteinuria status. An association between proteinuria and stroke has similarly been demonstrated (13). The excessive CV risk means that patient survival is dramatically reduced before the development of ESRD, and survival levels fall even further after development (1–5).

Development of DN

In the diabetic kidney, there are increases in the perfusion and the GFR and probably also in intraglomerular capillary pressure. Type 2 diabetes also causes growth of the kidney and enlargement of the glomeruli, which then are susceptible to damage. There is modification of the glomerular components (largely the basement membrane), particularly resulting from nonenzymatic glycation and the accumulation of advanced glycation end products. These combined mechanisms result in

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pathologic changes in the glomerular structure. Initially, albumin appears selectively in the urine; subsequently, other proteins appear nonselectively, followed by loss of filtrate and finally renal failure. In this sense, 35 to 40% of patients with diabetes will develop clinically manifest DN (14).

Studies have identified a number of factors that play a part in the development of DN (15–17). These include elevated BP and glycosylated hemoglobin and cholesterol concentrations; smoking; advanced age; high level of insulin resistance; male gender; and Afro-Caribbean, Asian, or Native American race. A family history of CV events also is an indicator of renal risk. Genetic factors also seem to play a part in the development of DN, as familial clustering of diabetes is found among both patients with type 1 and patients with type 2 diabetes. In addition, the finding of a family history of CV events is a powerful indicator of renal risk, with clusters of CV incidents being seen in first-degree nondiabetic relatives of patients with type 1 and type 2 diabetes (15). Hyperglycemia plays a crucial role in the development of DN, and an interaction has been described between genetic factors and blood sugar levels for the risk of onset of microalbuminuria in patients with newly diagnosed type 2 diabetes. The combination of a positive family history and poor glycemic control greatly increases the risk for development of DN.

Factors that Affect Progression of DN

DN progresses through five stages (18). Stage 1 is characterized by an increase in GFR. Stage 2 corresponds to a clinical silent phase with continued hyperfiltration and hypertrophy. In stage 3, known as initial nephropathy, albumin is present in the urine in very low quantities (microalbuminuria, *i.e.*, urinary albumin excretion >30 to 300 mg/d or 20 to 200 μ g/min) that cannot be detected by conventional assays but only by more sensitive methods. In this stage, BP tends to increase, although still within the normal range, and GFR may start to decline. At stage 4, overt nephropathy, urinary albumin excretion increases to >300 mg/d (macroalbuminuria), the BP almost invariably increases above normal, and the GFR progressively declines—by approximately 10 ml/yr in untreated patients—until renal replacement therapy is required (stage 5). Progression through these five stages is predictable in type 1 diabetes: Stage 1 accompanies the onset of diabetes and progresses through stage 2 to stage 3 during the course of approximately 10 yr. Then, progression from stage 4 to 5 may take 7 to 10 yr in patients without antihypertensive therapy. Recent data show a similar course also in type 2 diabetes; however, in this clinical setting, the progression from one stage to the other is difficult to follow.

A number of factors are known or suspected to play a part in the progression of DN (19), the most important of which is hypertension. Reduction of arterial BP below 130/80 mmHg has proved to be one of the most effective ways to slow progression of diabetic renal disease (20,21). Albuminuria also is a predictor of rapid progression irrespective of BP measurements. Antihypertensive agents that selectively reduce albuminuria consequently are very useful for the treatment of patients with diabetes and nephropathy. The involvement of

other factors, such as genetic predisposition, is currently being studied (22). Early studies suggested that controlling blood sugar levels had little effect on the further course of renal function in patients with diabetes and nephropathy. It had been thought that nephropathy progressed independent of blood sugar levels at this point in disease progression. However, more recent studies have shown that, even in patients with diabetes and clinically manifest nephropathy, lack of adequate control of blood sugar levels can affect filtrate loss (5). Smoking also is known to have a fundamental effect on the onset and progression of nephropathy, with filtrate loss in patients who have diabetes with renal failure and who smoke being twice that of nonsmokers (23).

The investigators of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study (24) examined the data that focused on the relationship between CV end points or hospitalization for heart failure and baseline or reduction in albuminuria. Patients with high baseline albuminuria (≥ 3 g/g creatinine) had a 1.92-fold higher risk for the CV end point and a 2.70-fold higher risk for heart failure compared with patients with low albuminuria (<1.5 g/g). Among all available baseline risk markers, albuminuria was the strongest predictor of CV outcome. The association between albuminuria and CV outcome was driven by patients who also had a renal event. It also was shown that albuminuria reduction was the only predictor for CV outcome: 18% reduction in CV risk for every 50% reduction in albuminuria and a 27% reduction in heart failure risk for every 50% reduction in albuminuria.

