Official Title: Effects of SGLT-2 Inhibition on Myocardial Fibrosis and Inflammation as Assessed by Cardiac MRI in Patients with DM2

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Research subject Informed Consent Form - v5

Approved by University of Washington Human Subjects Division 01DEC2020

Responsible Party:

Principal Investigator

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UNIVERSITY OF WASHINGTON
CONSENT FORM

Effects of SGLT-2 Inhibition with Dapagliflozin on Myocardial Fibrosis and Inflammation as Assessed by Cardiac MRI with T1 and T2 Mapping in Patients with Type 2 Diabetes

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Susan McKeeth Research Coordinator, Cardiology 206-744-8307

24-hour emergency telephone number - Dr. Zhao – 206-280-6173

Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

PURPOSE OF THE STUDY

We would like you to be part of this study to examine the muscle of your heart. We are asking you to be in this study because you have been diagnosed with Type 2 Diabetes. A number of studies have shown that over time heart muscle cells can become stiff (myocardial fibrosis); this is one of the main reasons for cardiac dysfunction (cardiomyopathy). **The purpose of this study is to look at whether a type of diabetes drug, SGLT-2 inhibitor dapagliflozin, will help keep heart muscle from becoming stiff.** We will use MR imaging before taking the drug and after 1 year of the drug to watch for changes. We plan to enroll at least 60 subjects in this part of the study and will enroll 30 subjects to serve as controls for the research blood samples.

Magnetic resonance imaging (MRI) uses radio waves from a large magnet and the body's response to the radio waves to create pictures of the inside of the body. In this study, we will look at the cells of the heart muscle by using standard MRI and magnetic resonance angiography (MRA). MRA is MRI with a contrast agent used to improve the pictures.

The U.S. Food and Drug Administration (FDA) has approved the contrast and the diabetes drug that will be used in this study.

STUDY PROCEDURES

Over approximately 12 months you will have 2 phone interviews, 6 clinical visits at our research clinic and undergo 2 MRI scans at one of the two UW research imaging centers (either the UW **B**io-**M**olecular **I**maging **C**enter in South Lake Union or the UW **D**iagnostic **I**maging **S**ciences **C**enter at UWMC; **BMIC** or **DISC**). Each center offers the same services; you will be scheduled based on availability. The second scan will occur approximately 12 months after the first scan.

Today's Screening Visit, CARL @ Harborview

The initial screening visit will be at the **C**linical **A**therosclerosis **R**esearch **L**ab (**CARL**); this visit will last about 1 hour. You will be measured for blood pressure, height, weight, body temperature and waist circumference. You will be asked about your current health, medical and surgical history and if you are taking any medicines.

We will conduct a fasting blood draw to collect a small amount of blood (approximately 20mL or 4 teaspoons) to determine your level of kidney function and other relevant laboratories. Fasting is no food or drink beyond water for at least 10 hours. The test for kidney function is called a creatinine test. This test will determine if it is safe to inject the contrast agent into a vein in your arm as part of the MRI. The other lab tests will include a cholesterol panel, fasting glucose, HbA1c as well as safety tests of AST, ALT, CPK and hsCRP which will give us an idea about any liver or heart disease.

Unlike CT scans or X-rays, MRI does not use radiation. Instead, it uses a powerful magnetic field to create images. You will be carefully screened with a series of questions to be sure you do not use or wear devices, implants or materials that could be damaged by the magnet, or cause damage to your body under the influence of the magnet. Examples of questions we will ask you include: Do you have a pacemaker, stents, or aneurysm clips? Have you been hurt by shrapnel? Are you pregnant?

You may refuse to answer any question; however, if the research team is unable to collect the required information to verify your safety in the MRI you will be withdrawn from study participation.

The **Clinic Visit 2** and **Baseline MRI visit** described below may occur in no particular order, or even the same day, to coordinate with MR Scanner availability and research laboratory analysis which requires specialized shared equipment.

Clinic Visit 2 – Baseline Clinic visit, CARL @ Harborview

This is the day of randomization, which will take place only if you meet all of the inclusion requirements. The following procedures will be done:

- Your pulse, blood pressure, weight and body temperature will be measured.
- Fasting blood samples will be taken, (approximately 60mL or 4 tablespoons). Additional plasma will be frozen at -80 degree and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity. This draw will also include extra blood to be used for mitochondrial function assessment.
- If you are a woman of childbearing potential you will provide a urine sample to test for pregnancy.
- You will be asked about your overall health and whether you have had any problems, drug side effects, discomfort or hospitalizations since your last visit.

