Association of diuretics with change in extracellular volume, natriuretic peptides, symptoms, and cardiovascular outcomes in CKD

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Department of Veterans Affairs

VA RESEARCH CONSENT FORM

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: [redacted] **VAMC:** _____

H-49171 - DIURETICS AND VOLUME OVERLOAD IN EARLY CKD

This study involves increasing diuretic (water pill) blood pressure medicines and checking the effect on the amount of extra fluid in the body, blood tests that can be related to extra fluid in the body, and symptoms of fatigue, depression, and quality of life.

Concise and Focused Presentation

A. WHAT IS THE STUDY ABOUT AND WHY ARE WE DOING IT?

We are asking you to choose whether or not to volunteer for a research study being funded by the Department of Veterans Affairs about whether diuretic blood pressure medicines decrease extra body fluid and early heart disease in patients with chronic kidney disease (CKD) stages 1-3. If you are not currently taking a diuretic medicine for your blood pressure, one will be started. If you are already taking a diuretic blood pressure medicine, the dose will be increased. The goals are to see if diuretic medicines change the amount of fluid in your body, certain blood tests that can be high in people with too much fluid in their body, and symptoms common in people with CKD. Funding for this study is provided by a VA Clinical Sciences Research and Development Career Development Award. None of the investigators or research team have any conflicts of interest with this study. Taking part in this study is completely voluntary.

B. WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

This study involves research about the effect of diuretic medicines on extra body fluid, early heart disease, and common symptoms in patients with CKD. By doing this study, we hope to learn whether diuretic medicines decrease 1) two common blood tests called brain natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-pro-BNP); 2) common symptoms of fatigue, depression, and quality of life; and 3) signs of heart and blood vessel disease such as high blood pressure, heart valve disease, or stiffening of the heart. Your participation in this research will last about 6 weeks.

C. WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You are being asked to participate in this study because you have evidence of stage 1-3 CKD and high blood pressure. Your participation may benefit you by getting better control of your blood pressure, and will lead to knowledge that will help others like you in the future.

D. WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

Risks of this study include low blood pressure, low sodium or potassium level, worsening of kidney function, discomfort from drawing blood, and the unlikely event of loss of confidentiality of research data. There are other types of blood pressure medicines that can be used to get your blood pressure under better control if you choose not to be a part of this study.

Persons who are pregnant may not participate in some parts of the study. Use of contraception is recommended for the 4 week duration of the study. Please notify the study team if you become pregnant by calling [redacted] or [redacted].

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E. DO YOU HAVE TO TAKE PART IN THE STUDY? WHAT ARE YOUR ALTERNATIVES?
If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer. If you choose not to participate in the study, you can continue regular care with your doctor.

F. WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?
The person in charge of the study is [redacted] of the Michael E. DeBakey VA Medical Center (MEDVAMC). If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study her contact information is: [redacted], or reach staff member [redacted] at [redacted].

G. SUMMARY OF THE RISKS, BENEFITS, AND ALTERNATIVES
By being a part of this study you may gain better control of your blood pressure, and the knowledge gained from the study may help others in the future. There is also a risk of low blood pressure, low sodium or potassium level, worsening kidney function, and discomfort from drawing blood. If you choose not to participate, you may continue care with your regular doctor.

Background

You are invited to take part in a research study. Please read this information and feel free to ask any questions before you agree to take part in the study.
This research study is funded by the Department of Veteran Affairs
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Purpose

This study includes patients who have CKD stages 1-3. Previous research showed that in patients with stages 1-3 (early to moderate stage) CKD, BNP and NT-pro-BNP were associated with heart events such as heart attacks, strokes, and heart failure. However, there are many reasons that might cause these blood tests to be high. The purpose of this research is to determine if the decrease in extra body fluid as a result of starting or increasing diuretic medicines leads to improvement in 1) BNP and NT-pro-BNP, 2) common symptoms, and 3) signs of early heart and blood vessel disease in people with CKD stages 1-3.

Procedures

The research will be conducted at the following location(s):
Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center.
This study involves two in person visits that will last about 1-2 hours each, as well as a telephone call lasting 5-10 minutes. The following procedures will be done as part of this study:

Screening Procedures: It will take approximately 10 minutes to conduct the screening procedures. These procedures will take place in the Michael E. DeBakey VA Research Commons or outpatient clinic space, and this information will be kept confidential. To help decide if you qualify to be in this study, the researchers will ask you questions about your health, including medicines you take and past medical problems.

