

Major Kidney Clinical Research Studies and Projects Inventory*

Renin Angiotensin System Study (RASS) of Diabetic Nephropathy

1. Administrative Data

(a) Name of study/research project and acronym:

Renin Angiotensin System Study (RASS) of Diabetic Nephropathy

(b) Type of study/research project (randomized clinical trial, epidemiological study, database, etc.):

Randomized, double blind, placebo controlled clinical trial

(c) Funding status (currently funded, study/project completed):

Currently funded

(d) Recruitment status (recruitment completed, currently recruiting):

Recruitment complete at 285

(e) For studies/project currently recruiting: indicate total sample size/ number currently enrolled, anticipated period of recruitment

(f) Data coordinating center principal investigator contact information (mailing address, phone, fax, e-mail address):

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(g) Number of recruiting sites, list of principal investigators at recruiting sites, and contact information as in (f) above:

Three recruiting sites: Minnesota, Montreal, and Toronto

Minnesota - Principal Investigator:

Michael Mauer, M.D.
Professor of Pediatrics

Kidney Disease Clinical Studies Initiative, Major Kidney Clinical Research Studies and Projects Inventory,*
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(i) Roster of Data and Safety Monitoring Board/Scientific Advisory Committee or other oversight committee(s):

External Advisory and Data Monitoring Committee (EAC):

Chairman:

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(j) Private sector support (type of support, e.g., financial, donation of drugs/placebo, etc.):

Merck (USA)—Study medication and partial financial support

Merck Frosst (Canada)—partial financial support

CIHR Canada—partial financial support

2. Study Design (for completed studies, a copy of the primary publication can substitute for information below)

(a) Objective:

A primary prevention study to determine if inhibition of the RAS could slow the development of a key diabetic glomerulopathy structural endpoint, increase in mesangial fractional volume [Vv(Mes/glom)].

(b) Study design:

This is a parallel, double-blinded, placebo-controlled trial with 285 patients with type 1 DM (95 per group) randomized to receive the angiotensin converting enzyme inhibitor (ACEI) enalapril, the angiotensin II receptor blocker (AIIRB) losartan, or placebo. All patients are normotensive,

normoalbuminuric, and have normal or increased glomerular filtration rates at study entry. The study is based on the primary endpoint of change in Vv(Mes/glom) from the baseline to the 5-year renal biopsy with baseline and interval measures of albumin excretion rate, glomerular filtration rate, blood pressure, and glycemia. Baseline, mid-point, and 5-year retinal fundus photography are also performed.

(c) Major inclusion criteria:

Subjects fulfilling the following criteria were eligible for this study:

- 16 years of age or older if a participant in an earlier natural history study, otherwise 18 years of age or older
- Type 1 diabetes (type 1 DM) for 2-20 years
- Type 1 DM onset prior to their a) 31st birthday, or b) 41st birthday if BMI <26 at time of diagnosis and patient must require insulin therapy within one year of diagnosis; or c) age 41- 45 at time of diagnosis if they have a positive CAD antibody or islet cell test
- Normal or increased GFR
- Normal blood pressure
- UAE <20 µg/min.

(d) Major exclusion criteria:

- BP > 135/85
- Pregnancy
- Already on anti-hypertensive medications
- Having persistent microalbuminuria.

(e) Description of the intervention(s):

Participants were randomized according to computer-generated blocks of six, with stratification by center (Minnesota, Montreal, Toronto) and gender, into the following three treatment groups:

- Enalapril (ACEI) 10 mg plus losartan (AIIRB) placebo once daily
- Losartan 50 mg plus enalapril placebo once daily
- Enalapril and losartan placebos, once daily

Approximately 40 months after randomization of the first participant, and after about one-third of the total study drug exposure time had expired, data became available indicating that the magnitude of proteinuria reduction was greater on higher doses of ACEI or AIIIRB (21). Consequently, the dose of each of the drugs was increased to 20 mg enalapril and 100 mg losartan by doubling the number of pills taken once per day.

(f) Baseline/eligibility visit schedule (number of visits, major assessments):

A series of pre-randomization clinic visits were used to determine eligibility. Patients on any antihypertensive medications were excluded. Blood pressure was measured with a Dinamap monitor, and hypertension was defined according to published standards for type 1 DM patients as BP >135/85 (26). Participants found to have a BP > 135 mmHg systolic or > 85 mmHg diastolic at the initial clinic visit had their BP re-measured on two additional occasions and were excluded if hypertension persisted. Patients with overt proteinuria (Dipstick® positive) or with urinary albumin excretion rate (AER) >20 µg/min in two of three overnight urine collections were excluded. Patients avoided nonsteroidal anti-inflammatory drug use during screening.

