

*Original Article***The Irbesartan Type II Diabetic Nephropathy Trial: study design and baseline patient characteristics**

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Abstract

Background. Diabetic nephropathy is the most common cause of end-stage renal disease in the developed world. Angiotensin-converting enzyme inhibitors have been demonstrated to be renoprotective in type I diabetes and are now the standard of care for both hypertensive and non-hypertensive type I diabetic patients with any level of proteinuria. The role of blockade of the renin-angiotensin system in type II diabetic patients is not defined. The Collaborative Study Group has initiated the Irbesartan Type II Diabetic Nephropathy Trial (IDNT), studying the effect of the angiotensin II receptor antagonist irbesartan on progression of renal disease and mortality in type II diabetic patients with overt nephropathy and hypertension. Here we report the study design and baseline patient characteristics.

Methods. To qualify, hypertensive type II patients, age 30–70 years, must have a 24 h urinary protein excretion of >900 mg and a serum creatinine 90–265 $\mu\text{mol/l}$ (1.0–3.0 mg/dl) in women and 110–265 $\mu\text{mol/l}$ (1.2–3.0 mg/dl) in men. Three treatment arms include irbesartan, placebo and amlodipine, with every attempt made to achieve similar blood pressure levels in all treatment arms. A total of 1650 patients will be enrolled utilizing ~225 clinics worldwide. The primary outcome measure is time to event to the composite end-point of doubling of serum creatinine, end-stage renal disease or death. The secondary outcome measure is time to composite end-point of fatal or non-fatal cardiovascular events. The average length of patient follow-up is expected to be ~36 months.

Results. The baseline characteristics of the study subjects are: age 59 ± 8 years, duration of diabetes 15 ± 9 years, height 168 ± 11 cm (5 ft 6 in), weight 87 ± 19 kg (192 lb), body mass index 31 ± 7 kg/m², blood pressure

156 ± 18 mmHg/ 85 ± 11 mmHg, serum creatinine 150 ± 53 $\mu\text{mol/l}$ (1.7 ± 0.6 mg/dl), creatinine clearance 66 ± 34 ml/min and 24 h urine protein 4.0 ± 3.5 g/day.

Keywords: angiotensin II receptor antagonist; diabetic nephropathy; renoprotection; type II diabetes

Introduction

Diabetic nephropathy is the most common end-stage renal disease (ESRD) diagnosis in most of the developed world, and is responsible for 43% of all new patients requiring renal replacement therapy in the USA [1]. The incidence rate of diabetic ESRD is increasing by 10% a year [1]. This near epidemic growth occurs despite recent advances in the understanding of the roles that glycaemic, blood pressure and dietary control, and angiotensin-converting enzyme inhibitors (ACEIs) play in the development and progression of this disorder [2]. The majority of research to date has focused on type I diabetes, despite the fact that the majority of patients with diabetes and ESRD have type II diabetes [3].

ACEIs play a unique role because of the 'renoprotection' that they afford: the property of slowing progression of renal disease independently of their effect on blood pressure [4–8]. They are now considered the standard of care for type I patients with both incipient (microalbuminuria) and overt nephropathy. Their role in patients with type II diabetes and nephropathy is undefined [9]. The present trial is being undertaken predominantly in order to evaluate in a high risk hypertensive population whether blockade of the renin-angiotensin system with the angiotensin II receptor antagonist (AIIRA) irbesartan affords similar renoprotection in patients who manifest overt diabetic nephropathy as a result of type II diabetes mellitus. This morbidity and mortality trial will also examine all-

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cause mortality as part of a composite primary end-point. Irbesartan's effects on these end-points will be compared with two other treatment arms: a placebo control group and a group receiving the calcium channel blocker (CCB) amlodipine as the primary antihypertensive agent. Every effort will be made to attain equivalence of blood pressure control in the three arms of the trial by utilizing other antihypertensive agents as needed (with the exclusion of ACEIs, AIIRAs or CCBs). The inclusion of the calcium channel blocker arm may help to determine specificity of any renoprotection afforded by any of these regimens. Herein we report the basic study protocol as well as a number of baseline characteristics of the study population.

