

A Controlled Clinical Trial of Angiotensin-Converting Enzyme Inhibition in Type I Diabetic Nephropathy: Study Design and Patient Characteristics

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ABSTRACT

A placebo-controlled, double-blind clinical trial has been initiated to determine whether angiotensin-converting enzyme inhibitor (ACEI) therapy with captopril (25 mg three times daily) slows the progressive loss of renal function in patients with type 1 diabetes mellitus. Entry criteria include: (1) ages 18 to 50 yr; (2) onset of insulin-dependent diabetes before the age of 30 yr, insulin dependent for at least 7 yr; (3) 24-h urine protein excretion >500 mg, plus: (a) diabetic retinopathy or (b) if no retinopathy, a renal biopsy diagnosis of diabetic nephropathy; (4) serum

creatinine (SCr) <2.5 mg/dL; (5) informed consent. Patients follow strict medical management protocols. Systemic blood pressure is controlled to pre-defined goals (<140-90 mm Hg). The primary outcome of the Study is a doubling of the patients' entry SCr to at least 2 mg/dL confirmed by a >50% decrease in GFR by radioactive iothalamate clearance technique. Baseline characteristics of the cohort at entry into the Study are (mean \pm SD): male/female, 52%/48%; age, 35 \pm 8 yr; duration of diabetes, 21 \pm 7 yr; duration of proteinuria, 2.8 \pm 3.3 yr; duration of retinopathy, 4.5 \pm 4.1 yr; 50% of cohort presented with hypertension, duration, 4 \pm 4.7 yr; blood pressure, 139/86 \pm 19/12; SCr, 1.35 \pm 0.44 mg/dL; GFR 78 \pm 32 mL/min; BUN, 24 \pm 11 mg/dL; proteinuria, 3.1 \pm 3.3 g/day; cholesterol, 236 \pm 50 mg/dL; total glycosylated hemoglobin, 11.1 \pm 2.1%. Analysis of baseline data with entry GFR yielded the following univariate linear associations: GFR had a weak but significant inverse correlation with urine protein/creatinine ratio ($r^2 = 0.19$), entry systolic blood pressure (-0.62 mL/min/1.73 m²/mm Hg; $r^2 = 0.13$), age at entry (-1.2 mL/min/yr; $r^2 = 0.07$), and serum cholesterol ($r^2 = 0.09$). GFR was not correlated with duration of diabetes ($r^2 = 0.006$), percentage of life as a diabetic ($r^2 = 0.02$), or blood glycohemoglobin ($r^2 = 0.007$). The elements of a controlled clinical trial are described. The baseline entry data confirm an association between reduced GFR and increasing hypertension, proteinuria, and cholesterolemia but not duration of diabetes, percentage of life as a diabetic, or severity of hyperglycemia.

Key Words: Diabetes mellitus, diabetic nephropathy, angiotensin-converting enzyme inhibition, captopril

The pathogenesis of both incipient and progressive nephropathy in diabetes mellitus involves several variables, including systemic hypertension, which has been shown to be a significant factor in determining overall morbidity and mortality. In 1976, Mogensen (1) reported the effect of blood pressure control on reducing the rate of loss or renal function. Studies by Parving *et al.* (2) and Christleib *et al.* (3) offered further evidence of the ameliorating effect of

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antihypertensive therapy with respect to the progressive loss of renal function in diabetic nephropathy. It has also been suggested that glomerular damage in diabetes mellitus may be the result of altered glomerular hemodynamics similar to that which has been demonstrated in the experimental model of ablation nephropathy and in the early stages of experimental diabetes (4,5). It has been further implied that the ability of angiotensin-converting enzyme inhibitors (ACEI) to dilate the efferent arteriole, effectively lowering intraglomerular blood pressure, may provide superior protection from intraglomerular hypertension. Studies done in animals have shown ACEI to be effective in preventing glomerular damage in the ablation model (6,7) and significantly more effective than triple antihypertensive therapy in preventing glomerular damage in streptozotocin-induced diabetic rats (8).

We report on the design and baseline characteristics of a multicenter, double-masked prospective clinical trial to investigate the ability of ACE inhibition therapy (captopril) to alter the progression of loss of renal function in the overt proteinuric stage of type I diabetic nephropathy. The design of this trial takes into account specific protocols that are required for the standardization of care of the population being investigated. However, in many respects, we present this protocol as a paradigm for future trials to be conducted in the diabetic nephropathy population. The principles of organization of clinical trials in general have been detailed by others (9).