Fasting blood samples were obtained for white blood cell count (WBC), serum electrolytes, hemoglobin A1C (HbA_{1C}), serum creatinine, and liver enzymes (ALT). Additional blood was obtained for DNA isolation and storage, and specimens of plasma and serum were saved at -70°C. Pregnancy tests were performed on all women of child-bearing age. If AER and blood pressure met study entry criteria patients were given a two-week supply of pills (placebo). Those failing to take ≥85% of these pills were excluded. Others then underwent measurement of glomerular filtration rate (GFR).

(g) Follow-up contact schedule (frequency, type of visit-phone, in-clinic, major assessments):

All participants are seen every three months by the study coordinators. Clinic visit dates are determined by date of randomization with a ± 2 week window around each visit date. At each visit the following are performed:

- Interim health history including medications
- Assessment of drug compliance
- Measurement of weight, height and blood pressure (see below)
- Overnight urine collection for UAE
- Blood for serum electrolytes and HbA_{1C}
- Intervention session
- Adverse event form completion. Patients are phoned at the midpoint between visits. Annually, patients also have 24-hr BP monitoring and formal GFRs performed.

(h) Primary outcome, secondary outcomes:

The principal objective of this trial is to determine if inhibition of RAS can prevent or retard the development of a specific histological lesions of diabetic nephropathy [Vv(Mes/glom)] in type 1 DM patients without hypertension, microalbuminuria, or reduced glomerular filtration rate (GFR). Secondary outcomes include effects of treatment on other renal structural endpoints, on renal functional endpoints, and on diabetic retinopathy (DR).

(i) Brief summary of power estimates used to justify sample size/duration, including critical assumptions (i.e., effect size estimates, estimated event rates, or rate of change in outcome measure):

A minimum of 95 patients is required per group (285 in total) to assess the primary hypothesis of the study. The sample size is based on the primary method of analysis, namely linear regression, and the primary outcome variable, Vv(Mes/glom), with assumptions about its distribution originating from 21 patients completing the NHS (24,25) and meeting all the eligibility criteria for the current study. The data on these patients indicated that the mean rate of change (r) over 5 years is 0.0533 (SD = 0.0684; range -0.06 to 0.19). A simple linear regression of r on the initial Vv(Mes/glom) shows that 27% of its variance is explained by this initial Vv(Mes/glom). Extending this analysis to a multiple linear regression model containing the initial Vv(Mes/glom), HbA_{1C}, GFR and diabetes duration, the variance explained increased to 35%. Thus, the standard deviation was reduced from its crude value of 0.0686 to 0.0557. Assuming that homogeneity of these factors will be greater in the trial, we can safely assume an adjusted standard deviation of 0.0557 for the change in Vv(Mes/glom).

The estimate sample size requirement is based on an overall two-sided significance level of $\alpha = 5\%$ and a power of 80% ($\beta = 20\%$). This is reduced to $\alpha = 2.5\%$ by a Bonferroni adjustment, which is necessary because of the two contrasts for the primary hypothesis of interest: losartan versus placebo and enalapril versus placebo. By applying the assumption that the annual rate of change (r) [Vv(Mes/glom)] can be reduced by 50% (i.e., from the expected 0.0553 to 0.0267), the trial requires 95 patients per group or 285 in total, respectively, allowing for a 10% drop out rate. Finally, if the two contrasts indicate a similar magnitude, the two treated groups (losartan and enalapril) will be combined into one and contrasted with placebo to increase power. Secondary analyses will examine additional renal structural and renal functional endpoints.

(j) Web site:

None

3. Data and Biological Sample Resources

(a) Biological samples collected in ongoing studies/research projects (specify the type of sample- blood, urine, etc., the amount, and the point in the study when samples were collected, e.g., baseline visit #1, baseline visit #2, follow-up visit #1; specify months after randomization/study entry)

See Appendix A (RASS Testing Schedule).

(b) Biological samples currently in storage from completed trials (grid showing sample collection time, type of sample, amount, and number of study participants sample was collected from, and physical location of where the samples are stored)

See Appendix A (RASS Testing Schedule).

(c) Brief summary of typical informed consent provisions (template informed consent form acceptable), including major variables in participant consents, if applicable. For example, “use for other studies or not”, “allow genetic studies or not.” Does consent include use of samples in other studies that are not part of the main study?

See Appendix B (RASS Consent Form).

(d) Data collected (grid of data collection by time/clinic visit with specificity on the type of information collected—e.g., quality of life with SF-MOS 36, measurement of kidney function by GFR, serum creatinine measurement, etc.)