Subjects and methods

Collaborative Study Group structure

The Collaborative Study Group (CSG, see Appendix for complete list of structure and members) consists of ~208 collaborating clinics, three Clinical Coordinating Centres (CCCs) and a Biostatistical Coordinating Centre (BCC). The CCCs oversee the proper execution of the study protocol and the CCC in the USA provides central laboratory analysis of specific parameters critical to study outcomes. The BCC is responsible for data analysis as well as the statistical design of the trial. The BCC also prepares the safety and efficacy reports for the Data and Safety Monitoring Committee (DSMC) which includes experts in the fields of nephrology, diabetes, statistics and ethics who are not associated with any of the collaborating clinics.

An Executive Committee is made up of a rotating membership of selected collaborating investigators and oversees the design of the trial 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. An Outcome Confirmation and Classification Committee (OCCC) consisting of selected collaborating investigators provides classification of study outcomes and stop points. The DSMC together with the principal investigators from the USA CCC and BCC monitors the results of the trial in an unblinded fashion with respect to risks and benefits to the patients. Interim statistical analyses are reviewed at least yearly in order for the committee to advise continuation or early stopping of the trial on the basis of current results.

Study design

This trial is an international, prospective, randomized, double-blind, placebo-controlled trial in hypertensive patients with diabetic nephropathy due to type II diabetes mellitus. Patients will be randomized into one of three arms: (i) angiotensin II receptor antagonist; (ii) calcium channel blocker; and (iii) placebo control, with each group receiving additional antihypertensive agents (with the exclusion of ACEIs, AIIRA or CCB) to achieve equivalent blood pressure values in each of the three groups. The study protocol and patient consent form are reviewed and approved by each individual clinic's Institutional Review Board for Human Investigation. All patients entered into the trial signed an informed consent and were eligible based on the eligibility and exclusion criteria prior to randomization (Table 1).

Enrolment of 1650 patients will occur in ~225 active centres. Randomization began in March 1996 and was expected to end in March 1998. Due to a slow early enrolment rate, the DSMC decided to extend enrolment until December 1998 or until 1650 patients were randomized, whichever occurred first. The average length of patient follow-up is expected to be ~36 months.

Statistical considerations

Hypotheses and end-points. The primary and secondary hypotheses and end-points/outcome measures are presented in Table 2.

Sample size. The sample size estimate for this trial was determined to test the hypothesis that the time to reach the primary composite end-point in irbesartan-treated type II diabetic patients with hypertension and diabetic nephropathy will be greater than that for placebo-treated type II diabetic patients with hypertension and diabetic nephropathy. The projected rates of progression of renal failure and mortality were derived from reports in type II diabetics and the captopril trial in type I diabetics with diabetic nephropathy [5], utilizing suggestions that progression of renal disease in type II patients is similar to that observed in type I patients with diabetic nephropathy [3].

The sample size calculations were based on formulas discussed in Lachin and Foulkes [10]. For purposes of sample size calculations, the total duration of this trial was expected to be 4 years, with a 2 year enrolment period and a minimum 2 year follow-up after the last patient is enrolled for an average follow-up of 3 years. The projected 3 year cumulative total incidence rate of the composite end-point is 36% in the placebo group and consists of a 26% incidence of doubling of baseline serum creatinine, ESRD and non-cardiovascular death, and a 10% incidence of cardiovascular death.

The sample size calculations assume a uniform (constant) enrolment rate and that within both treatment groups, the distribution of the times until first occurrence of the composite end-point is exponential with a constant hazard (risk) rate. To ensure that a risk reduction of 26% can be detected with 0.90 power with a log rank test at the two-sided alpha level of 0.05, it would be necessary to randomize 520 patients per arm, allowing for a total of 316 events in the irbesartan and placebo treatment arms. To account for rescue therapy with an ACEI or an AIIRA for treatment of complications associated with non-fatal cardiac events, a total of 550 patients will be randomized to each group.