Using the Irbesartan in Diabetic Nephropathy Trial (IDNT) (25) cohort, the investigators examined the baseline characteristics of individuals with type 2 DN and hypertension predictive for cardiac events. IDNT identified 1715 individuals who had type 2 DN and hypertension and had serum creatinine of 1.0 to 3.0 mg/dl and urinary albumin excretion rates ≥ 900 mg/d. A CV composite end point that consisted of CV death, nonfatal myocardial infarction, hospitalization for heart failure, stroke, amputation, and coronary and peripheral revascularization was used. Of the 1715 individuals, 518 (30.2%) had at least one of the CV composite end points. Older age, male gender, longer duration of diabetes, history of CV disease, history of congestive heart failure, high urinary albumin:creatinine ratio, and low serum albumin were strong predictors for CV events; of these, history of CV disease (relative risk 2.00) and high urinary albumin:creatinine ratio (relative risk 1.29) at baseline were highly predictive of CV events. In conclusion, among individuals with hypertension and DN, both the degree of albuminuria and lower serum albumin levels provide additional prognostic information concerning CV risk, in addition to traditional coronary risk factors.

Role of Hypertension in Onset and Progression of DN

The prevalence of hypertension and type 2 diabetes increases with age. Up to 90% of patients with type 2 diabetes are hypertensive, and virtually all patients with type 2 diabetes are already hypertensive at the time of onset of nephropathy. On

the contrary, most patients with type 1 diabetes are normotensive, and their BP progressively increases above age-adjusted normal ranges, as defined according to World Health Organization/International Society of Hypertension criteria (20), only after the onset of nephropathy. However, patients who have type 1 diabetes and eventually develop nephropathy tend to have higher BP than age-matched patients who have type 1 diabetes and remain free of renal disease. Therefore, high BP or a predisposition to high BP seems to play a major role in the onset and progression of nephropathy in both type 1 and type 2 diabetes (26). Then, BP progressively increases with worsening renal function, and control of arterial hypertension may become very difficult in patients with overt nephropathy, in particular in those with type 2 diabetes, and target BP seldom is achieved despite combined treatment with three or more antihypertensive medications. High BP also may contribute to the onset and progression of other micro- and macrovascular complications. Indeed, an estimated 35 to 75% of diabetic complications can be attributed to hypertension (27–29). This also is because hypertension, in addition to obesity, dyslipidemia, and microalbuminuria, is a component of the metabolic syndrome (28).

Role of Antihypertensive Therapy

In type 1 diabetes with nephropathy, there is a clear relationship between mean arterial pressure (MAP) and the annual percentage increase in urine albumin excretion. In patients with essential hypertension, the hypertension is tolerated by the kidneys for many years without the onset of albuminuria. The diabetic kidney is very sensitive, however, to increases in BP. In patients with no renal disease, the glomerular microcirculation is protected by the high preglomerular resistance to variations in systemic BP. In patients with DN, there is afferent vasodilation (preglomerular), and a major part of the aortic pressure is transmitted to the glomerular vascular bed, thereby increasing glomerular pressure. Even at normal BP, the glomerular capillary pressure rises and is particularly pronounced when there is hypertension in the systemic circulation. This explains why even small increases in BP (still within the normal range) can have such a deleterious effect on renal function and why hypertension plays such an important role in the development of nephropathy. Evidence of a causative role for hypertension in nephropathy was provided by Parving *et al.* (30) and Mogensen (31). They showed that by reducing BP, filtrate loss in DN could be delayed. Analyses of long-term clinical trials have shown that the lower the BP over a range of values, the greater the preservation of renal function. Currently, however, it is believed that lowering BP is not enough. It is becoming increasingly important to reduce proteinuria. Antihypertensive drugs that attenuate increases in proteinuria or reduce proteinuria from baseline levels by at least 30% provide greater slowing of renal disease progression compared with agents that do not have this effect (6–12).