See Appendix A (RASS Testing Schedule).

(e) Any provisions for distributing resources outside of the study? What is the sharing plan?

None at this time.

4. Ancillary Studies

(a) Process and contact person (name, address, phone, fax, and e mail address) for application to perform ancillary studies:

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(b) List of ancillary studies approved, completed, and ongoing (including source of funding and amount):

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SCI – Compliance Ancillary Study (approved, ongoing and funded by NIH as part of the main RASS grant):

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Fundus Photography Ancillary Study (approved, ongoing and funded by NIH as part of the main RASS grant):

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5. List of Publications and Presentations (full citations, also note manuscripts in progress):

Mauer M, Zinman M, Gardiner R, Drummond K, Suissa S, Donnelly S, Strand T, Kramer M, Klein R, Sinaiko A; ACEI and AIIRP in Early Diabetic Nephropathy; Effects of Renin Angiotensin System (RAS) Blockade on Diabetic Nephropathy, a Primary Prevention Trial, The RAS Study (RASS) Rationale: Study Design and Cohort Description; *JRAAS*, *in press* Jan 03.

*Cooperative Agreement, Contract, and Selected Investigator-Initiated, NIDDK-Supported Studies

Appendix A. RASS Testing Schedule

Renin Angiotensin System Study (RASS) Testing Schedule

Test	Baseline	2 Wks	Quarterly ± 3 weeks	Annual ± 4 weeks	5 Year* ± 4 weeks	2 Wks Post Meds D/C ± 2 days	1 Mo Post Med D/C ± 1 week	2 Mos Post Yr 5 ± 1 week
K+	X	X**		X	X			
Serum Creatinine	X	X**		X	X			
ALT	X		1st	X	X			
WBC	X		1st	X	X			
A _{1c}	X		X	X	X			
Pregnancy	X		X	X	X			
Coags	X				X			
Plt	X				X			
Hct	X				X			
Urine Albumin	X		X	X	X		X	X
Saved Specimens 6 Serum (1 ml) 6 Plasma (1 ml) 3 Urine (3.5 ml)	X X X			X X X	X X X			X
GFR	X			X	X			X
DNA	X				X***			
Skin Biopsy	X				X***			
Kidney Biopsy	X				X			
Fundus Photos	X				X			
24 Hr Blood Pressure	X			X	X			X (±1 month)
SCI Forms	X			X	X			
Renins	Prior to Med Increase		1 st after Med Increase	12 Mo. after Med Increase	X			X
BP	X		X	X	X	X	X	X

Renins: Renin testing coincides with the medication increase dates for each patient and are drawn at the following times:

Baseline – before medications are increased

+ 3 month visit following medication increase

+12 month visit - one year from the baseline renin draw.

Two months following discontinuation of study meds

* End of study (Exit Biopsy Visit)

** K+ and serum creatinine will be done 2 weeks after study medications are initiated, and again 2 weeks after medications are increased (see Renin Chapter)

*** If the participant has not had a skin tissue biopsy or has not had the DNA drawn, these should be done at this visit.

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Two weeks post-biopsy (+/ 2 days):

Two weeks following discontinuation of study meds, the participant will return for a blood pressure follow-up, using the RASS BP procedure.

One month post-biopsy (+/- 1 week):

At one month following discontinuation of study meds, blood pressure should be checked and an overnight urine collected for AER. *

Two month's post-biopsy (+/- 1 week):

At two months following discontinuation of study meds, blood pressure should be checked, an overnight urine collected for AER, fasting saved specimens and renins should be collected, and a GFR and 24 hrBP should be done (24 hr BP must be done in +/- 1 month window).*

* If the one and two month AER's are discordant, (i.e., one normal and one showing microalbuminuria or proteinuria, or one showing microalbuminuria and one overt proteinuria {>200 µg/min}), review instructions with the participant and have them do a third collection, at least two weeks after the last one.

Appendix B. RASS Consent Form

Renin-Angiotensin Inhibition and Early Diabetic Nephropathy Lesions

A Study of the Early Treatment of Diabetic Kidney Disease with Antihypertensive Medications

CONSENT FORM

Teen or Adult with Insulin Dependent Diabetes

Participant's Name:

Address:

City:

Social Security Number:

Introduction

You are invited to become part of a medical research study which is designed to determine if certain drugs used to treat high blood pressure (antihypertensive medications) can slow or stop the development of the early stages of diabetic kidney disease. This study is conducted by the University of Minnesota, under the direction of Dr. Michael Mauer, Professor of Pediatric Nephrology, in collaboration with two other centers in Canada.