Procedures and Evaluations During the Research: If you agree to be in the study, you will be asked to sign this consent form. You will undergo the following tests and procedures:

1) Medical history: Demographic information including age, sex, race, and ethnicity; medicines you are taking; past medical problems; surgeries you have had will be discussed at the first visit.
2) Vital signs: Blood pressure, heart rate, and weight will be measured at each visit.
3) Physical examination: The study doctor will then conduct a brief physical examination at each visit, including measuring your blood pressure, looking for swelling in your legs, and listening to your heart and lungs.
4) Blood tests: Approximately 15-20 mL (3-5 tsp) of blood will be drawn from a peripheral vein at each visit. The blood will be analyzed for kidney function, potassium, BNP and NT-pro-BNP.
5) Urine tests: At the first visit you will be asked to provide a urine sample (approximately 10-100 mL) in a cup as well as a 24-hour urine sample. We will measure the amount of protein in that urine sample in the cup. We will give you a jug to pee in for a 24 hour period of time.
6) Extracellular water measurement: This will be obtained by measuring the resistance to a very small painless electric current through your body. Leads will be placed on your hands and feet to measure the resistance. This procedure should take about 30 seconds. This equipment is FDA approved to measure extracellular water in healthy individuals and has been safely used in patients with kidney disease before.
7) Fat free mass and fat mass: These measurements are obtained during the measurement of extracellular water and indicate what percentage of your cells are fat cells.
8) Vascular resistance measurement: Leads will be placed on your chest and neck. Similar to the measurements of extracellular water, this equipment measures the resistance to a small painless electric current in your body. This procedure should take approximately five minutes. This equipment has been safely used in patients with kidney disease.
9) Symptom questionnaires: You will be asked to fill out 3 questionnaires asking about fatigue, depression, and quality of life. If you wish to not provide an answer to any of the questions on the questionnaires you may leave select questions blank and proceed with the rest of the study.
10) Transthoracic echocardiogram: As close as possible to the first visit you will receive a transthoracic echocardiogram. You will lie down on your back and a technician will use an ultrasound to look at pictures of your heart. This takes about 20 minutes.

After undergoing the above listed procedures, a diuretic medicine will either be started or the dose

increased to treat your high blood pressure as would be otherwise appropriate for your clinical care. If you are already taking a diuretic (hydrochlorothiazide, chlorthalidone, furosemide, bumetanide, or torsemide), the dose will be increased. If you are not already taking one of these medicines, you will be started on a low dose of chlorthalidone if your CKD is stage 1, 2, or 3a, or torsemide if your CKD is stage 3b. Diuretic prescriptions will be ordered to be picked up at the Michael E. DeBakey clinical pharmacy window, to be started the day after the first visit.

Study personnel will contact you by phone 2 weeks after your first visit to as you about your home blood pressure measurements and ask about any side effects from the study medicine.

Most of the procedures listed above will take place again at the second study visit approximately 4 weeks after the first visit. The transthoracic echocardiogram will only take place as soon as possible after your first study visit. The measurements (extracellular water, fat free mass and fat mass, vascular resistance, ambulatory blood pressure, transthoracic echocardiogram) and blood and urine lab tests (urine albumin and creatinine levels, kidney function, BNP, NT-pro-BNP) in this study are designed for research, not for medical purposes. They are not useful for finding problems or diseases. Even though the researchers are not looking at this information to find or treat a medical problem, you will be told if they notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment.

Procedures for storing of extra or leftover samples: Blood samples will be obtained from peripheral veins, and you will provide a urine sample. Most of the blood and all of the urine samples will be sent to the Michael E. DeBakey VA laboratory for analysis. Some of the blood samples will be frozen and sent outside the VA for analysis. No additional samples will be collected.

If you decide to participate, your participation would last about 6 weeks.

The study doctors keep your research records private in the same way as your other medical records. No one has access to your records except as required by law. Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. During the course of the study, we will collect private information such as you name, partial social security number, and any medical records contained in the VA computer system including the medications you are taking, your past medical history, and results of your physical examinations, laboratory tests, X-rays, and cardiology tests such as echocardiograms. All paper records will be maintained in a locked cabinet at the Michael E. DeBakey VA Medical Center. All identifiable electronic information will be stored on the VA-secured network. If you have an adverse experience during the course of this study, your entire medical record may be used and disclosed as clinically necessary, as well as pursuant to federal and state laws and regulations.

In accordance with VA guidelines, all records of this research will continue to be securely maintained after completion of the study. If Dr. [redacted] leaves the VA facility, the research records will be retained by the institution.

VHA complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 and all other laws that protect your privacy. We will protect your health data according to these laws. Despite these protections, there is a possibility that your health data could be used or disclosed in a way that it will no longer be protected.