Role of ACE Inhibitors

Interest in the role of ACE inhibitors in delaying the progression of DN began in 1986, when an experimental model of renal

damage, comparing the effects of enalapril with a triple combination of the antihypertensive agents hydralazine, reserpine, and hydrochlorothiazide, demonstrated that enalapril produced an equally good reduction in MAP to the triple therapy (32). In addition, enalapril produced a reduction in proteinuria and less pronounced glomerulosclerosis. A kidney-protecting effect of this kind had been observed previously, when salt depletion was achieved either *via* diet or the use of diuretics (33). The antiproteinuric and kidney-protecting effects of the ACE inhibitors originally were thought to be attributable purely to hemodynamic effects, relieving the glomerulus by opening the efferent arterioles (postglomerular), thereby reducing glomerular capillary pressure (31). However, it has become apparent that ACE inhibitors also affect glomerular function by their effects on glomerular size, glomerular permeability, and increasing negative electrical charge of the glomerular membrane (34,35). A meta-analysis of 12 trials in 698 patients who had type 1 diabetes with microalbuminuria and were followed for at least 1 yr revealed that ACE inhibitors reduced the risk for progression to macroalbuminuria by 62% compared with that of the placebo group (36). Parving and Hovind (37) showed that the beneficial effect of ACE inhibitors on preventing progression from microalbuminuria to overt nephropathy is long lasting (8 yr) and is associated with preservation of normal GFR. Ravid *et al.* (6) originally described the beneficial effect of ACE inhibition in normotensive, nonobese microalbuminuric patients with type 2 diabetes by demonstrating that only 12% of the patients in the ACE inhibitor group developed nephropathy, compared with 42% in the placebo arm. The BP, however, tended to be lower in the ACE inhibitor group, and the study was not powered to assess whether the reduced risk for microalbuminuria was due to ACE inhibition therapy or just to more BP reduction. Consequently, current medical opinion suggests that patients with diabetes and microalbuminuria, even while they are normotensive, should be treated with ACE inhibitors or combinations thereof, as per the National Kidney Foundation Algorithm (38).

Role of Angiotensin Receptor Antagonists

A study conducted by Parving *et al.* (39) examined the effect of blockade of the renin-angiotensin system (RAS) with a new class of agents, the angiotensin receptor blockers (ARB), in hypertensive patients with type 2 diabetes and microalbuminuria. A total of 590 hypertensive patients with type 2 diabetes and microalbuminuria were enrolled in this multinational, randomized, double-blind, placebo-controlled study of irbesartan, at a dose of either 150 or 300 mg/d, and were followed for 2 yr. The primary outcome was the time to the onset of DN, defined by persistent albuminuria. Ten (5.2%) of the 194 patients in the 300-mg/d group and 19 (9.7%) of the 195 patients in the 150-mg/d group reached the primary end point, as compared with 30 (14.9%) of the 201 patients in the placebo group (hazard ratios 0.30 and 0.61 for the two irbesartan groups, respectively).

Two studies examined the role of ARB on the progression of renal disease in patients with type 2 diabetes and macroalbuminuria. The RENAAL study (40) showed that as compared with conventional treatment alone (*i.e.*, treatment without ACE

inhibitors or ARB), losartan combined with conventional treatment decreased the level of urinary protein excretion by 35% and reduced the risk for the composite end point doubling serum creatinine, ESRD, or death by 22%. This beneficial effect was achieved at comparable BP control in the two treatment arms. In the IDNT trial (41), the risk for the combined end point of a doubling of the baseline serum creatinine level, the onset of ESRD, or death from any cause was 20% lower in patients who were treated with irbesartan than in those who were treated with conventional therapy and 23% lower than in those who were treated with amlodipine. These studies also showed a reduction in the rate of heart failure with ARB but no differences in the overall rate of death or the rate of death from CV causes.

Few studies have compared directly the renoprotective effects of ARB and ACE inhibitors in patients with type 2 diabetes. In a prospective study, 250 patients with type 2 diabetes and early nephropathy were randomly assigned to receive either the ARB telmisartan (80 mg/d, in 120 patients) or the ACE inhibitor enalapril (20 mg/d, in 130 patients) (42). The primary end point was the change in the GFR between the baseline value and the last available value during the 5-yr treatment period. After 5 yr, the GFR decreased by 17.9 ml/min per 1.73 m² of body surface area with telmisartan and by 14.9 ml/min per 1.73 m² with enalapril, with a treatment difference of 3.0 ml/min per 1.73 m². On the basis of predefined criteria, this difference was not enough to conclude that telmisartan is inferior to enalapril in providing long-term renoprotection in patients with type 2 diabetes. These findings do not necessarily apply to people with more advanced nephropathy, but they support the clinical equivalence of ARB and ACE inhibitors in people with conditions that place them at high risk for CV events. The role of short-term “dual blockade” of the RAS in hypertensive, microalbuminuric patients with type 2 diabetes also has been evaluated (43). A combination of candesartan and lisinopril was even more effective than monotherapy for reducing BP in such patients, and the same trend was apparent for the reduction in urinary albumin excretion rate.