Background Information

People with Type I, or insulin-dependent diabetes, have a 25-35% risk of developing serious kidney disease which is called diabetic nephropathy. This kidney disease leads to kidney failure 15-40 years after diabetes first begins.

Diabetic nephropathy, develops silently without warning signs or symptoms, for the first 10-30 years of insulin dependent diabetes mellitus. By the time warning signs such as high blood pressure, increased protein loss in the urine, or a drop in the filtering ability of the kidney are detectable, kidney damage has already reached a stage where treatment can only slow, but probably not fully stop, the progress toward kidney failure.

Currently, there are no reliable indirect ways (such as blood or urine tests or blood pressure measurement) to detect the earliest stages of diabetic kidney disease. Thus, for many years after the onset of diabetes, doctors are unable to distinguish people who will develop serious complications from those whose kidney function will remain normal throughout their lives.

The most accurate way to detect the early stages of diabetic kidney disease is to obtain a very small piece of kidney tissue through a needle which is inserted through the skin of the back into the kidney. This procedure is called a kidney biopsy. The tissue undergoes very specialized studies which examine the filtering parts of the kidney, called glomeruli, as well as other kidney structures.

This study proposes to determine if the long term use of certain antihypertensive medications can slow or arrest the early changes of diabetes in the kidney. The study compares a kidney biopsy taken at the beginning of the study and a repeat kidney biopsy five years later to determine whether these drugs can slow or stop the development of early diabetic kidney damage.

The renin-angiotensin system, one of the regulators of blood pressure and kidney function, might play a role in the development of diabetic kidney disease. This could be because this regulatory system influences blood flow and pressure within the kidney which could be damaging to diabetic patients. Alternately, the renin-angiotensin system might influence the production of certain proteins which can accumulate in the filter system of the kidney leading to structural changes and eventually to failure of the kidney as a filter.

Two types of antihypertensive drugs can block the renin-angiotensin system. The first type, angiotensin converting enzyme inhibitors such as enalapril (Vasotec), blocks the production of angiotensin, the molecule that affects the kidney. The second type, angiotensin receptor blockers such as losartan (Lozaar), directly blocks the interaction of angiotensin with the kidney cells.

As these two drugs act somewhat differently, both will be tested in this study. It would not be possible to prove a benefit of these drugs unless some patients did not receive this treatment. Therefore, patients agreeing to participate will have initial (baseline) studies of kidney function and a kidney biopsy and then be randomly assigned to one of 3 equal size groups. One group will receive the angiotensin converting enzyme inhibitor, enalapril; the second group will receive the angiotensin receptor blocker, losartan; and the third group will receive a pill without active ingredients (placebo). Neither you nor the doctors or nurses in this study will know which group you have been assigned to until after the study has been completed. Throughout the study you will be encouraged to practice careful blood sugar control by your diabetologist and his/her staff.

At the end of the study we will determine whether either or both of the active drugs were able to slow the rate of development of the structural changes in the kidney which can ultimately lead to serious kidney disease or diabetes.

This study will also evaluate the Study Commitment Inventory (SCI), an instrument designed to see if it is possible to predict adherence to research study protocols. This aspect of the study explores the use of paper and pencil instruments to predict and potentially facilitate participant's commitment to research studies. This type of assessment should have general relevance for use in research. It is possible that by considering the potential impact of factors listed on the SCI (e.g. barriers to participation), potential research subjects will be better informed and may more fully understand factors which can affect their study commitment at the time they choose to volunteer for studies or decline to participate.

Purpose of the Study

This study will determine whether early treatment with drugs which can block the renin-angiotensin system can slow or stop the development of the structural changes of diabetes in the kidney which can ultimately lead to diabetic nephropathy.

Approximately 285 people participating at medical centers located in Minneapolis, Minnesota, USA; Montreal, Quebec and Toronto, Ontario, Canada will participate in this study.

You have been invited to participate because you are 18-64 years old (16-64 years old if you are a participant in the NHDN Study) and have had insulin-dependent diabetes for at least 2 but not more than 20 years. Type 1 diabetes must have been diagnosed prior to your 41st birthday, or if it was diagnosed between 41 through 44 years of age, you must have an islet cell antibody, or GAD antibody test, with a positive result, to verify Type 1 diabetes. If your diabetes was diagnosed between the ages of 31 through 44, your Body Mass Index (BMI) must have been <26 at the time of diagnosis, and you must have required insulin therapy within one year of diagnosis.

If you have high blood pressure, substantial increases in protein (albumin) in your urine or other signs of reduced kidney function by routine tests, you will not be eligible to enter this study. In addition, if you decide you do not wish to, or would be unable to have the tests required by this study, you may refuse to participate and your care will continue as before.