Patient population

This randomized, double-blind, placebo-controlled trial will be conducted worldwide. Qualifying men and women with type II diabetes mellitus, hypertension, proteinuria of ≥ 900 mg/24 h, and serum creatinine levels 90–265 $\mu\text{mol/l}$ (1.0–3.0 mg/dl) in women and 110–265 $\mu\text{mol/l}$ (1.2–3.0 mg/dl) in men will be randomized to one of three treatments: irbesartan, amlodipine or placebo. The efficacy analyses will be based on data from all randomized patients at all worldwide sites. All patients who receive at least one dose of study drug will be included in the safety analyses.

Baseline comparability

Demographic (age, gender, ethnicity, etc.), disease status and other baseline characteristics will be summarized by treatment group and for all randomized patients. χ^2 (qualitative

Table 1. Inclusion and exclusion criteria

I. Inclusion criteria
A. Age 30–70; (<30 in patients with biopsy-proven diabetic nephropathy)
B. Clinical history of type II diabetes
1. Hyperglycaemia not requiring insulin
2. Hyperglycaemia requiring insulin with either
a. the period between diagnosis and insulin usage >1 year; or
b. elevated fasting or stimulated C-peptide level
C. Diabetic nephropathy
1. 24-h urine protein excretion \geq 900 mg
2. Serum creatinine between 90 and 265 μ mol/l (1.0–3.0 mg/dl) in women and between 110 and 265 μ mol/l (1.2–3.0 mg/dl) in men
D. Hypertension
1. Seated SBP >135 mmHg and/or seated DBP >85 mmHg untreated; or
2. Receiving antihypertensive medication
II. Exclusion criteria
A. Age of onset of type II diabetes <20 years
B. Type I diabetes
C. Absolute requirement for an ACEI, AIIRA or CCB
D. Cardiovascular disease
1. Unstable angina, myocardial infarction, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty within 3 months of study entry
2. New York Heart Association class III or IV heart failure
3. Transient ischaemic attack within 6 months of study entry
4. Stroke within 3 months of study entry
E. Serum potassium outside of normal range

Table 2. Primary and secondary hypotheses and end-points/outcome measures

I. Primary outcome is time to a composite end-point of
A. doubling of baseline serum creatinine
B. end-stage renal disease (renal transplantation, need for permanent dialysis or a serum creatinine \geq 530 μ mol/l (6.0 mg/dl), or
C. death (all-cause mortality)
II. Secondary outcome is time to a composite end-point of fatal or non-fatal cardiovascular events
A. cardiovascular death
B. non-fatal myocardial infarction
C. hospitalization for heart failure
D. stroke
E. above-the-ankle amputation, or
F. revascularization (cardiac, carotid, peripheral vascular)

data) or analysis of variance (quantitative data) will be used to compare the treatment groups. Any imbalances among the treatment groups for variables which are strongly suspected of having a bearing on progression of renal disease or mortality (e.g. age, ethnicity, lipids) will be investigated to assess their effects on the efficacy comparison.

Efficacy analysis

The primary analysis will be intention to treat. The primary comparison will be between irbesartan and placebo. The time-dependent outcome measures include the primary composite end-point of doubling of baseline serum creatinine, ESRD or all-cause mortality, each of the individual components of the primary end-point, the combination of ESRD or all-cause mortality, the combination of ESRD or doubling of serum creatinine and the secondary and tertiary composite end-points of fatal or non-fatal cardiovascular events. All time-dependent outcome measures will be summarized by using the Kaplan–Meier [11] procedure to estimate a survival curve for each treatment group. For the primary and second-

ary end-points including the composite cardiovascular end-points, hypotheses concerning the treatment groups will be tested with the log rank test at the 0.05 level of significance. Additionally, for these time-dependent outcome measures, treatment effects will be modelled using the Cox [12] proportional hazards model.

The influence of baseline prognostic factors upon the estimates of treatment effects (hazard ratios) with regard to the primary composite end-point of doubling of baseline serum creatinine, ESRD and mortality and other time-dependent outcome measures will be examined. These analyses will be performed with a Cox regression model with covariate terms for treatment and the baseline prognostic factor as well as a term(s) for the second order interactions involving treatment. Additionally, prognostic factors will be chosen based upon evidence of any imbalances that may exist between the treatment groups. If, for example, irbesartan achieves a clinically significant reduction compared with placebo in blood pressure, then the relevant variables will be added to the Cox regression model as time-dependent covariates to examine the potential confounding upon the mortality/morbidity results.