METHODS

Collaborative Study Group Structure

The Collaborative Study Group consists of 27 collaborating clinics, a Clinical Coordinating Center (CCC), and a Biostatistical Coordinating Center (BCC). The CCC oversees the proper execution of the study protocol and provides central laboratory analysis of specific parameters critical to study outcomes. The BCC is responsible for data management and analysis as well as for the statistical design of the study. An Executive Committee is made up of selected collaborating investigators and oversees the design of the study and the execution of study protocol. A Clinical Review Committee (CRC) consisting of selected collaborating investigators monitors adherence to the study protocol and reviews the medical management of all patients. The CRC provides classification of study outcomes and stop points.

A National Institute of Health-appointed Advisory Board/Patient Safety Monitoring Committee has a membership of experts not associated with any of the collaborating clinics. This Committee monitors the results of the study in an unblinded fashion with respect to risks and benefits to the patients. Interim

statistical analyses are reviewed every 3 months in order for the Committee to advise continuation or early stopping of the study on the basis of current results.

Sample Size

On the basis of published data describing the proportion of type I diabetic patients who progress to renal failure (10–16), the collaborating clinical investigators estimated that 50% of patients with established proteinuria (>500 mg/24 h) would lose 50% of their baseline GFR over a 2-yr duration. Arbitrarily, a one-third reduction in hazard rate for patients treated with ACEI compared with placebo was chosen to be clinically significant. An estimated study sample size of 400 was derived from these assumptions to provide a power of 0.88. The collaborating investigators felt that the 400 patients could be recruited within 2 yr, yielding a minimal follow-up of 2 yr to a maximal follow-up of 4 yr. The mean follow-up of the 400 patients will be 3 yr.

Study Goals

The primary goals of the study are to determine whether patients with glomerulopathy due to type I diabetes mellitus respond to ACEI therapy with a significantly decreased (1) rate of loss of GFR, defined by the primary outcome of doubling of the baseline serum creatinine to at least 2 mg/dL; (2) urine protein excretion rate; and (3) end-stage renal failure rate and mortality rate. A secondary goal is to study the "natural history" of type I diabetic nephrotic patients managed with ACEI therapy versus those who are managed with blood pressure control.

Patient Population

The study protocol and patient consent form were reviewed and approved by each individual clinic's Institutional Review Board for Human Investigation. All patients entered into the study had signed informed consent and fulfilled the entry (Table 1) and exclusion (Table 2) criteria before randomization into the study.

Patient Visit Schedule

Patients entered a prerandomization period extending up to 4 wk. During this period, a baseline history and physical were performed to document eligibility. Baseline renal function was documented by the obtaining of two serum specimens 1 to 4 wk apart for creatinine agreeing to within 0.3 mg/dL. Estimation of GFR by iothalamate clearance technique was performed before randomization. After randomization, routine follow-up visits were scheduled at 2 wk, 4

TABLE 1. Eligibility Criteria

Ages 18 to 49 yr
 Onset of Type I (Insulin-Dependent) Diabetes Mellitus Before the Age of 30 yr and at Least 7 yr of Insulin Therapy
 Proteinuria Greater Than or Equal to 500 mg/24 h
plus
 Diabetic retinopathy^a
 or
 If no diabetic retinopathy, a renal biopsy diagnosis of diabetic nephropathy, confirmed by the CCC Renal Pathologist
 Serum Creatinine Less Than 2.5 mg/dL

^a Diabetic retinopathy includes any current or previously documented microaneurysm, hemorrhages, or exudates by standard ophthalmologic examination or demonstration by fluorescent angiography or stereoscopic retinal photographs that diabetic microvascular lesions exist.

TABLE 2. Exclusion Criteria

The following patients are excluded from the randomized study:

1. Women currently pregnant or lactating or women of childbearing potential planning or intending pregnancy during the study period
2. Patients who have documented an absolute need for calcium channel blocking agents or ACEI for the control of systemic hypertension
3. Patients with previously documented adverse side effects to captopril, including hypersensitivity reactions
4. Patients with a serum potassium level ≥ 6.0 mEq/L
5. Patients with a grossly unacceptable diet on the basis of a diet evaluation by the clinic director. If the diet is unacceptable, the patient should be instructed on an appropriate diet and the prerandomization visits should be rescheduled after a 3-month period
6. Patients with a white blood cell count of $< 2,500/\text{mm}^3$
7. Patients with bilateral renal artery stenosis (previously documented)
8. Patients whose state of mental or physical competence will not allow them to complete the study
9. Patients with systemic lupus erythematosus, scleroderma, or connective tissue disease
10. Patients with significant dermatologic disease
11. Patients with congestive heart failure (AHA Class III or worse)
12. Patients with significant gastrointestinal disease that would impair absorption of medication
13. Concomitant use of any investigational drug within 30 days before the first prerandomization visit or during study

wk, 3 months, and at 3-month intervals thereafter for a minimum of 2 yr or until the proposed end of the Study. Routine follow-up visits consisted of a detailed history of the patients' health since the previous visit, physical examination, and laboratory including a complete chemistry profile, complete blood

count, and 24-h urine collection. Interim visits for blood pressure management or other medical care were scheduled as required.