DNA Storage and Future Use

Another purpose of this study is to gain a better understanding of a genetic basis for the kidney complications of diabetes mellitus. To accomplish this we will store DNA from the study participants for genetic analysis; these test will be performed should a genetic linkage to diabetic kidney disease be suggested by other studies. If you agree to be in this part of the study, we will draw 5-30 ml (1-6 teaspoons) of blood from you, using standard blood drawing procedures. The genes of blood cells (DNA) will be isolated from the blood cells and used to study gene composition.

The DNA and the cell lines that are obtained from the blood cells will be placed in permanent storage in the laboratory and may be used for the analysis of genetic characteristics of kidney complications of diabetes mellitus. By signing this form, you are also giving consent for any future studies of the genetics of diabetic kidney complications that we may perform in the laboratory with the blood that we are drawing at this visit. The blood may not be used for other purposes without your written consent. In some cases, this material may be transferred to other research groups for analysis for the same purpose. You will not be notified if your material has been transferred to another researcher; however, your identification (including your name) will remain confidential and will not be transferred with the samples. All DNA and cells in permanent storage will be identified by study number only. The study number list that indicates name, address, and diagnosis will be kept in the study office.

You will not be informed of the results of your DNA analysis since the information is not diagnostic or characteristic of a specific risk of kidney disease. However, if the results of these studies are published,

upon request, you will be given a copy of the publication. The genetic analysis will not affect your medical care or the care you will receive for your diabetes mellitus or other conditions.

Study Procedures: Overview

If you choose to join this study, you will have kidney tests done in the Clinical Research Center at the University of Minnesota Hospitals. These tests will be directed by Michael Mauer, M.D., a doctor who is a kidney specialist.

These tests will study both your kidney structure and your kidney function. To study structure, it is necessary to do a kidney biopsy. To study kidney function, it is necessary to collect blood samples after injecting a substance into your blood that is filtered through your kidneys.

The kidney function test and biopsy will be done at the beginning of this study and five years later. These will require that you stay one day and one night in the Clinical Research Center on each occasion.

A kidney function test without the biopsy will be done yearly for the intervening four years on an out-patient basis in the Clinical Research Center and will require one-half day each year. Ambulatory 24 hour blood pressure monitoring and completion of the Study Commitment Inventory will be done annually. The study pills will need to be taken once each day for the five years of the study.

Other studies include overnight urine collections, and blood tests once every 3 months.

Fundus photography (colored eye photographs/slides) will be done at or near your date of randomization, at or near Quarterly Visit 10 (mid-point of the study), and again, at or near the endpoint of the study. These photographs are designed to document and measure the anatomic changes in your eyes over a 5 year period. The completed photographs will be sent to a central Fundus Reading Center for screening for retinopathy or any evidence of eye disease. You will receive the preliminary results of this test in a timely fashion should these results indicate any need for further investigation or treatment.

Study Procedure: Kidney Biopsy

A kidney biopsy is a standard procedure done in all major medical centers to diagnose different kinds of kidney disease. This procedure is done only by a kidney specialist who has experience doing such biopsies.

A biopsy of your kidney means that a special needle will be used by a kidney specialist to take a small sample, or sliver, of tissue from the kidney. The amount of tissue to be taken is less than 1/2,500th of the kidney. The sample's absence will not change your kidney function.

To locate your kidney precisely before the biopsy, a kidney ultrasound will be done. An ultrasound is a painless test in which sound waves are reflected off the kidney and recorded electronically on a video monitor. Kidney size will be measured from these recordings.

The biopsy needle will be passed through the skin and muscle of your back in the area over your kidney. The skin and muscle will be numbed with an injected anesthetic (1% lidocaine). The injection will cause mild, temporary discomfort similar to, but is less painful than the injection used by dentists before filling a tooth. If you wish, you may request medication to relax you before the biopsy. It will be given

into the I.V. that was used earlier that day for your kidney function studies (see below), so the I.V. will be left in place until the biopsy is completed.

The risks associated with a needle biopsy of the kidney include the possibility of significant bleeding around the kidney which could result in some pain. This occurs in less than 1 out of 200 biopsies. Such bleeding usually lasts for a very short period and involves a small amount of blood. Bleeding into the urine collecting system of the kidney that causes discomfort or temporary blockage of the kidney or bladder may also occur in less than 1 out of 200 biopsies.

Repeated episodes of bleeding due to damage to a blood vessel (artery) within the kidney may occur in less than 1 in 1,000 biopsies. In that case, the damaged vessel may need to be obstructed with material delivered through a catheter (a small tube) guided into the damaged artery from an artery in the leg. This would result in the permanent loss of blood flow to a small portion of one kidney, but is unlikely to measurably affect overall kidney function.

