RESEARCH CONSENT FORM

Basic Information

Title of Project: **Dapagliflozin and Vascular Health in Patients with Type 2 Diabetes**

IRB Numer: H-41648
NCT 05139914
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Overview

We are asking you to be in a research study. A research study is an organized way of collecting information about scientific questions. This form will tell you what you should expect if you agree to be in the study. There are programs in place to make sure that investigators fulfill their obligations listed in this form.

It is your decision whether or not to join the study. We are asking you to be in this study because you have type 2 diabetes mellitus. We are doing this research to understand how a type 2 diabetes medication called dapagliflozin impacts blood vessel health. We want to test the function of endothelial cells, which line blood vessels. If you agree, you will be randomly assigned to receive either dapagliflozin or placebo for 6 weeks. Then for two weeks you won't receive any study medication. Then you will receive dapagliflozin or placebo for 6 more weeks. This time it will be the opposite of what you received in the first six week period. We will test your blood vessel health before and after each treatment. During the test of blood vessel health, you may receive nitroglycerin under your tongue. This is a medication that relaxes blood vessels and lasts for about 10 minutes. You will be in the study for 14 weeks if you decide to stay for the whole study. You will find more information about what will happen in this study later in this form.

The main risks of being in the study are discomfort and slight risk of bruising or infection at the puncture site during blood and cell sample collection. Dapagliflozin has several known potential risks. The more frequently reported side effects of dapaglifozin include urinary tract infections, genital yeast infections, low blood sugar, and dehydration. We also use the medication nitroglycerin to measure blood vessel relaxation. Nitroglycerin may cause headache and a low risk of low blood pressure. You will find more information about risks later in this form.

Your doctor may also be an investigator in this research study. Being an investigator means your doctor is interested in both you and the study. Your doctor's goal as an investigator is to collect information to answer the scientific questions asked in this research study, in order to help future patients. This is different from their role as your doctor, where their goal is to treat you as a patient. You may want to

get another opinion about being in the study from a doctor who is not an investigator in this study. You can do so now or at any time during the study. You do not have to agree to be in this study even though it is offered by your doctor.

Purpose

The purpose of this study is to determine whether blood vessel health is different in people who have type 2 diabetes mellitus when treated with dapagliflozin compared to when they are not. The study will help us understand if dapagliflozin has benefits for heart and blood vessel health in people with type 2 diabetes.

What Will Happen in This Research Study

You will be one of approximately 50 subjects asked to participate in this study.

The research will take place at the following location (s): Boston University Medical Campus

The study consists of a screening visit (that may be combined with first study visit) and four study visits to Boston University Medical Campus. Each study visit will last about two hours. You will go through two treatment periods each lasting six weeks. During one period you will take dapagliflozin 10mg per day (1 capsule per day) for six weeks. During the other period, you will take a similar appearing capsule (a "placebo") for six weeks that does not contain dapagliflozin.. There will be a two week period in between the two treatment periods when you take no treatment. The order of treatments (dapagliflozin first or placebo first) will be randomized by a computer (like flipping a coin). Everyone in the study will take real dapagliflozin for half the time. Your study doctors will not know if you are taking the real drug or the placebo. In an emergency your study doctor can find out if you are taking the active drug or placebo.

We will ask you not to eat, drink, or smoke after midnight on the day of the study visits. You are permitted to drink water but not any other beverages (such as tea, coffee, soda) on the day of the study visit.

Screening Visit:
The screening visit will take about 30 minutes. Up to a month before the study, we will interview you and may collect a 10ml (about a tablespoon of blood) to test for your A1C level and/or pregnancy test if applicable, measure your blood pressure, and your height and weight to determine whether you are eligible for the study. In some cases, this visit may be combined with Visit 1.

Visit 1:
This study visit will take about 2 hours. We will measure your heart rate and blood pressure in both arms and legs. We will test the ability of your blood vessels to dilate by performing an ultrasound study of your arm. The ultrasound involves holding a probe on your arm to measure the size of the vessels. We also record the pulse at your fingertips. We will take measurements before and after we inflate a blood pressure cuff on your upper arm for 5 minutes. We will also record your pulse from the neck, arm, and leg using a small probe. We will also record ultrasound images of your blood vessels before and after

you take a dose of nitroglycerin under the tongue. Nitroglycerin is a medicine that relaxes blood vessels and is used for people who have heart problems. If you have a history of migraine headaches, a previous history of an allergy or side effect from nitroglycerin, or are on a medication for erectile dysfunction, we will not perform the nitroglycerin portion of the study.