- You will be asked if you have had any changes in the medicines you take.
- You will start taking study medication.

You will either receive 10mg tabs of dapagliflozin or identical looking placebo – inactive medication. You have an equal chance of receiving dapagliflozin or placebo. Which treatment you receive is decided at random by a computer (purely by chance, like the tossing of a coin). The term "study drug" refers to both dapagliflozin and placebo in this form. Neither you nor the Study Site personnel will know which treatment you have received. After the first dose, the study drug must be taken daily. We will not ask you to make any changes to your other diabetes medications. You will continue on your standard care with the addition of the study drug/placebo. The study drug is yours and should not be taken by anyone else.

Baseline MRI visit, BMIC/DISC - may occur ±14 days from Clinic visit 2 described above
The MRI will last about 1 hour. The MRI Technologist will review your answers to the safety questions and any related medical records to make sure it is safe to proceed. You will be asked to place personal items, such as credit cards, watches, and jewelry in a lock box before you enter the MRI scanner room.
If not completed for the study previously, and you are a woman of childbearing potential you will be asked to provide a urine sample to test for pregnancy.

You will then enter the scanner room. Before the MRI scan begins, a small needle will be inserted into a vein in your arm or hand. This is so that the contrast material can be injected later during the MRI scan. The contrast will improve the pictures of the muscle cells. The MR Technologist will place two ECG leads on your chest, stickers used to measure your heart beat, to "time" the cardiac scan. A "coil" which acts as an antenna will be laid across your chest and held in place with a soft foam strap. Scientists at the University of Washington (UW) have designed the computer program that runs the MRI scanner used for this study.

Throughout the MRI scan you will lie down on a flat movable bench. The MRI magnet has a tube-like opening, and the bench will go into the opening, so that your body will be inside the magnet. During the scan, you will hear a series of loud knocking and banging noises. You will be given earplugs to help quiet the noises. You may speak through a loud speaker to the technologist at any time during the scan. The technologist will let you know when it is best to clear your throat or move. You may be asked to hold your breath for up to 30 seconds when the heart scan is taking place. This will limit the amount of extra movement for the images. Our research staff will follow the U.S. Food and Drug Administration (FDA) established safety guidelines for MRI.

First during the scan you will have images made without contrast. Then during the scan, a small amount of gadolinium-based contrast material is injected. The contrast is Gadavist®and the dose is based on your weight.
You may stop the exam at any time for any reason.

Telephone Interview

Approximately 2 weeks after starting the study drug we will contact you by phone to see how you are doing. The following interview areas will be addressed:

- You will be asked about your overall health and whether you have had any problems, drug side effects, discomfort or hospitalizations since your last visit.
- You will be asked if you have had any changes in the medicines you take.
- You will be asked about taking the study medication and if you have been having any trouble remembering or missed any days.
- If you have had any health problems or adverse reactions to the study medications you will be asked to return to the study clinic for an Unscheduled Visit. You may be instructed to stop the medication until you can be seen by the study team.

3, 6 and 9 month Clinic visits, CARL @ Harborview

We will ask you to return to the clinic for three visits to track any health changes. The following procedures will be done:

- Your pulse, blood pressure, weight and body temperature will be measured.
- Fasting blood samples will be taken, (approximately 20mL or 4 teaspoons).
- You will be asked about your overall health and whether you have had any problems, drug side effects, discomfort or hospitalizations since your last visit.
- You will be asked if you have had any changes in the medicines you take.
- You will return unused study medication and medication bottles, whether they are empty or not, and you will receive a new supply of study medication.

Unscheduled Clinic visit, CARL @ Harborview

If you have a significant clinical event of interest to the study we will ask you to return to the clinic to meet with us and discuss the event and assess any health changes. The following procedures will be done:

- Your pulse, blood pressure, weight and body temperature will be measured.
- Fasting blood samples will be taken, (approximately 20mL or 4 teaspoons).
- You will be asked about your overall health and whether you have had any problems, drug side effects, discomfort or hospitalizations since your last visit.
- You will be asked if you have had any changes in the medicines you take.
- You will return unused study medication and medication bottles, whether they are empty or not, and you will receive a new supply of study medication.

Final Clinic visit, CARL @ Harborview

The following procedures will be done:

- Your pulse, blood pressure, weight and body temperature will be measured.
- Fasting blood samples will be taken, (approximately 70mL or 5 tablespoons). Additional plasma will be frozen at -80 degree and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and

toxicity. This draw will also include extra blood to be used for mitochondrial function assessment.