Study plan

The trial consists of screening, enrolment, titration and maintenance periods.

Screening period. Patients will be screened for inclusion and exclusion criteria. Serum creatinine and 24 h urine for protein and creatinine clearance are obtained. A ‘baseline’ seated systolic and diastolic blood pressure is determined from which a patient’s blood pressure control ‘goal’ is determined (see ‘Titration period’). ACEIs and AIIRAs must be discontinued for at least 10 days prior to collection of the first 24 h urine.

Enrolment period. A second serum creatinine is obtained; the difference between the screening and enrolment period serum creatinines must not be greater than 25% to ensure stable renal function, in order for the patient to qualify for ran-

domization. If calcium channel blockers were continued during the screening and enrolment periods, they must be stopped prior to randomization.

Titration period. Patients are randomized 1:1:1 to regimens of irbesartan, amlodipine or placebo. The overall goal is to maximize the dose of coded study drug and to minimize the use of other antihypertensive agents. To allow for titration to the highest tolerated dose of coded study drug, discontinuation of other antihypertensive medications may be required between randomization and week 4. The doses of study drug administered initially are irbesartan 75 mg, amlodipine 2.5 mg or placebo once daily (Level I). At the end of week 2, the dose of study drug will be increased to irbesartan 150 mg, amlodipine 5 mg or placebo once daily in all patients as tolerated (Level II regimen) and further increased to irbesartan 300 mg, amlodipine 10 mg or placebo at the end of week 4 in all patients as tolerated (Level III regimen).

The target blood pressure control goal for the majority of patients is a systolic blood pressure of <135 mmHg, and for all patients a diastolic blood pressure of <85 mmHg. (i) If the baseline seated systolic blood pressure (SeSBP) is >145 mmHg at the first screening visit, the target SeSBP goal is a decrease of at least 10 mmHg. (ii) The maximum allowable target SeSBP goal is 160 mmHg. All patients must return at the end of 8 weeks to confirm that target blood pressure goals have been reached.

Maintenance period. Patients will be seen every 3 months beginning at the end of month 3. Serum chemistries are obtained and blood pressure is taken. If at any scheduled visit the blood pressure is above a patient's goal, a change in medication is made and patients are seen within 7 days. This is repeated until the patient reaches blood pressure goal. Twenty-four hour urine collections for protein and creatinine clearance are obtained every 6 months. All randomized patients who discontinue the study drug for any reason other than death will be followed for the entire duration of the trial; patients who undergo renal transplantation or dialysis will be followed for vital status only. Information about hospitalization for any cause is collected at each visit.

Medical management protocols

Diabetes care. Metformin can only be used in accordance with FDA restrictions regarding renal insufficiency. Troglitazone usage is being discouraged for this trial. Dietary recommendations should be in keeping with those of the American Diabetes Association [13]. Maintenance of HbA1C levels below 11% is encouraged.

Hyperkalaemia. Subjects will have their serum potassium measured at all scheduled follow-up visits. Values >6.0 mEq/l require corrective measures and the possible discontinuation of study drug. Every attempt is made to keep patients on the highest dose (level) of study drug that avoids further episodes of hyperkalaemia. This may include the usage of loop diuretics, mineralocorticoids or potassium exchange resins.

Early rise in serum creatinine. Subjects will have their serum creatinine measured by the regional study laboratory at all scheduled follow-up visits. If during the first 8 weeks following randomization the serum creatinine rises by 50% and at least 88 $\mu\text{mol/l}$ (1.0 mg/dl), the subject is defined as having an early rise in serum creatinine event. The subject will be evaluated for (i) medications which alter serum creatinine, (ii) plasma volume depletion, (iii) infected urine, (iv) obstructive uropathy and (v) decreased cardiac output.