Unfortunately, RAS inhibitor therapy seldom is offered to individuals who have advanced chronic kidney disease because of safety concerns. In a *post hoc*, secondary analysis of the RENAAL trial (44), angiotensin antagonism risk/benefit profile was assessed in 1513 individuals with type 2 diabetes and overt nephropathy. Incidence of ESRD, hospitalizations for heart failure, withdrawals for adverse events, and proteinuria during losartan or conventional treatment were compared within three tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl). Losartan decreased the risk for ESRD by 24.6, 26.3, and 35.3% in the highest, middle, and lowest tertiles, respectively. For every 100 patients with serum creatinine >2.0, 1.6 to 2.0, or <1.6 mg/dl, 4 yr of losartan therapy was estimated to save 18.9, 8.4, and 2.9 ESRD events, respectively. Losartan also decreased the hospitalizations for heart failure by 50.2 and 45.1, in the highest and middle tertiles, respectively. Proteinuria decreased more on losartan than on placebo in all tertiles. Therefore, ARB are a suitable and well-tolerated treatment for individuals with type

2 diabetes even with GFR levels approaching renal replacement therapy.

Role of Calcium Channel Blockers

The results of studies with calcium channel blockers (CCB) in DN have been mixed, with an increase in albuminuria actually being observed in some studies, using dihydropyridine calcium antagonists (dCCB) (45). It is clear that differences exist between various classes of calcium antagonists and their effect on reducing proteinuria, thereby providing nephroprotection. Non-dihydropyridine CCB (ndCCB) have been shown to reduce proteinuria and retard the progression of DN (10,46). Long-term studies demonstrate that ndCCB, such as verapamil and diltiazem, slow progression of nephropathy significantly better than β blockers and that their effect in preserving the kidneys is comparable to that of lisinopril, an ACE inhibitor (10,46). A meta-analysis of randomized trials of ndCCB and dCCB in hypertensive patients with proteinuric renal disease found that at comparable BP control, ndCCB reduced proteinuria by approximately 30% as compared with baseline, whereas dCCB had no appreciable effects on urinary proteins. These findings were taken to suggest ndCCB as preferred agents to lower the BP alone or in combination with a RAS inhibitor in patients with chronic proteinuric nephropathies (47). In many cases, dCCB add no value in the absence of an ACE inhibitor. A long-term study of the effects of ramipril and felodipine therapy alone or in combination on nondiabetic renal disease progression (the NEPHROS study), measured as loss of GFR, found that ramipril alone and in combination with felodipine reduced proteinuria to a similar extent, whereas felodipine alone significantly increased proteinuria (48). More recently, the Ramipril Efficacy In Nephropathy 2 (REIN-2) found that intensified BP control by add-on felodipine treatment in 338 patients who had nondiabetic chronic nephropathies and were receiving background ACE inhibitor therapy failed to reduce proteinuria and limit progression to ESRD (49). An important issue is that dCCB have a vasodilating action on the preglomerular sections of the blood vessels (afferent), and, consequently, there is a risk for glomerular hypertension if systemic BP is not at a normal level. Drugs such as nifedipine, amlodipine, and felodipine therefore should be used only to normalize BP.

A direct comparison between an ARB and a CCB was attempted by the MicroAlbuminuria Reduction With VALsartan (MARVAL) study in patients with type 2 diabetes and microalbuminuria (50). A total of 332 patients with type 2 diabetes and microalbuminuria, with or without hypertension, were randomly assigned to 80 mg/d valsartan or 5 mg/d amlodipine for 24 wk. A target BP of 135/85 mmHg was aimed for by dose-doubling followed by addition of bendrofluzide and doxazosin whenever needed. The primary end point was the percentage change in albuminuria from baseline to 24 wk. The albuminuria at 24 wk was 56% of baseline with valsartan and 92% of baseline with amlodipine, a highly significant between-group effect ($P < 0.001$). Valsartan lowered albuminuria similarly in both the hypertensive and the normotensive subgroups. More patients reverted to normoalbuminuria with valsartan

(29.9 versus 14.5%; $P = 0.001$). In summary, for the same level of attained BP and the same degree of BP reduction, valsartan lowered albuminuria more effectively than amlodipine in patients with type 2 diabetes and microalbuminuria.