- You will be asked about your overall health and whether you have had any problems, drug side effects, discomfort or hospitalizations since your last visit.
- You will be asked if you have had any changes in the medicines you take.
- You will return unused study medication and medication bottles, whether they are empty or not.
- You will fill out a new MRI Screening form to ensure no changes have taken place that affect your ability to participate in the MRI.

Final MRI visit, BMIC/DISC - may occur up to 14 days from Final Clinic visit described above

The MRI will last about 1 hour. The MRI Technologist will review your answers to the safety questions and any related medical records to make sure it is safe to proceed. You will then undergo the exact same MRI scan procedure as before.

You may stop the exam at any time for any reason.

Telephone Follow-up Call

We will call you approximately 2-4 weeks after you have completed the final MRI to again ask if you have had any health changes since stopping the study. This brief (about 15 min) phone call will mark the end of the study.

In total the study will take approximately 8 hours of your time over the year and daily study medication compliance. The blood tests described above will require approximately 20-70mL each time, a total of approximately 210mL which is about 1 cup.

Study Visit Summary Table:	**CARL @ Harborview**				**BMIC *or* DISC**
	Consent, MRI Safety Screening, medical history	Study drug dispensing	Health event & side effect assessment	Vital signs, blood sample	Review MRI Safety and complete MRI Scan
Screening Visit, Today	Yes			Yes	
Baseline		Yes	Yes	Yes	
1st MRI visit					Yes
Telephone Interview			Yes		
3, 6 and 9 Month visits		Yes	Yes	Yes	
Final Clinic			Yes	Yes	
Final MRI					Yes
Telephone Follow-up call			Yes		
Unscheduled Clinic Visit *(only if necessary)*		Yes	Yes	Yes	

Your contact information will be retained by the study team. This is so we may ask you for additional information or medical record access that is not currently part of the approved study. For example, it may someday be scientifically valuable to send you a mailing or attempt a phone interview to ask about your health status and any clinical events after the final MRI scan visit.

RISKS, STRESS, OR DISCOMFORT

MRI: There are no known side effects associated with magnetic resonance imaging. However, having an MRI may mean some added discomfort for you. You may feel claustrophobic ("closed in") when in the scanner. Lying still for up to 60 minutes may be uncomfortable. The MRI machine is loud; you may find the noise unpleasant. This is why we will ask you to wear earplugs, which are provided. Because some coils can focus energy into a small part of the body, there is a remote chance you may feel warmth in some area of your body. If this occurs, please tell us immediately.

You and your primary care physician will be notified if the Investigators identify a potentially clinically significant finding during image review. However, this study and MRI images are for research purposes only and are not clinical procedures. Further clinical confirmation, evaluation and treatment plans will be left to you and your physician(s). Additionally, although more than one individual will be reading the images it is still possible that a finding not related to heart muscle may be missed and the reviewers are not board-certified Radiologists therefore it may be the case that there are findings even if they are not identified by the reviewers.

MAGNET: Because the MRI machine acts like a large magnet, it could move objects containing iron in the MRI room during your examination, which could possibly harm you. We will take precautions to prevent this from happening. Loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

CONTRAST MATERIAL (GADOLINIUM): The contrast material that will be used during the MRI study, Gadavist®, is a gadolinium agent that has been approved by the FDA. The specific amount of contrast you receive will depend on your body weight. As with any drug, there may be unanticipated side effects. Some of the most frequent adverse events that have been reported during previous clinical use are nausea, headache, dizziness, metallic taste, warmth and tingling (occurred in less than 3% of patients). Allergic responses including difficulty breathing, faster heart beats, or severe nausea has been reported in less than 1% of patients. The small needle used to inject contrast might cause redness or bruising at the site of the injection. Throughout the MRI a physician is on-call and available to provide care, if necessary.

Nephrogenic Systemic Fibrosis (NSF): In a very small percentage of patients who already have impaired kidney function, gadolinium-based contrast medium has been shown to cause a new disease, called nephrogenic systemic fibrosis, or nephrogenic fibrosing dermopathy (NSF/NFD).