Medical Management Protocols

Insulin therapy and diet are managed by the patients' diabetologist or the participating investigator according to the current recommendations of the American Diabetes Association. However, dietary protein restriction may not be less than 0.8 g/kg/day. Total glycohemoglobin is determined semiannually by the Central Laboratory (CL) to assure comparable control of diabetes in the two treatment groups. Twenty-four-hour urine specimens collected quarterly are analyzed in the CL for total protein, creatinine clearance, urea nitrogen, and phosphorus. The CL monitors renal function by serum creatinine determinations obtained quarterly and annual estimation of GFR by iothalamate clearance technique.

Patients are randomized onto coded medication of either (1) the treatment group receiving captopril (25 mg three times daily) or (2) the placebo control group receiving placebo (25 mg three times daily), regardless of their blood pressure. Because systemic hypertension independently affects the progression of diabetic nephropathy, specific blood pressure control goals are defined before randomization to assure equivalent blood pressure control for both the treatment group and the placebo control group over the course of the study.

The seated office blood pressure measured by standard methods in the clinic during the baseline physical determines the patients' blood pressure control goal for the remainder of the Study. The blood pressure control goals for the study are:

1. Seated office diastolic blood pressure < 90 mm Hg
2. Seated office systolic blood pressure:
 - a. if baseline blood pressure is 140 to 149 mm Hg, decrease to < 140
 - b. if baseline blood pressure is 150 to 169 mm Hg, decrease at least 10 mm Hg
 - c. if baseline blood pressure is > 170 mm Hg, decrease to < 160

The recommended management of hypertension involved a stepped-care approach in order to maintain each patient within his or her specified blood pressure control goal. Investigators were not limited with respect to the pharmacologic approach to anti-hypertensive therapy except with regard to the strict avoidance of calcium channel blocking agents and ACEI.

If a patient's blood pressure control goal could not be attained with maximal therapy or if there was felt to be an absolute need for a calcium channel blocker,

then the patient was defined as having reached a "failure to control blood pressure" stop point.

Significant Clinical Events/Stop Points

Clinical complications requiring the permanent discontinuation of the coded medication and no further adherence to treatment protocols are defined as stop points. Patients reaching stop points continue to be monitored off of the coded medication until the end of the study follow-up period. The investigators and the patients remain blinded to the coded medication unless there is a life-threatening situation that requires knowledge of into which group the patient was randomized.

The specific protocols that follow were designed to detail the medical management of clinical complications that ultimately either return the patient to standard protocol (if the condition improves or resolves) or lead to a predefined stop point.

Doubling of Baseline Creatinine

The primary study end point is defined as a doubling of the baseline serum creatinine to at least 2 mg/dL. The Investigator should take any measures necessary to correct possible conditions that might increase serum creatinine for reasons other than the progression of diabetic hypertension. If all other possible reasons are ruled out and if the serum creatinine is confirmed in the CL on two serum specimens to be double the baseline and at least 2 mg/dL, then the stop point is declared, the coded medication is discontinued, and an exit GFR is performed to confirm a 50% loss of renal function.

Early Creatinine Rise

This phenomenon is defined in case of the rare patient who may enter the study with undocumented bilateral renal artery stenosis and may experience an adverse glomerular hemodynamic event from the use of an ACEI. If a patient's serum creatinine increases more than 50% during the first 4 wk of the study, the investigator should take corrective measures for the possible causes of the increased serum creatinine such as:

1. medications that alter serum creatinine
2. plasma volume depletion
3. infected urine
4. obstructed uropathy
5. decreased cardiac output

If corrective measures are implemented and the serum creatinine remains 50% higher than at baseline, the stop point is declared, the coded medication is stopped, and the patient must be considered for a diagnostic work-up of renal artery stenosis.

Adverse Drug Side Effects

The following protocols were developed in the event that patients might experience adverse side effects from the drug regimen defined by the study protocol.

Captopril-specific side effects such as skin rash, dysgeusia, or cough of more than mild severity are treated by the discontinuation of the coded medication for a 2-wk period. If upon reinstatement of the coded medication the patient again experiences the adverse-side effect of more than mild severity, a stop point is declared and the coded medication is discontinued permanently.