We will place a soft plastic catheter in a vein in your arm (IV catheter) to collect 75ml (5 tablespoons) of blood. We will then insert a soft J-shaped wire through the same catheter into the vein in your arm and then remove the wire. We will repeat the wire insertion up to five additional times. We have learned that during this process a small number of endothelial cells lining the blood vessel stick to the wires and can be washed off to study under the microscope. The cell and blood collection will be performed by a nurse or a physician and no more than four attempts will be made to collect the cells. We will then repeat the same process to collect endothelial cells (but not additional blood) on your other arm.

We will then provide you with a supply of dapagliflozin or placebo to take at home (one capsule per day, taken with or without food). Dapagliflozin is a medication that is approved to treat people with type 2 diabetes mellitus. We are using it in this study to test its effect on endothelial cells and ability of blood vessels to relax. We will schedule your next visit, which will be in approximately 6 weeks. Please let us know right away whether your doctor makes any changes in your medications during the course of the study and make sure you tell your doctor that you are participating in the research study.

We will call you in 3 weeks to ask about how you are tolerating the Dapagliflozin and to answer any questions that you have.

Visit 2:
We will ask you to bring back your bottle of dapagliflozin/placebo with all remaining pills. We will repeat the study procedures as described in Visit 1, above.

Washout period:
Then you will have approximately a 2 week rest period when you will not take any study treatments.

Visit 3:
We will repeat the study procedures as described in Visit 1, above

We will then provide you with a supply of dapagliflozin or placebo to take at home (one capsule per day) and schedule your next visit, which will be in approximately 6 weeks depending on your schedule. Please let us know right away whether your doctor makes any changes in your medications during the course of the study.

Visit 4:
We will ask you to bring back your bottle of dapagliflozin/placebo with all remaining pills. We will repeat the study procedures as described in Visit 1, above.

The blood samples will be used to measure blood levels of cholesterol, blood sugar, and other markers that may relate to heart disease risk. In addition, we will also save your cells to study whether specific protein levels relate to the function of your arteries. These samples will be labeled with a code number and not your name.

We will collect ribonucleic acid (RNA) from your cells. RNA is a molecule that is in all of your cells and carries information to tell the genes what proteins to make. Measuring the RNA levels will help us better understand links between type 2 diabetes and blood vessel health. We are not studying DNA, which is the molecule in your genes.

Storage of blood and cell samples and data for future research

Permission for storage of study samples for future research. The blood and cell samples will be frozen indefinitely in a locked freezer for future studies of blood vessel health. Study samples that have no identifying information will be released to either a) BU/BMC investigators including those NOT on the research team for this study; b) investigators at external universities; c) industry research partners; d) government research partners. No cell lines will be established. Samples will not be used for genetic testing. Data will also be stored for potential future use. The study team will review requests for use for release of samples from the repository to ensure that research is consistent with the aims of the repository. All unused sample will be required to be returned to the repository. All data will be encrypted and not identified. We will not release any identifiable information with the sample. You can withdraw your permission for long-term storage at any time by calling Dr. Naomi Hamburg at 617-358-1202. You do not have to agree to long-term storage to participate in this study.

Please circle yes, if you agree and no, if you do not agree, to storage of data, blood and cell samples for future research:

Yes No Subject initials:

The ways we will protect your privacy and confidentiality are described in a separate section later in this form.

Test results

- Some research measures that we make are not necessarily the same as tests done by your doctor. We are collecting information on many people to answer our research questions. Not everyone doing the research tests is a doctor or a nurse. You or your doctor should not rely on the research measurements to make any diagnosis, treatment or health planning decisions. If you or your doctor decides that follow-up tests and treatments are necessary, then you or your insurance will be billed for the costs.

  The ultrasound test you will have in this study is for research purposes only. However, we might see something that could be important to your health. If we do, we will ask you if you want us to explain what we noticed. If you would like, we will also tell your doctor. You or your doctor should not rely on the research measurements to make any diagnosis, treatment, or health planning decisions. If you or your doctor decides that follow-up tests and treatments are necessary, then you or your insurance will be billed for the costs.

- The test of blood vessel health we are doing in this study are for research purposes only. We will not tell you the results because it is known whether the results have any meaning for your health.

- We will provide you with results of some of the tests that we do. If we test for your A1C level and/or for pregnancy at screening we will share the results with you. We will let you know if you should follow-up with your doctor.

Risks and Discomforts

Taking blood samples will cause momentary discomfort and on rare occasions fainting. There is a slight chance that a bruise or infection that will develop at the puncture site.

There is a very slight possibility for the J-shaped wire inserted into the vein for endothelial cell collection to malfunction. Because only a very small part of the wire is placed in the vein beyond the plastic catheter and the wire is very gently moved to get the cells, it is extremely rare for a part of the wire to break off and go into the body. In the very rare case that this happens, you might need a procedure to remove the part of the wire that broke off from your body. It could also puncture a blood vessel. We have performed this procedure in over 2500 individuals and never observed any complications regarding the wires. All the J-wires are inspected prior to the procedure and the procedure is performed by a trained and experienced nurse or physician.