NSF is a debilitating and potentially fatal disease that involves the skin, muscle and internal organs. This condition occurs exclusively in those who already have impaired kidney function. Only subjects with acceptable renal function (eGFR≥50) will be recruited for this study. If at your first visit your blood test reveals an impaired kidney function (eGFR<50) you will be withdrawn from the study and no MRI will take place, this will mark the end of your study participation. If at one of the follow-up visits your blood test reveals an impaired kidney function (eGFR<45) the MRI scan can be safely performed **without** using the gadolinium-based contrast. As described, we will test your blood before each scan to assess your renal function.

The FDA has issued a safety communication indicating that gadolinium may be retained in the body long-term. The risks of this retention are unknown. To date, we have not seen any evidence that these small amounts of gadolinium cause health problems. If there are any new findings, we will revise our guidelines for using gadolinium injections.

BLOOD SAMPLE: Each blood sample may cause the usual small discomfort and possible bruise at the site of needle puncture.

PREGNANCY: This study does not include pregnant women. If you are a woman of childbearing potential you will be asked to provide a urine sample for a pregnancy test prior to enrollment. If you do not provide the sample you will be withdrawn from the study. If you are a woman of childbearing potential you must be willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator, from the time of signing the informed consent until two weeks after the last dose of study drug.

STUDY DRUG Farxiga® (dapagliflozin): Dapagliflozin works by eliminating sugar (glucose) from the body to help with blood sugar control in patients with Type 2 Diabetes. The glucose is eliminated in the urine. The drug can sometimes eliminate up to about 70 grams of glucose per day, this may result in rapid weight loss and/or tiredness. The glucose can act as diuretic causing frequent urination and could lead to dehydration or hypotension (low blood pressure). Symptomatic hypotension can occur after starting dapagliflozin particularly in patients with lowered kidney function (eGFR less than 60), patients aged 70 or above, or patients on loop diuretics (such as furosemide, bumetanide, torsemide, or ethacrynic acid). The increased amount of glucose in the urine can also increase the risk for and worsen the infections already associated with diabetes, particularly urinary tract infections and female genital fungal infections (like a yeast infection). Dapagliflozin has also been associated with an increase incidence of nasopharyngitis, which is swelling of the nasal passages and the back of the throat often experienced with the common cold and possibly leading to sinus infection.
Especially when added to other diabetic mediations, Dapagliflozin can lower blood sugar causing hypoglycemia with symptoms of shaking, sweating, fast heartbeat, dizziness, hunger, headache, and/or irritability. Hypoglycemia would require immediate treatment with taking in sugary food or drink and then checking your blood sugar. Make sure that you discuss with your care provider what to do if you have these symptoms.

The FDA has warned of rare but serious infection of the genitals and area around the genitals being reported with this class of drug. This infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. Although rare, we ask that you seek medical attention immediately if you experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell. These symptoms can worsen quickly, so it is important to seek treatment right away.

Only subjects with acceptable renal function (eGFR≥50) will be recruited for this study. Dapagliflozin is approved for eGFR of 45 or higher. If at your first visit your blood test reveals an impaired kidney function (eGFR<50) you will be withdrawn from the study and, this will mark the end of your study participation. If at one of the follow-up visits your blood test reveals an impaired kidney function (eGFR<45) the study drug will be discontinued and you will be asked to return for an unscheduled visit to ensure your kidney function returns to your baseline level. As described, we will test your blood before randomization and again at each visit to assess your renal function. Studies have shown an increased risk of bone fractures in subjects with an eGFR between 30 and 60 mL/min/1.73m2 (compared to those receiving placebo).

Elevated LDL cholesterol (3%) is an infrequent adverse effect of dapagliflozin. Rare and serious adverse effects include hypersensitivity reactions (0.3% may develop any of these symptoms: hives, itching, shortness of breath, skin rash, and swelling of the mouth, lips, and tongue), ketoacidosis (0.3%), acute kidney injury (as a result of untreated, severe dehydration), and increased risk of bladder cancer.

Ketoacidosis is a serious condition that can lead to hospitalization and death. If you have symptoms of nausea, tiredness, vomiting, trouble breathing, and abdominal pain, call your care provider immediately. They may check your blood or urine for ketones and stop your study drug if positive.

Should these or any other adverse effects from the medication occur, please contact the study team and/or your doctor as soon as possible for treatment options.

ALTERNATIVES TO TAKING PART IN THIS STUDY

The alternative to this study is not to participate. All medications used in our study are approved by the FDA and available with a prescription from a physician.

BENEFITS OF THE STUDY

You will not receive any medical benefits from taking part in the study. This study is for research only. This study is not meant to treat, diagnose, or prevent any disease. However, your participation may help future patients with Type 2 Diabetes and heart disease.