Neutropenia, defined as a neutrophil count of $<2,000/\text{mm}^3$, requires immediate discontinuation of the coded medication and a confirming visit within 24 h. If the neutrophil count is confirmed to be $<2,000/\text{mm}^3$, a stop point is declared.

Nonspecific side effects such as dizziness, postural hypotension, or fatigue of more than mild severity are treated by first adjusting any noncoded medications such as diuretics, beta blockers, or central or peripheral adrenergic antagonists. If the adverse side effect persists and the noncoded medications cannot be further adjusted, the coded medication is discontinued for 2 wk. If upon reinstatement of the coded medication, the patient again develops the adverse side effect of more than mild severity, a stop point is declared and the coded medication is discontinued permanently.

Hyperkalemia

A serum potassium level of 6 mEq/L or more necessitates investigation into the immediate cause, including a review of the dietary intake of potassium, volume depletion, and possible potassium-sparing medications (potassium-sparing diuretics are to be avoided).

If the potassium remains 6 mEq/L or more despite any possible corrective measures, a stop point is declared. The coded medication is stopped, the hyperkalemia is treated, and the patient should be worked up for hyporeninemic hypoaldosteronism, which is reported to be relatively common in this patient population.

Failure To Control Blood Pressure

See above.

RESULTS AND DISCUSSION

Baseline Characteristics

The baseline characteristics of the 409 randomized patients are presented in Tables 3 through 5. The average patient entering the trial was 35 yr old and had diabetes for 22 yr. At entry into the study, they

have had retinopathy for 5 yr and developed proteinuria about 2 yr after the onset of retinopathy. A significant proportion of the patients had nephrotic-range proteinuria (mean, 2.9 ± 3 gm/dL) and were beginning to develop signs of progressive renal damage, with a mean serum creatinine of 1.25 mg/dL and GFR of 78 mL/min/1.73² m. Diabetes was only moderately well controlled in this patient population.

TABLE 3. Baseline characteristic—Clinical

Baseline Characteristics	Mean	±SD
Clinical		
Sex (No. of men)	209	52%
Age at Entry (yr)	34.5	±7.6
Duration of Diabetes (yr)	21.5	±6.7
Age at Onset (yr)	13.1	±7.3
Duration of Retinopathy (yr)	4.7	±4.1
Duration of Renal Disease (yr)	2.9	±3.3
History of Neuropathy (N)	193	48%
Duration of Neuropathy (yr)	4.7	±3.7
History of Hypertension (N)	233	59%
Duration of Hypertension (yr)	4.0	±4.9

TABLE 4. Baseline characteristics—laboratory

Baseline Characteristics	Mean	±SD
Laboratory		
24-h Urine Protein (g/24 h)	2.81	±2.58
Serum Creatinine (mg/dL)	1.25	±0.42
Iothalamate GFR (mL/min/1.73 m ²)	77.5	±32.4
24-h Creatinine Clearance (mL/min)	82.1	±40.0
Glycosylated Hemoglobin (%)	11.7	±2.83
Serum Cholesterol (mg/dL)	234	±59.7
Urine urea N ₂ (g/24 h)	11.0	±4.95

TABLE 5. Baseline characteristics—hypertension

Baseline Characteristics	Frequency	% of Cohort
Hypertension		
Positive History of Hypertension	233	59
Baseline Seated Blood Pressure >140/90	194	49
Receiving Antihypertensive Therapy	227	57
Group I: diuretics, ACEI, or calcium channel blocker	132	58
Group II: beta, central, or peripheral adrenergic antagonists ± Group I drugs	88	39
Other: hydralazine, minoxidil ± Group I and/or Group II	7	3

Total glycosylated hemoglobin measured by the cis-diol affinity chromatography method (Isolab Inc, Friend's Wood, TX) was $11.7 \pm 2.8\%$ (nondiabetic normal range, 4 to 8%). Dietary history revealed an average intake of 1,900 calories per day consisting of 47% carbohydrate, 33% fat, and 20% protein. Total urine urea nitrogen excretion was 11 g/day, equating to an average estimated dietary protein intake of 1 g of protein/kg body wt/day.