Clinically Relevant Research Results

The results generated from this research study are not expected to have any clinical relevance to you.

Sharing and Future Research Studies with Identifiable Private Information

Your identifiable private information collected as part of this research, even if the identifiers are removed, will not be used or distributed for future research studies.

Sharing and Future Research Studies with Identifiable Biospecimens

Your identifiable biospecimens collected as part of this research, even if the identifiers are removed, will not be used or distributed for future research studies.

Confidentiality

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Specific information concerning HIV
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Partial Social Security # (Last four digits)
- Identifiable biospecimens
- Questionnaire, Survey, and/or subject diary
- Other: Ultrasound images

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

While this study is being conducted you will have access to your research related health records. This will not affect your VA healthcare, including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

Potential Risks and Discomforts

Risks of Increasing or Starting a Diuretic Blood Pressure Medicine: The diuretic blood pressure medicines being used for this study are all commonly prescribed, FDA-approved medicines for the treatment of high blood pressure. Increasing one of these medicines to treat high blood pressure is considered standard of care. These medicines work to lower blood pressure by increasing how much fluid your kidneys remove from the body as urine. Risks of these medicines include worsening kidney function, low blood potassium level, low blood sodium level, low blood pressure, dizziness, falling, or loss of consciousness. Other potential side effects include dry mouth, constipation, headache, muscle cramps, gout, numbness or tingling, feeling thirsty, or nausea. We will check your blood pressure and blood tests at the second visit to check for these problems. Low blood potassium or sodium levels may make you feel weak or confused.

Risks of Extracellular Volume and Vascular Resistance Measurements: A small electric current (maximum 200 microamps) will be introduced into your body. The major risks from this procedure are for patients who 1) are pregnant, or 2) have a cardiac defibrillator or pacemaker. The researchers will ask you questions regarding these risk factors, and you should notify them if these risk factors are present. You will be not be eligible to participate in this study if any of these risk factors are present. There is no discomfort associated with this procedure. There is a risk of skin irritation from the adhesive from the machine that takes these measurements.

Transthoracic Echocardiogram: There is little to no risk associated with transthoracic echocardiograms.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant:
Males: Participating in this study poses no additional risk specific to males.
Females: If you are part of this study while pregnant or breast-feeding an infant, it is possible that you may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding females

cannot participate in the study.

Drawing Blood: There may be some discomfort, bruising, or bleeding at the site where the blood is drawn. Rarely, fainting occurs because of drawing blood.

Questionnaires: Some people become uncomfortable at being asked questions about depression or quality of life; if, for any reason, you wish not to answer specific questions or you wish to terminate the session, you will be able to do so.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: Better control of high blood pressure

Benefits to society: The results of this study could lead to important future studies to incorporate BNP and NT-pro-BNP into risk stratification and individualized diuretic therapy for patients with early-to-moderate stage CKD.. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: Continued care by your regular doctor.

Investigator Withdrawal of Subject from a Study

The investigator or sponsor may decide to stop you from taking part in this study at any time. You could be removed from the study for reasons related only to you (for example, if you move to another city, if you have a pacemaker placed, or if you become pregnant) or because the entire study is stopped. The sponsor, investigator, Food and Drug Administration, or Institutional Review Board may stop the study at any time.

Subject Costs and Payments

You or your insurance will not be responsible for costs related to this research. Neither you nor your insurance will be billed for any costs related to this research.

If you choose to participate, you will be paid $25.00 for each of the two in-person study visits. If you drop out of the study before completing all the study visits, you will be paid for the visits that you completed. If you complete both visits, you will receive a total of $50.00. You will be paid in the form of a Payment will occur by Direct Deposit through the VA Agent Cashier's Office.

Subject Name: _____ **Date:** _____

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Research Related Injury

If you choose to participate and experience one of the risks detailed above related to the clinically indicated starting or dose increase of diuretic medications, your diuretic dose can be decreased to its prior dose or stopped.
Please see the Subjects' Rights section for information on the VA's policies pertaining to medical treatment for research related injuries.

Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, [redacted], and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: [redacted] at [redacted] during the day and [redacted] at [redacted].

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is [redacted]. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

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Under Federal Regulations, the VA Medical facility shall provide necessary medical treatment to you as a research subject injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by the Michael E. DeBakey VA Medical Center. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You do not waive any liability rights for personal injury by signing this form.

You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled. Your participation will not affect the way you now pay for medical care at the VAMC. If you would like to verify the validity of the study and authorized contacts, you may speak with the Michael E. DeBakey Veterans Affairs Medical Center Research Office at [redacted] or [redacted].

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Investigator or Designee Obtaining Consent	Date
Witness	Date