The clinic director should take corrective measures and, if

the serum creatinine is still elevated by 50% and at least 88 $\mu\text{mol/l}$ (1.0 mg/dl), the coded medication is stopped. If the serum creatinine decreases (to a value below the 50% and at least 88 $\mu\text{mol/l}$ (1.0 mg/dl) increase), the subject will be rechallenged with a lower dose (level) of coded medication. If after reinstating the coded medication, the serum creatinine again begins to rise, the investigator shall declare a stop point due to the subject being unable to tolerate the coded medication. Although off study drug, the subject would continue to be seen at regularly scheduled study visits.

Doubling of serum creatinine. The primary study end-point is defined as a doubling of the baseline serum creatinine, confirmed by the central laboratory. To verify that the doubling of the serum creatinine is due to the progression of diabetic nephropathy, the investigator must determine whether the subject is taking medications which alter serum creatinine or if any of the potentially reversible conditions listed in 'Early rise in serum creatinine' (above) are present. If any of these conditions are present, the investigator should take corrective measures and recheck the serum creatinine. If the subject's serum creatinine is still equal to or greater than twice the baseline value, the patient has reached a creatinine doubling stop point. The coded study medication is discontinued; however, the subject continues in the routine follow-up visit schedule until dialysis, transplantation, death or end of trial.

End-stage renal disease. ESRD is defined as the permanent need for dialysis (as deemed necessary by the investigator), renal transplantation or a serum creatinine $\geq 530 \mu\text{mol/l}$ (6.0 mg/dl) repeated and confirmed by the central laboratory. Patients reaching an ESRD stop point will have the coded medication discontinued and no further visits are required although vital status is monitored until the end of the trial.

Results

Baseline characteristics

The baseline patient characteristics ($n=1640$) are presented in Tables 3 and 4. The average patient is 59 years old and has been diabetic for 15 years. About one half of the patients have a history of neuropathy, and two-thirds a history of retinopathy. The study subjects are on average 168 cm (5 ft 6 in) tall, and weigh 87 kg (192 lb). The mean serum creatinine is 150 $\mu\text{mol/l}$ (1.7 mg/dl) and the 24 h urine protein excretion is 4.0 g/day. Almost three-quarters of the patients are white, reflecting almost one half of the study patients being recruited from clinics in Europe. The international breakdown of patient enrolment is provided in Figure 1.

Each of the baseline demographic, laboratory and physical examination characteristics were compared with the baseline creatinine clearance and the baseline 24 h urinary protein excretion using Spearman correlations for ordinal scale variables and Kendall Tau-B correlations for categorical variables. Those comparisons with a P -value <0.05 are presented in Table 5. Although there are a number of statistically significant associations, the r values in many of these comparisons are extremely low; the number of observations ($n=1640$) allowing even weak associations to be statistically significant. Although the correlations are all weak,

Table 3. Baseline characteristics—clinical

Baseline characteristic	%	Mean \pm SD
Sex (% male)	66.8	
Race		
White	73.3	
Black	13.7	
Hispanic	4.8	
Asian/Pacific Islander	3.8	
Other	4.4	
Smoking history		
Currently smokes	17.1	
Smoked in past	44.5	
Never smoked	38.4	
History of CHF	7.5	
History of coronary event	16.5	
History of stroke	11.6	
History of impotence (men)	51.2	
History of claudication	23.3	
Age at entry (years)		58.9 \pm 7.7
Duration of diabetes (years)		14.9 \pm 8.5
History of retinopathy	66.3	
Duration of retinopathy (years)		4.3 \pm 4.3
History of neuropathy	47.9	
Duration of neuropathy (years)		4.2 \pm 3.8
Height (cm)		167.8 \pm 10.6
Weight (kg)		87.2 \pm 19.1
Body Mass Index BMI (kg/m ²)		31.0 \pm 6.9
Seated systolic blood pressure		155.8 \pm 18.4
Seated diastolic blood pressure		85.4 \pm 10.7

Table 4. Baseline characteristics—laboratory

Baseline characteristic	Mean	\pm SD
Serum creatinine (μ mol/l)	150.3	53.0
	(1.7 mg/dl)	(0.6 mg/dl)
Creatinine clearance (ml/min)	66.1	33.8
24 h urine protein (mg/day)	4016	3502
Total cholesterol (mg/dl)	229	58
HbA1C (%)	8.1	1.7
Potassium (mEq/l)	4.6	0.5

each of the diabetic complications, e.g. retinopathy, gastropathy, etc., are all negatively correlated with creatinine clearance (the risk of a non-renal complication increases with decreases in creatinine clearance). This seems to indicate simply that one major complication (nephropathy) is associated with the development of other complications and may reflect overall severity of disease. The strongest correlations are those that are the easiest explained, e.g. serum albumin, total protein and lipid levels to 24 h urinary protein excretion.