Analysis of the baseline data was performed to determine whether any single characteristic recorded at baseline predicted the level of kidney function defined by the baseline iothalamate GFR. A simple linear regression model of baseline GFR versus each of the 84 baseline characteristics was prepared, in-

TABLE 6. Univariate Linear Associations with Baseline GFR^a

	Slope	R ²
Serum Creatinine (mg/dl)	-55.9	0.51
SUN (mg/dl)	-1.74	0.34
CBC Hemoglobin (g/dL)	+8.4	0.25
RBC count	+22.8	0.20
Total Protein/Total (g)	-5.9	0.19
CBC Hematocri (1%)	+2.2	0.18
Serum Uric Acid (mg/dL)	-8.66	0.16
Antihypertensive Agents Past 2 months (1 = yes)	-24.9	0.14
Seated BP—Systolic (mm Hg)	-0.62	0.13
24-h Urine, Total Protein (g)	-4.3	0.12
Serum Cholesterol (mg/dL)	-0.16	0.09
History of Systemic Hypertension (1 = yes)	-19.9	0.09
Age at Entry (yr)	-1.2	0.07
% of Life as Diabetic	+0.24	0.02
Glycohemoglobin (%)	0.98	0.007
Duration of Diabetes (yr)	-0.36	0.006

^a CBC, complete blood count; BP, blood pressure.

^b Slope, change in GFR (mL/min/1.73 m²) for each unit increase in the variable tested.

TABLE 7. Iothalamate Clearance: Mean \pm SD (mL/min/1.73 m²)^a

	Documented Past History of Hypertension	
	BP < 140/90	BP > 140/90
No Antihypertensive Therapy	98.6 \pm 30.2 (15)	90.0 \pm 27.1 (20)
Group I BP Therapy	80.9 \pm 41.8 (41)	65.5 \pm 30.7 (58)
Group II BP Therapy	63.4 \pm 27.3 (22)	55.9 \pm 24.6 (64)
Other BP Therapy	59.1 \pm 15.0 (2)	35.5 \pm 7.8 (3)

^aBP, blood pressure. Group I, diuretics, ACEI, or calcium channel blocker; Group II, beta, central, or peripheral adrenergic antagonists \pm Level I drugs; Other, hydralazine, minoxidil, \pm Group I and/or Group II.

cluding an estimate of the regression line (intercept and slope) and variability around the estimated regression line. The coefficient of determination (R²) indicates the percentage of GFR variability explained by a single predictor.

The results of the univariate linear regression analysis for association with level of GFR are presented in Table 6.

Although the results of the associations of declining GFR with increased serum creatinine, BUN, urinary protein/creatinine ratio, and cholesterol, as well as decreased hemoglobin, red blood cells, and hematocrit were easily predicted by clinical experience, the association of hypertension was very interesting and warranted further analysis. Table 7 presents the level of GFR (in milliliters per minute per 1.73 square meters) with the level of antihypertensive therapy for 225 hypertensive patients whose blood pressure was either above or below the American Heart Association (AHA) cut-off for a normal blood pressure of 140/90 mm Hg at the baseline visit. The level of antihypertensive therapy was categorized into three groups according to loosely followed regimens of progressively more potent medications. Table 7 demonstrates that the requirement for antihypertensive therapy correlates with the decrease in GFR. Table 8 confirms this observation in the remaining 158 patients defined at entry into the study either by the patient or the referring physician as having no history of hypertension.

It is interesting to note in Table 6 the lack of association between the level of GFR and several parameters. Age at entry into the study, percentage of life as a diabetic, duration of diabetes, as well as total glycosylated hemoglobin level measured by affinity chromatography, had little or no association with the level of GFR at entry into the study.

The Study of ACE Inhibition in Type I Diabetic Nephropathy is scheduled for completion December 31, 1992. Its design and implementation are based on a minimum follow-up period of 2 yr. The ongoing review of data derived from this study supports the initial assumptions regarding the required sample size. Our interim analysis of stop points, patients lost

TABLE 8. Iothalamate Clearance: Mean \pm SD (mL/min/1.73 m²)^a

	No History of Hypertension	
	BP < 140/90	BP > 140/90
No Therapy	93.8 \pm 26.1 (94)	84.1 \pm 25.7 (35)
Group I or Group II BP Therapy	84.8 \pm 27.7 (21)	70.1 \pm 36.8 (8)

^aBP, blood pressure.

^bNo history of hypertension defined by patient or referring physician.

to follow-up, and drop-outs indicates that we will be able to attain the objectives set out in our study goals. These are scheduled to be reported after the data close-out is completed in January 1993. Although the primary goals of this study relate to the ability of a pharmacologic agent to prevent progressive renal dysfunction, it must be pointed out that morbidity and mortality within the population with diabetic nephropathy are also dependent upon factors that affect vascular pathology. The course of coronary artery disease plays a particularly important role in this group (17–19). Our study was not designed to compare therapeutic agents in this respect; however, our experience with 409 patients may add significantly to the understanding of the risk factors that correlate with clinical cardiovascular events in this population. We hope that our experience will stimulate succeeding trials in order to optimize the life expectancy for these patients.

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