Blood-tinged urine occurs in one out of 10 to 15 biopsies, but this almost always clears without treatment within 24 hours.

Perforation of your intestine or of a large blood vessel is extremely unlikely as is injury to other organs such as your liver or pancreas.

In general, the chance is less than 1 in 3,000 that you may need to have an operation because of bleeding or other complications following biopsy. The chance is less than 1 in 7,500 that your kidney would have to be removed.

In order for the kidney biopsy to be objectively evaluated, those studying your kidney tissue will not be aware of any medical information concerning you. However, if any findings arise during the study which could affect your health and which might influence your treatment, you and your diabetes specialist will be informed immediately so that medical treatment can be started. Likewise, any results of the study which might affect your willingness to participate in this study will be shared with you.

Study Procedure: Kidney Function Test

At years one through five, the kidney tests involve injecting a substance, Iohexol, into your blood and then collecting blood samples for approximately 4 hours thereafter to measure your kidney filtering rate.

For the Iohexol study, one small needle will be placed in one of your arms for drawing blood and for administering the Iohexol. Placing the needle requires a puncture similar to that which occurs when blood is drawn for your routine laboratory tests and, therefore, you may experience mild discomfort. The needle is left in place for approximately four hours and then removed. The needle is painless once placed. At the beginning of the study and four years later when kidney biopsies are done, the needle will be left in to be used for giving some relaxing medicine (sedation) before the biopsy, should you request this. Approximately 3 tablespoons of blood will be drawn which will be quickly replaced by your body and thus there will be no harm to your health.

Iohexol has been widely used and has an excellent safety record. Very occasionally, allergic reactions to Iohexol may occur. If you have ever had an allergic reaction to x-ray dyes or iodine containing substances you should not participate in this component of the study.

Infusion, blood withdrawal, and urine collection will be performed at your bedside in the Clinical Research Center of the University of Minnesota Hospital.

Study Procedure: Fundus (Eye) Photographs

Fundus (eye) photographs will be done in the Eye Clinic, by a trained photographer. You will receive eye drops while in the Eye Clinic to dilate your pupils. Once your pupils are dilated, you will have a set of seven (7) sets of photographs taken of each eye and a photograph of your lenses. This procedure should take approximately 1 hour. After the photographs are taken your eyes will remain dilated for a few hours. Bright sunlight may cause discomfort and you may want to have someone drive you home following this procedure. You should bring sunglasses with you, or disposable sunglasses will be available upon request.

Study Procedure: Skin Biopsy

The skin biopsy will be done on the skin already numbed for the kidney biopsy. Using a special instrument called a punch, a small area of superficial skin (about this size - o) will be removed. No complications are expected from this procedure. Studies will be performed with cells grown from this small piece of skin. These will include evaluation of cell growth patterns and of cell regulation of extracellular matrix production and removal.

Study Procedure: Study Drugs

You will be assigned to one of three groups, two of which will receive active drugs and one will receive placebo (inactive ingredients in the form of a pill). You will be required to take the pills once daily for the five years of the study. Since neither you nor the doctors or nurses will know which group you are in, you need to be aware of the possible side effects of both of the study medications, which are now described.

Drugs interfering with the renin-angiotensin system can cause serious damage to the unborn child (fetus) if taken after the first trimester (12 weeks) of pregnancy. Therefore, if you are a female of child bearing age and have missed a menstrual period you must discontinue the medication and contact the study personnel immediately. Further, as a female of child bearing age you will have pregnancy tests done every 3 months. As a female participant in this study of child bearing age you are encouraged to adopt reliable contraceptive methods for the duration of the study. If you should decide to become pregnant the study drugs will be discontinued until after delivery.

There is a small chance (less than 1%) that these drugs can cause allergic type swelling of the face, extremities, lips, tongue or airway. You will be given antihistamines to take in case this develops. Since tongue or airway swelling can interfere with breathing, in an extreme case you may need to proceed to an emergency room to receive an injection of adrenaline. If this swelling is thought to be due to the study drugs you will not take them again.

It is possible, especially if you have become dehydrated, that you could feel dizzy or faint from these medications. This has occurred in about 1% of hypertensive patients, but would be less likely in patients in this study whose blood pressure will be normal as a condition of entry into the study. Should this happen you should discontinue the study medication and contact the study personnel.