Discussion

In 1993, the Collaborative Study Group's study of the effect of the ACEI, captopril, was reported in patients with type I diabetic nephropathy [5]. This was a study of the time to event of a doubling of serum creatinine

which occurred in 21% of patients receiving placebo plus standard antihypertensive therapy as opposed to 12% of patients receiving captopril. The risk reduction for this end-point was 51% ($P=0.004$). There was also a 51% risk reduction for the time to event analysis of the combined end-point of ESRD or death ($P=0.006$). The mean rate of increase in serum creatinine in the placebo group was $44 \pm 71 \mu\text{mol/l/year}$ ($0.5 \pm 0.8 \text{ mg/dl/year}$), compared with a mean increase of $18 \pm 71 \mu\text{mol/l/year}$ ($0.2 \pm 0.8 \text{ mg/dl/year}$) for the captopril group. These dramatic results implied that captopril was renoprotective in patients with type I diabetes. The natural question remained, however, whether these results could be applied to patients with type II diabetic nephropathy.

The pathogenesis of the glomerular lesion seems likely to be the same in patients with type I and type II diabetes. There are, however, pathological and clinical differences in these two distinct patient groups [3]. The type II population presently being studied is older (59 ± 8 years vs 34 ± 8 years) and more obese (body mass index (BMI) $31 \pm 7 \text{ kg/m}^2$ vs $25 \pm 4 \text{ kg/m}^2$) than the patients in the type I captopril trial. Their hypertension is worse ($156/85 \text{ mmHg}$ vs $138/85 \text{ mmHg}$) and they have significantly more established vascular disease, including generalized atherosclerosis, renal vascular disease, coronary artery disease and cerebrovascular disease. Known associations with type II diabetes include hyporeninaemia associated with hyperkalaemia and acute renal failure in the presence of renal artery disease. Thus, the risk of using an agent that inhibits the physiological role of angiotensin II should be higher in this population [3,9].

This trial is evaluating whether or not the AIIRA irbesartan is renoprotective in patients with type II diabetic nephropathy. Thus, compared with the 'captopril trial', we have changed two variables (ACEI to AIIRA and type I to type II diabetes). The basis for studying an AIIRA is well founded since they have renoprotective and proteinuria lowering properties similar to ACEIs in many models. There are reasons to believe that the renoprotection afforded by AIIRAs may be superior or inferior to that of ACEIs. ACEIs prevent the enzymatic breakdown of bradykinin, while AIIRAs have no effect on this vasodilatory hormone. The preservation of bradykinin and its effect on the efferent arteriole may be responsible for some of the salutary effects of angiotensin-converting enzyme inhibition, although the effect of bradykinin on renal haemodynamics appears to be species dependent [14–16]. Since renoprotection with ACEIs is the gold standard, we would have preferred to have a fourth treatment arm utilizing such an agent. This, however, would have required an increase in trial size from 1650 to 2100 patients in order to maintain the same study power; the patient recruitment and cost of which did not seem feasible.

A major factor in the success of any nephropathy trial rests in choosing a population of patients in whom renal disease is progressive so that the potential salutary effects of a treatment can be demonstrated. We felt