SOURCE OF FUNDING

The study team and the University of Washington is receiving financial support and the study drug from AstraZeneca.

CONFIDENTIALITY OF RESEARCH INFORMATION

We will collect data for this study in a confidential manner. Your identity will remain confidential. Your data will be given a unique code to protect your privacy. The study coordinator will keep a document with your name, phone numbers, and the name and phone number of your doctor. This is so that we can contact you or your doctor if needed. The results from this study will be used in scientific reports and presented at scientific meetings. They will not contain any information identifying you. We may use the images and study information for future studies. The images and information will not contain any information identifying you.

If you agree to take part in this study, we will access and review your medical records. Records will be accessed to confirm your eligibility including information about your Diabetes diagnosis and treatment and any implants or operations that may exclude you from participating for safety reasons. We may review hospital discharge summaries, radiology records, your medical history, operative reports (about an operation), and other records needed to verify MR compatibility of any foreign bodies and your Diabetes diagnosis.

Dr. Zhao and her staff will have access to this information. They will have access to other information resulting from this study. If we cannot locate your records, we may contact you to help us find their location.

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

The following people or groups may see information that identifies you as a participant in this study:

- Members of Dr. Zhao's research team
- The University of Washington Institutional Review Board
- State and Federal regulators

All data and samples collected, but without personal history information (name, date of birth, address, etc.) will be kept indefinitely so that they may be used in future studies.

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.
Your participation in this study will be noted in your UW medical record.

OTHER INFORMATION

You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled.
We may remove you from the study if you are found to be ineligible. This could be due to medical record review, or laboratory or study visit evaluation at any of the visits, or if we cannot be certain that it is safe for you to participate.

You may not take another SGLT2 Inhibitor class drug as this is a safety concern (drugs like canagliflozin (Invokana), empagliflozin (Jardiance) and ertugliflozin (Steglatro) work the same way). You also may not take any other investigational drug. If your physician requires one of these medications we will withdraw you from further study participation. Please be sure to contact the study team if you have any questions about new prescriptions from your physician and if they may conflict with the study.

It will not cost you anything to be in this study. You will receive a payment for taking part in this research study. To cover travel costs and your time, you will receive $65 for each MRI scan visit and $20 for each clinic visit. You will receive up to $210 for the scheduled visits. If you have any extra clinic visit(s) you may receive $20 for each visit. You will receive the $65 for the MRI visit whether or not you finish the scan. Payment will be sent by mail to the address you provide.

We offer parking validation for subjects who park in one of Harborview Medical Center's parking lots and at the MRI Facility. Directions to these validated lots will be provided.

Neither you nor your insurance company will be charged for the following items:

- Study drug
- Study procedures
- Study visits
- Study laboratory tests

We will share the fasting glucose and HbA1c research results with you or your physician(s). Results can be sent by mail to the address you have provided. To ensure timely and correct delivery please promptly let us know of any address changes.

RESEARCH-RELATED INJURY

If you think you have a medical problem or illness related to this research, contact **Dr. Zhao, at 206-280-6173** right away. She will refer you for treatment.

It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call her at the number(s) listed at the top of this form. This number is monitored 24 hours a day.

For a life-threatening problem, call 911 right away or seek help immediately. Contact **Dr. Zhao, at 206-744-8308** when the medical emergency is over or as soon as you can.

The costs of the treatment may be billed to you or your health insurance just like other medical costs, or it may be covered by the UW's discretionary Human Subjects Assistance Program (HSAP), depending on a number of factors. The researcher may request HSAP coverage by following established procedures. If you wish to request HSAP coverage yourself, contact the researcher or the UW Human Subjects Division at hsdinfo@uw.edu or 206-543-0098. You may also call collect to the UW Human Subjects Division at 206-221-5940 if you do not otherwise have access to a telephone. Ask the researcher if you would like information about the limits and conditions of the HSAP. The UW does not normally provide any other form of compensation for injury. However, the law may allow you to seek payment for injury-related expenses if they are caused by malpractice or the fault of the researchers. You do not waive any right to seek payment by signing this consent form. We will bill your health insurance for treating problems that result from your Type 2 Diabetes or from standard clinical care. If you have no health insurance or your insurance refuses to pay, we will bill you.

Printed name of study staff obtaining consent	Signature	Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed on the first page of this consent form. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098 or call collect at (206) 221-5940. I will receive a copy of this consent form.

Printed name of subject	Signature of subject	Date

Copies to: Researcher & Subject