A small number of patients (much less than 1%) have developed abnormally low white blood cell counts while taking similar medications. Your white blood cell count will be followed every 3 months. If a low count and absolute neutrophil count develops, you will be referred to a hematologist for evaluation. Absolute neutrophil is the total number of white blood cells, called neutrophils, in 1 ml of your blood. These cells are important, especially in fighting bacterial infections. Based on the decision of the hematologist, you may have to discontinue the medication. If the low white blood cell count is thought due to the study drug you will not take it again.

Rarely (much less than 1%) serious liver damage could result from these drugs. Should your skin become yellow (jaundiced) you are to discontinue the medication and contact the study personnel immediately. If liver dysfunction is thought to be developing from these drugs you are taking you will not take them again.

The study drugs can cause the potassium levels in your blood to increase and this could affect the functioning of your heart. You should not start any water pills (diuretics) without discussing them with the study personnel and should avoid potassium supplementation or potassium-containing salt substitutes.

Persistent cough in the absence of infection will develop in about 2% of patients taking ACE inhibitors and will be severe enough to require discontinuation of the medication in about one-half of these (1%).

If you have to undergo surgery under a general anesthetic your blood pressure may drop too low on the study drugs. You should stop these drugs at least 2 days before surgery and contact the study personnel as soon as you are aware that surgery might be necessary.

Since blood pressure lowering effects of antihypertensive medications may be additive, if you need additional BP medication, it will be prescribed by study personnel.

Patients given lithium for manic/depressive psychiatric disorders may have their blood levels of lithium go too high while taking the study medication. You should inform the study personnel before lithium therapy is started.

Overall it can be expected that you have about a 3 in 100 chance of having your medication temporarily or permanently discontinued because of side effects attributable to the study medications.

Other Considerations

If you develop high blood pressure during the course of the study, routine blood pressure medications will be used to control your blood pressure. The medications used to treat high blood pressure, if it develops, will not include the drugs that are specifically being studied, unless your blood pressure is not reduced to normal by other medications.

Your blood pressure will be checked at each quarterly visit, and at baseline and on an annual basis, you will be asked to wear an ambulatory 24 hour blood pressure monitor. The monitor is portable and can be removed for short periods of time to shower, exercise, etc. It will measure your blood pressure every 20 minutes for the 24 hour period.

One of the first indications of kidney disease caused from diabetes that we are able to measure is the development of microalbuminuria. This is therefore one of the outcome assessments of the study. During the study neither you nor your doctor will be aware of the results of these tests unless you develop a more advanced indication of kidney disease called proteinuria, a level of protein in the urine detectable by ordinary dipstick tests. The current recommendation of the American Diabetes Association is to monitor for the development of lesser amounts of urinary protein called microalbuminuria and to treat with an angiotensin converting enzyme inhibitor (one of the drugs being studied) if microalbuminuria develops. Studies to date have not conclusively found that this treatment will prevent further development of serious kidney disease. Therefore, this recommendation will not be followed during the study. You will, however, be removed from the study and receive treatment with these drugs if you develop proteinuria, since studies have shown this to be beneficial.

Study Procedure: Office Visits

During this five-year study you will be asked to continue regular visits to your diabetes specialist as well as to briefly visit our nurse coordinator at our study center every three months. You will be asked to bring a urine sample collected overnight to each study center visit. In addition, you will have blood drawn for a glycosylated hemoglobin (A1c) test as well as for a white blood cell count, a serum potassium measurement and liver function tests. If you are female we will also do a urine or serum pregnancy test at each visit.

Before you are randomized to the study, the RASS staff will explain an adherence evaluation component, the Study Commitment Inventory (SCI), to you in detail. You will be asked to complete some psychological tests, namely the SCI, SCL-90, Beck Helplessness Scale, and the Multidimensional Health Locus of Control Scale. An abbreviated version of the SCI and other instruments will be completed by each participant on an annual basis. Subjects will also complete instruments about their response to the SCI and rate their adherence to the RASS. The entry and study conclusion questionnaires will take approximately 30 minutes to complete and the annual forms should take about 20 minutes. There are no anticipated major risks associated with the SCI study. The only potential risk is mild anxiety from answering questions. You will be identified on these forms by an identification number and initials only.

Benefits of Participation

The purpose of this study is to explore whether blocking the renin-angiotensin system using enalapril (Vasotec) or losartan (Lozaar) can diminish the risk of developing the kidney disease of diabetes.

The study may be of direct benefit should the results indicate that the kidney disease of diabetes is slowed or prevented by such treatment and you are in the group(s) receiving this treatment. If you are in the placebo group and our studies indicate a benefit of such treatment you will be offered this treatment at the completion of the study. This study is designed to detect the development of high blood pressure as early as possible and to treat this should it occur, regardless of the group to which you are assigned. There is some evidence that this antihypertensive treatment can slow progression of diabetic kidney disease.