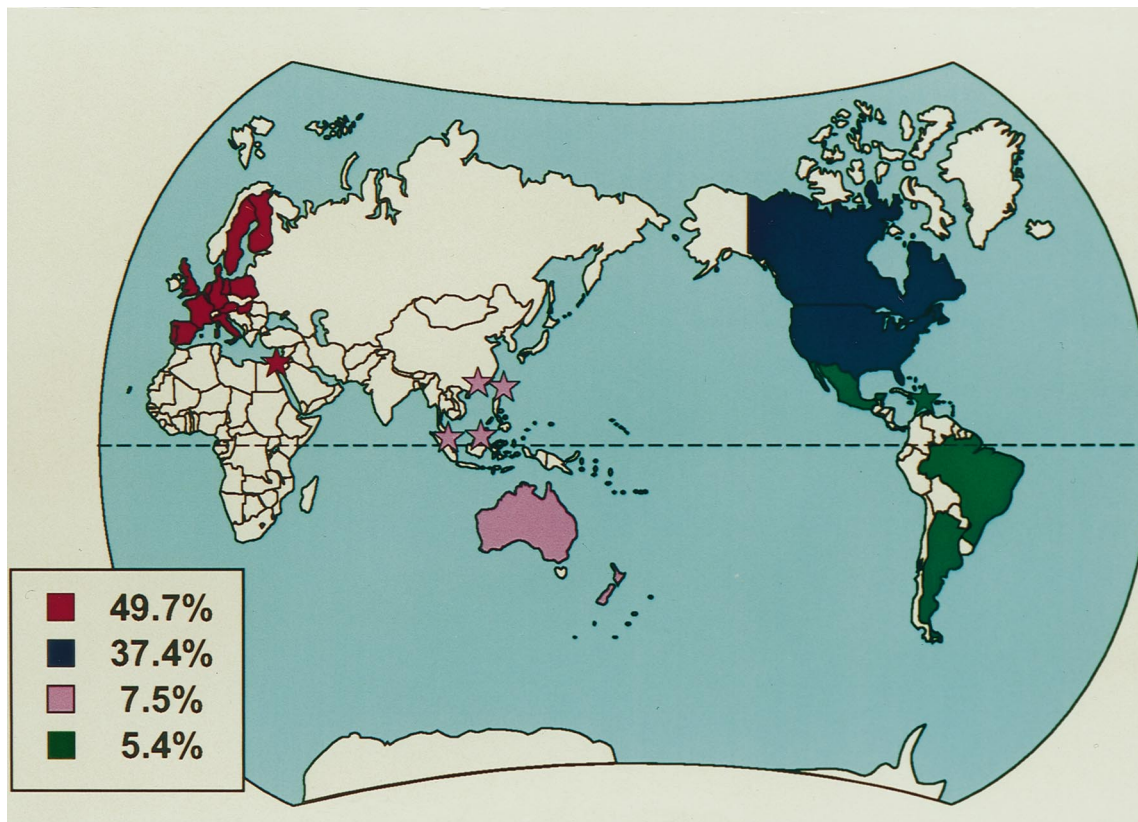


Fig. 1. World map demonstrating international breakdown by percentage of study population by four regions: red comprises Europe and Israel; blue comprises the USA and Canada; pink comprises Australia, New Zealand and South East Asia; and green comprises Latin America. See Appendix for complete listing of CSG clinics and members.

that this required inclusion criteria that selected patients that had already progressed to a degree, and therefore chose a minimum of 900 mg of daily urinary protein excretion and a serum creatinine that reflected early renal insufficiency. In fact, the average patient enrolled in this study is excreting 4 g of daily urinary protein and has lost half of their renal function. Thus, we feel that this represents a population of patients in whom a downhill course in renal function is predicted and who are, therefore, well suited for an interventional study.

We have chosen a renal end-point based on serum creatinine as opposed to a method of isotope clearance that estimates glomerular filtration rate (GFR). Although the latter are more accurate measures of renal function, and change in GFR over time (slopes) can be generated for each patient and thus compared between treatment groups, these tests need to be performed frequently if reliable curves are to be generated. This is especially true for many patients in whom little deterioration in GFR may be seen over the course of a study. Frequent use of GFR measurements is both cumbersome and expensive. Serum creatinine values, on the other hand, are easy to perform, quite reproducible and inexpensive. Although the same serum creatinine value may represent different GFR values in different patients, unless creatinine production in a given patient increases considerably during the course

of the trial, an increase in that patient's serum creatinine will reflect a deterioration in GFR. Since creatinine secretion increases as GFR falls, increases in serum creatinine may actually underestimate a reduction in GFR, and GFR may fall without a significant change in serum creatinine. In this regard, a doubling of serum creatinine should represent at least a 50% reduction in GFR. Indeed this is what we found in the type I captopril trial where we measured GFR through the urinary clearance of [125 I]iothalamate [5]. It is for these reasons that we believe that an end-point based on a patient's doubling of serum creatinine is a more practical measure of deterioration in renal function than one based on relatively infrequently obtained GFR measurements.