Role of Combined Therapy with ACE Inhibitors and CCB

In many ways, ACE inhibitors and ndCCB complement each other's actions. The combination of an ACE inhibitor, which reduces the formation of angiotensin II, and a CCB, which weakens the effect of angiotensin II on the target organ, theoretically should be more effective than either drug alone.

Studies by Berne *et al.* (51) indicated that ACE inhibitors improve glucose use and insulin sensitivity in hypertensive patients with type 2 diabetes and favorably modify the disease course. As a result, in the treatment of hypertension in patients with type 2 diabetes, ACE inhibitors have been the drugs of choice for initial monotherapy in patients with albuminuria/proteinuria (52). If the BP response is inadequate, then the additional use of an ndCCB or a diuretic therefore might be a prudent course of action (53). In the TRAVEND study, the effect of antihypertensive combinations on metabolic control and albuminuria in patients with type 2 diabetes showed that the combination of verapamil plus trandolapril allowed better metabolic control than enalapril plus hydrochlorothiazide (54).

There is increasing concern regarding the metabolic effects of antihypertensive drug therapy and their impact on CV risk reduction that results from the treatment of hypertension (55). Hypertensive patients who take β blockers or diuretics or both have an increased risk for diabetes compared with hypertensive patients who do not take those agents (56). The combination of trandolapril with verapamil reduces albuminuria to a greater extent than with either agent alone (12,57) or more compared with a β blocker and a low-dose diuretic combination, although BP lowering was similar (58). The metabolic, antihypertensive, and albuminuria-modifying effects of the verapamil plus trandolapril combination compared with those of a β blocker low-dose diuretic combination in hypertensive patients with type 2 diabetes was investigated in two separate studies (58,59). The two approaches produced similar decreases in BP. The verapamil plus trandolapril combination was found to be metabolically neutral, whereas the atenolol plus chlorthalidone combination further aggravated insulin resistance. This indicates that the verapamil plus trandolapril combination is a potentially valuable therapy for hypertension that accompanies type 2 diabetes, because the benefits of the ACE inhibitor may be amplified by providing superior BP control with added renal and CV protection. In a further study, in patients with hypertension and type 2 diabetes, those who were taking the combination verapamil plus trandolapril had significant lower HbA_{1c} values compared with patients who were treated with atenolol plus chlorthalidone (60). Data of all these studies make the combination verapamil plus trandolapril very attractive in hypertensive patients with diabetes. Clinical data from Bakris *et al.* (12) demonstrated that combination therapy in patients with type 2 diabetes and nephropathy also has a good safety profile. Similar results were obtained using another ACE inhibitor,

lisinopril, combined with a slow-release formulation of verapamil.

Preventing Nephropathy in People with Diabetes: BENEDICT

Microalbuminuria is an early marker of DN. Microalbuminuric patients with type 1 and type 2 diabetes almost invariably progress to macroalbuminuria and overt DN. Although treating patients with diabetes by reducing the progression from microalbuminuria to macroalbuminuria may delay renal disease progression (*i.e.*, secondary prevention), prevention of the onset of microalbuminuria could be considered as the primary means of preventing DN. ACE inhibitors and ndCCB have specific renoprotective properties in diabetes. Whether early treatment with ACE inhibitors in normoalbuminuric patients with diabetes can effectively prevent progression to microalbuminuria (*i.e.*, primary prevention) remains to be established. However, preliminary evidence available in hypertensive patients with type 2 diabetes suggests that the incidence of microalbuminuria may be reduced by ACE inhibition therapy (11). Preliminary evidence also is available to show that the combination of ACE inhibitors with CCB might be able to delay the onset and limit the progression of nephropathy in hypertensive patients with diabetes more effectively than either of the two agents alone (61). A study of 60 patients with type 2 diabetes and proteinuria ≥ 300 mg/d found that, at comparable BP control, the fixed-dose combination VeraTran (trandolapril 2 mg/d plus verapamil SR 180 mg/d) more effectively than trandolapril alone (2 mg/d) reduced proteinuria and slowed GFR decline over 6 mo of follow-up (62). Furthermore, the combination of ACE inhibitors and CCB seems to yield a lower side effect profile than either agent alone (45). Finally, the combination of both agents in hypertensive patients with diabetes might reduce the need for additional diuretic therapy, which has been associated with an excess mortality in type 2 diabetes.

The Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) was a prospective, randomized, double-blind, parallel-group study that was organized in two phases. Phase A was aimed at assessing the efficacy of the ACE inhibitor trandolapril, the ndCCB verapamil, and the trandolapril plus verapamil combination (VeraTran) as compared with placebo in prevention of microalbuminuria in hypertensive patients with type 2 diabetes and normal urinary albumin excretion rate. Phase B was aimed at assessing the efficacy of VeraTran as compared with trandolapril alone in prevention of macroalbuminuria in hypertensive patients with type 2 diabetes and microalbuminuria (62,63). Primary efficacy variables were the onset of microalbuminuria for phase A and the onset of macroalbuminuria for phase B. Outcome data were adjusted for prespecified baseline variables such as age, gender, smoking status, and baseline albuminuria. Phase A has been concluded, and data were reported in November 2004 (63); Phase B is still ongoing, and the final results are expected at the end of 2006. BENEDICT phase A recruited 1204 hypertensive, normoalbuminuric patients who had type 2 diabetes and were 40 yr or older. Eligible individuals were enrolled after a run-in period of

up to 6 wk. The run-in period was 2 wk in patients with no previous antihypertensive treatment, 3 wk in patients who previously had taken ndCCB, and 6 wk in patients who were taking RAS inhibitors. At completion of the run-in period, patients were randomly allocated to four treatment arms: Trandolapril alone (2 mg/d; $n = 301$ patients), verapamil SR alone (240 mg/d; $n = 303$), verapamil SR (180 mg/d) plus trandolapril (2 mg/d; $n = 300$), or placebo ($n = 300$). Baseline characteristics and simultaneous treatments of patients who were randomly assigned to the four treatment groups were comparable. Patients were to be maintained in metabolic control (target $HbA_{1c} < 7\%$), and BP had to be $\leq 120/80$ mmHg. To achieve this goal, patients could be given additional antihypertensive drugs. The median follow up was 3.6 yr. The average BP was 139/80 mmHg with combination therapy and 142/83 mmHg with placebo (the difference was significant at $P < 0.002$). On follow-up, significantly fewer patients in the VeraTran group received additional antihypertensive treatment.

Microalbuminuria developed in 17 (5.7%) of 300 patients in the group that received verapamil SR plus trandolapril and in 30 (10%) of 300 patients in the placebo group. The onset of microalbuminuria was significantly delayed by a factor of 2.6 ($P = 0.02$). The relative reduction of risk for progression from normo- to microalbuminuria with verapamil SR plus trandolapril was 61%. The difference between the groups remained significant also after adjustment for follow-up systolic and diastolic BP. Hence, the results exceeded expectations that were based on BP changes alone. The effect of the two experimental drugs used alone also was analyzed. Microalbuminuria developed in 18 (6.0%) of 301 patients who were taking trandolapril alone and in 36 (11.9%) of 303 patients who were taking verapamil. Hence, as compared with placebo, trandolapril delayed the onset of microalbuminuria by a factor of 2.1 ($P = 0.01$) and decreased the risk for microalbuminuria by 53% ($P = 0.01$), whereas verapamil had no significant effects. Comparisons of patients who received an ACE inhibitor *versus* those who did not showed significant differences between groups in favor of the ACE inhibitor ($P < 0.0001$). Microalbuminuria developed in 35 (5.8%) of the 601 patients who received ACE inhibitor therapy and in 66 (10.9%) of the 603 who did not. Comparisons of patients who received an ndCCB *versus* those who did not yielded no significant results. Three patients in the placebo group, one in the trandolapril group, and one in the verapamil group had a fatal CV event. No fatal CV events were reported in patients who received VeraTran. These data confirm that, provided intensified metabolic and BP control is pursued, patients with diabetes and normal urinary albumin excretion do not have a substantial excess CV risk as compared with patients without diabetes.

The BENEDICT study showed that DN can be prevented by early intervention. The renoprotective effect of ACE inhibition did not seem to be enhanced by the addition of an ndCCB. These findings suggest that in hypertensive patients with type 2 diabetes and normal renal function, an ACE inhibitor may be the medication of choice for controlling BP. The apparent advantage of ACE inhibitors over other agents includes a protective effect on the kidney against the development of microalbu-

minuria, which is a major risk factor for CV events and death in this population. Nephrologists and diabetologists now have a new goal: To prevent patients who have diabetes from progressing to nephropathy, the final aim being to limit CV events.

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