Ultrasound has no known risks. During inflation of the blood pressure cuff, you will feel tightness and numbness in the arm and hand. This discomfort will pass within a few seconds after release of the cuff.

The nitroglycerin may cause a headache or a fall in blood pressure. It will be given under the direction of a physician while you are lying down. If you have had problems with this dose of nitroglycerin in the past or if you have an allergy to nitroglycerin, none will be given to you. You should not take nitroglycerin if you have taken Viagra, Cialis, or Levitra within the last 7 days because this could cause a greater drop in your blood pressure.

Dapaglifozin is a medication used for treatment of type 2 diabetes mellitus and improves blood sugar control. The dose being used in this research study is the same as the FDA-approved dose. Dapagliflozin has been described to have a low rate of adverse effects that include:

- Low blood sugar that may be more common if you are taking insulin or sulfonylurea medications
- Dehydration (less than 1 in 100) that can make you feel dizzy or weak
- Genital yeast infections and urinary tract infections in both men and women (1-10%)
- Allergic reaction (<0.1%))
- Nausea
- May be associated with higher rates of bladder cancer (10 in 6045)
- Increase in LDL cholesterol level (1-10%)
- Very rarely a serious infection in the penis or vagina or in the peroneal region called necrotizing fasciitis
- Dizziness or headache (1-10%)
- Very rare with elevated levels of acid in the blood called ketoacidosis

There may be unknown risks/discomforts involved. Study staff will update you in a timely way on any new information that may affect your health, welfare, or decision to stay in this study.

If you get pregnant while you are in this study, it could be bad for the fetus/baby. You must use birth control if you are able to get pregnant and will have sex while you are in this study. Only some birth control methods work well enough to be safe while you are in this study. These methods are oral contraceptives (the pill), intrauterine devices (IUDs), contraceptive implants under the skin, contraceptive rings or patches or injections, diaphragms with spermicide, and condoms with foam. You should not be in this study if you are able to get pregnant and cannot use one of these birth control methods if you have sex.

Potential Benefits

You will receive no direct benefit from being in this study. The primary goal of this research is to collect information about the scientific questions asked in this study. Your being in this study may help the investigators better understand how to optimize treatment of patients with diabetes.

Costs

The study drug will be provided by the Study. There are no costs to you for being in the study. Items and services done only for study purposes will be provided at no cost to you. They won't be billed to your health insurance either.

Payment

You will receive $50 for the screening visit and $200 for each of the 4 study visits, for a total of $850 that will be provided using by check after each study visit. You must give us your Social Security Number or Individual Taxpayer Identification Number to receive this payment.

Confidentiality

We must use information that shows your identity to do this research. Information already collected about you will remain in the study record even if you later withdraw.

We will store your information in ways we think are secure. We will store biological samples taken from your body (such as urine, blood, or cells) in a locked freezer. We will store paper files in locked filing cabinets. We will store electronic files in computer systems with password protection and encryption. Only the people listed later in this section will be given access to your information. However, we cannot guarantee complete confidentiality.

The repository has standard operating procedures to protect your confidentiality. We store biological samples taken from you in a locked freezer in a locked room.

If you agree to be in the study and sign this form, we will share information and biological samples that may show your identity with the following groups of people:

- People who do the research or help oversee the research, including safety monitoring.

- People from Federal and state agencies who audit or review the research, as required by law. Such agencies may include the U.S. Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and the Massachusetts Department of Public Health.
- Any people who you give us separate permission to share your information.

We will share research data where we have removed anything that we think would show your identity. There still may be a small chance that someone could figure out that the information is about you. Such sharing includes:

- Publishing results in a medical book or journal.
- Adding results to a Federal government database.
- Using research data in future studies, done by us or by other scientists.
- Using biological samples in future studies, done by us or by other scientists.
- People who will get your data and your biological samples as we described in the section **What Will Happen in This Research Study**. These people are expected to protect your information and biological samples in the same way we protect it.

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.

Use and Sharing of Your Health Information

The research team has to use and share your health information to do this study, including information that may identify you. By agreeing to be in this study and signing this form, you are giving us your permission where needed to use and share your health information as described in this form.

Health information that might be used or shared during this research includes:

- Information that is in your hospital or office health records. The records we will use or share are those related to the aims, conduct, and monitoring of the research study.
- Health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

The reasons that your health information might be used or shared with others are:

- To do the research described here.
- To make sure we do the research according to certain standards set by ethics, law, and quality groups.
- To comply with laws and regulations. This includes safety-related information.