There is increasing evidence that proteinuria, in itself, plays a pathogenic role in the progression of renal failure. In this regard, agents that lower proteinuria may be more likely to preserve renal function than those that do not lower, or indeed increase, proteinuria. Thus, the effect of an antihypertensive agent on the level of proteinuria may be a surrogate for whether or not an agent offers renoprotection. CCBs may either increase or decrease proteinuria depending on the class being studied [17–19]. Amlodipine is a dihydropyridine CCB and has been shown to increase proteinuria in some models. This CCB was chosen for use in this trial because it was

Table 5. Correlations of baseline creatinine clearance (C_{Cr}) and 24 h urinary protein excretion to other baseline characteristics

Baseline characteristic	r values ^a	
	C_{Cr}	24 h urine protein
Age	ns	-0.15
Height	0.08	0.10
Weight	ns	0.18
BMI	ns	0.12
Duration of diabetes	-0.06	0.05
Seated systolic BP	ns	0.21
Seated diastolic BP	0.14	0.08
Creatinine clearance		-0.08
Serum		
Total cholesterol	ns	0.27
Total triglycerides	ns	0.16
Albumin	0.21	-0.55
Total protein	0.08	-0.45
Potassium	-0.07	ns
Haemoglobin	0.36	-0.17
History of		
Retinopathy	-0.05	0.08
Gastroparesis	-0.09	ns
Neurogenic bladder	-0.05	ns
Hypoglycaemia	-0.10	ns
Weight loss in last 3 months	-0.07	ns
Orthostatic hypotension	-0.04	ns
Chronic diarrhoea	-0.16	ns
Claudication	ns	0.06
Congestive heart failure	-0.08	0.07

^aPositive r values indicate positive associations and negative r values indicate negative associations, ns indicates not statistically significant at the 5% level.

the only CCB that was approved for use (and thus available for study) in all of the countries worldwide in which patients were going to be enrolled.

Reports of increased cardiovascular morbidity in type II diabetics with hypertension have brought into question the safety of some CCBs in this population [20]. These results are by no means ubiquitous, and further study hopefully will define the safety profiles of specific CCBs given to specific patient populations [21].

The majority of this recently reported work was done in patients with minimal to no diabetic renal involvement. Mortality from cardiovascular disease in type II diabetes is accelerated when renal disease is present [1,3]. This may relate to the higher prevalence as well as severity of hypertension that accompanies renal disease. The recently released results of the UK Prospective Diabetes Study Group (UKPDS) trial in patients with type II diabetes demonstrated the importance of aggressive blood pressure control on the reduction of death related to diabetes [22]. In that study, patients were randomized to a blood pressure goal of either <150/85 mmHg or <180/105 mmHg (actual blood pressures attained during the study were lower at 144/82 mmHg vs 154/87 mmHg, respectively). Our blood pressure goal (135/85 mmHg for the majority of patients) is actually lower than those goals. Thus, any potential class-specific differences that irbesartan or amlodipine may have on cardiovascular risk may

be overshadowed by the risk lowering effects of the relatively aggressive blood pressure control that we are striving for. Our trial is powered for primary endpoints that relate predominantly to renal events. We do, however, have a considerable list of secondary endpoints related to cardiovascular and peripheral vascular disease.

The use of ACEIs for type I diabetic nephropathy and other non-diabetic proteinuric diseases is one of the great medical success stories and probably the greatest nephrology success story of the last decade [23]. The impact on morbidity, mortality and cost of medical care is far from being fully appreciated [24]. With type II diabetes being the most common cause of renal failure in most parts of the world, the implications for similar renoprotection in this population of patients is enormous.

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