By inviting you to participate, the study team is not suggesting that you have any greater than usual risk of developing diabetic kidney disease. However, if you are developing such kidney changes, then the increased efforts to improve blood sugar control accompanied by control efforts to keep your blood

pressure normal may well slow further progression of this disorder. If the studies indicate that, with or without treatment, you are not developing the changes of diabetes in your kidney, this would provide reassurance to you that your risk of ultimately developing kidney disease of diabetes is low.

By participating in this study, you may develop a better understanding of your diabetes and its risks. By participating in the Study Commitment Inventory, you may be better informed and may more fully understand factors that can affect study commitment at the time you volunteer to participate.

The kidney biopsy, kidney function tests, and skin biopsy are for research purposes only and would not be done as a part of your routine diabetes care.

Compensation

The cost of the medical care, kidney tests and other tests associated with this study and hospitalization at the Clinical Research Center at the University of Minnesota Hospitals that are required by this research study will be free of charge to you. There is no charge for the study visits, tests, procedures or study medications.

The cost of the diabetes clinic visits, and other treatment recommended as a routine part of your diabetes management, including the cost of blood glucose testing supplies, will be paid by you or your health insurance.

Research-related injury compensation – In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away.

Confidentiality

Any information obtained in connection with this research study that can be identified with you will remain confidential and will be disclosed only with your permission. In any written reports or publications, you will not be identified or identifiable.

Contacts and Questions

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), contact Patient Relations Office, B310 Mayo Memorial Building, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455; telephone (612) 273-5050.

If you have questions about this study or wish to report a study-related injury or problem, you may reach the nurse coordinator, Trudy Strand, RN or Dr. Mauer at (612) 626-2922. If you need to reach a study doctor at night or weekends, call the Fairview-University Medical Center operator at (612) 273-3000 and ask to have Dr. Mauer paged. If you have questions about the Study Commitment Inventory, you may contact William Robiner, Ph.D., L.P. at (612) 625-7143.

You will receive a copy of this consent form. During the course of this study, you agree not to participate in another study unless you first notify the study team.

Alternatives to Participation

The alternative to joining this study is not to participate. You may decline to participate, or withdraw once the study has begun, without limiting your ability to receive future care from the Fairview University Medical Center. Even if you have the first kidney biopsy and kidney function test, you can decline to participate in subsequent years. If the study staff decides it is in your best interest, or if you significantly fail to follow the study requirements, your participation in this study may be ended without your permission.

You and your parents or legal guardians are making a decision whether or not you will participate. As part of making this decision, you must indicate your answers to the following questions:

- You agree to participate in these studies: YES NO
- You agree to have the kidney function tests: YES NO
- You agree to have the kidney biopsies: YES NO
- You agree to have the skin biopsies: YES NO
- You agree to have the DNA testing: YES NO
- You agree to have the eye photographs: YES NO
- You agree to complete the Study Commitment Inventory Forms: YES NO

At the end of the RASS study (Quarterly Visit #20), we will be stopping the study medication that you have been taking for five years. It is possible, if you were taking either Enalapril or Losartan that your blood pressure and/or kidney function status may change once this happens.

In your best interest, and for research purposes, we feel it is important that we monitor your blood pressure and kidney function on 3 separate occasions during the two months following discontinuation of the medications. This would be done as follows:

2 weeks following medication discontinuation – blood pressure check

4 weeks following medication discontinuation – blood pressure check, overnight urine collection for protein.

8 weeks following medication discontinuation – blood pressure assessment, overnight urine collection for protein, Glomerular Filtration Rate, renins, saved blood and urine specimens, and the 24 hour blood pressure study.

Kidney Disease Clinical Studies Initiative, Major Kidney Clinical Research Studies and Projects Inventory,*
Renin Angiotensin System Study (RASS) of Diabetic Neuropathy

If, on these evaluations your blood pressure or the amount of protein (albumin) in your urine is elevated, Enalapril or Losartan would then be prescribed for you.

I agree to the 3 visits stipulated above. YES NO

We are requesting your permission to contact you in the future when there are studies which have been approved by our Institutional Review Board (IRB) and may be of interest to you.

I give you permission to contact me for future IRB approved studies of potential interest to me.

YES NO

You and your parents or legal guardian's signatures (if needed) below indicate that you have read the information in this consent and have decided to participate in this study.

Participant Signature DATE: _____

Witness Signature DATE: _____

Parent or Legal Guardian Signature DATE: _____

Principal Investigator Signature DATE: _____