The people and groups that may use or share your health information are:

- Researchers involved in this research study from Boston Medical Center, Boston University, and/or other organizations
- Other people within Boston Medical Center and Boston University who may need to access your health information to do their jobs such as for treatment, research administration, payment, billing, or health care operations

- People or groups that the researchers use to help conduct the study or to provide oversight for the study
- The Institutional Review Board that oversees the research and other people or groups that are part of the Human Research Protection Program that oversees the research
- Research monitors, reviewers, or accreditation agencies and other people or groups that oversee research information and the safety of the study

We ask anyone who gets your health information from us to protect the privacy of your information. However, we cannot control how they may use or share your health information. We cannot promise that they will keep it completely private.

The time period for using or sharing your health information:

- The time period is not known, because research is an ongoing process. We cannot give you an exact date when we will either destroy or stop using or sharing your health information.

Your privacy rights are:

- You have the right not to sign this form that allows us to use and share your health information for research. If you do not sign this form, you cannot be in the research. This is because we need to use the health information to do the research. Your decision not to sign the form will not affect any treatment, health care, enrollment in health plans, or eligibility for benefits.
- You have the right to withdraw your permission to use or share your health information in this research study. If you want to withdraw your permission, you must write a letter to the Principal Investigator at the address listed on the first page of this form. If you withdraw your permission, you will not be able to take back information that has already been used or shared with others. This includes information used or shared to do the research study or to be sure the research is safe and of high quality. If you withdraw your permission, you cannot continue to be in the study.
- When the study has been completed for everyone, you have the right to request access to the health information that we used or shared to make your treatment or payment decisions. If you ask for research information that is not in your medical record, we might not give it to you, but we will explain why not. You may use the contact information on the first page of this form to find out how to get your health information. You may also contact the HIPAA Privacy Officer at Boston University at HIPAA@BU.EDU.

Compensation for Injury

If you think that you have been injured by being in this study, please let the Principal Investigator know right away. Use the phone number on the first page of this form. If you have a health emergency, get care first. You can seek treatment for the injury at Boston Medical Center or at any healthcare facility you choose. Tell the doctors that you are in this study.

There is no program to provide compensation for the cost of care for research related injury or for other expenses. Other expenses might be lost wages, disability, pain, or discomfort. You or your insurance will be billed for the medical care you receive for a research injury. You are not giving up any of your legal rights by signing this form.

Re-Contact

We would like to ask your permission to contact you again in the future. This contact would be after the study has ended. Please initial your choice below:

____Yes_____No You may contact me again to ask for additional information related to this study

____Yes ____No You may contact me again to ask for additional biological samples related to this study

Yes No You may contact me again to let me know about a different research study

Subject's Rights

By consenting to be in this study you do not waive any of your legal rights. Consenting means that you have been given information about this study and that you agree to participate in the study. You will be given a copy of this form to keep.

If you do not agree to be in this study or if at any time you withdraw from this study you will not suffer any penalty or lose any benefits to which you are entitled. Your participation is completely up to you. Your decision will not affect your ability to get health care or payment for your health care. It will not affect your enrollment in any health plan or benefits you can get. You will only be paid for the study activities that you complete before withdrawing.

During this study, we may find out something that might make you not want to stay in the study. If this happens, we will tell you as soon as possible. You should also tell us if you ever have concerns about being in the study.
We may decide to have you stop being in the study even if you want to stay. Some reasons this could happen are if staying in the study may be bad for you, or if the study is stopped.

Questions

The investigator or a member of the research team will try to answer all of your questions. If you have questions or concerns at any time, contact Dr. Naomi Hamburg at 617-358-1202. Also call if you need to report an injury while being in this research. Contact Dr. Naomi Hamburg at 617-358-1202 if there is no answer at that phone number or if you are calling after normal business hours.

You may also call 617-358-5372 or email medirb@bu.edu. You will be talking to someone at the Boston Medical Center and Boston University Medical Campus IRB. The IRB is a group that helps monitor research. You should call or email the IRB if you want to find out about your rights as a research subject. You should also call or email if you want to talk to someone who is not part of the study about your questions, concerns, or problems.

Subject: _____
Printed name of subject

By signing this consent form, you are indicating that

- you have read this form (or it has been read to you)
- your questions have been answered to your satisfaction
- you voluntarily agree to participate in this research study
- you permit the use and sharing of information that may identify you as described including your health information.

_____
Signature of subject Date

Researcher:
Printed name of person conducting consent discussion

I have personally explained the research to the above-named subject and answered all questions. I believe that the subject understands what is involved in the study and freely agrees to participate.

_____
Signature of person conducting consent discussion Date

To be completed by witness if researcher reads this form to the subject
This consent form was read to and apparently understood by the subject in my presence.

Printed name of witness (a person not otherwise associated with the study)

Signature of witness Date