VUMC Institutional Review Board
Informed Consent Document for Research

Study Title: **Mechanism(s) Underlying Cardiovascular Effects of ARB/NEP Inhibition – Aim 2**
Date: **11/17/22**
PI: **Lynne Stevenson, MD**

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

What is the purpose of this study?
You are being asked to take part in this research study because you have heart failure. We want to find out if bradykinin, a chemical that occurs naturally in our bodies and helps control blood pressure, affects how a heart failure medication called Entresto (sacubitril/valsartan) works on blood pressure, urine production, and the excretion of sodium in the urine. To do this, we will measure the effect of Entresto on blood pressure, urine production, and the excretion of sodium while you are receiving a drug that blocks the effects of bradykinin, called icatibant, versus while you are receiving a placebo (blank). We will use a drug called PAH to measure the blood flow to your kidney, and a drug called iohexol to measure kidney function. Understanding how this chemical affects the body's response to Entresto may help us better understand how to treat heart failure without causing side effects. About 80 people will take part in this study.

If you decide to take part in this study, you will be taken off your regular medication and be given a study medication. You will have a screening visit and 4 study visits over about 7 weeks. You will be asked to collect your urine on four different days. Study days will involve having blood draws, giving urine samples, having blood pressure measured, being given other study medications, and lying down for several hours during the study day.

If you are a woman who could become pregnant, we will ask for a urine sample for a pregnancy test on each study day. If you are pregnant, you will not be allowed to be in the study.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:
Inconveniences
- Not eating or drinking after midnight on the night before each study

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- Collecting all your urine in a jug for 24 hours for 4 days
- Traveling to the CRC and picking up your medications

Risks of the Catheters
Putting a catheter into your vein may cause bleeding, bruising, or infection (uncommon). We will use careful and sterile techniques to minimize these side effects

Entresto
Rarely (~1/1000 people) Entresto may cause swelling of your face, lips, tongue, and throat (angioedema) that, if severe and not treated, could cause trouble breathing and death. Get emergency medical help right away if you have symptoms of angioedema or trouble breathing. Do not take Entresto again if you have had angioedema while taking Entresto. People of African descent who take Entresto may have a higher risk of having angioedema than people who are not of African descent and take Entresto. People who have had angioedema before may have a higher risk of having angioedema than people who have not had angioedema and will be excluded from the study. For people who have tolerated an ACE inhibitor such as enalapril before, the risk of angioedema is lower.

Entresto can cause high potassium, changes in kidney function, and low blood pressure. Low blood pressure may cause you to feel light-headed. Call your doctor if you become dizzy or lightheaded, or you develop extreme fatigue.

During a study with 27-month treatment with Entresto, 2.2% of patients developed a decline in kidney function. In this study you will receive Entresto for 6 ½ weeks. For this reason, the risk of any decrease in kidney function is unlikely. We will monitor for it, and should we see a change in kidney function, we will reduce the dose of the study medication. If you do not tolerate the lower dose, we will stop the study.

Please also notify your research study team if you develop cough or rash or other signs of allergic reactions while taking the study medications, especially if you have had these side effects in the past on ACE inhibitor or ARB medications.

Firazyr
When given under the skin Firazyr can cause irritation. We have not observed this when we give it intravenously. At doses up to four times higher than the dose given in this study, Firazyr caused abnormalities of liver tests in 4/100 patients (uncommon).

Iohexol

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Iohexol can cause kidney injury when given at higher doses or to patients who have certain diseases affecting the kidney such as multiple myeloma. We will not study you if you have multiple myeloma. Rarely (~1/2,891 patients) iohexol can cause a hypersensitivity (allergic type) reaction. If this happens, we will give you drugs to block the reaction and stop the study immediately. If you have a history of allergy to contrast or to shellfish, we will not give you iohexol.

Para-aminohippurate (PAH)
The side effects of PAH may include flushing, tingling, nausea, vomiting, warmth, desire to move your bowels or urinate (uncommon); or flushing and abdominal pain (rare).

Heart Medicines
Because we are replacing your usual ACE inhibitor or ARB with study drug during the study periods, we do not anticipate a change in your heart failure. Should you notice a change in symptoms including increased fatigue, shortness of breath, and swelling, please contact the research nurse, Tricia Wright, R.N. at 615-322-8837.

If you cannot reach the research staff, please page Dr. Stevenson at 615-835-7267. The study will be stopped, and you will be restarted on your regular medicines.

Risks that are not known:
There may be risks that we do not know about at this time.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study: We may learn more about how to treat heart failure.

Procedures to be followed:
Screening Visit
If you decide to take part in the study, you will come to the Vanderbilt Clinical Research Center (CRC). We will ask you about your medical history. You will have a complete physical. We will take your blood (about 4 teaspoons) to check that you are healthy enough to participate.

If your physical and bloodwork show that you are eligible to continue with the study, we will ask you to stop taking your ACE inhibitor or angiotensin receptor blocker (ARB) if you are taking one of these medications.

Beginning the next morning and again four days later, we will ask you to collect all the urine you make for 24 hours in jugs that we will provide for you.

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Study Day 1
You will come to the CRC in the morning two days after you stopped taking your ACE inhibitor or ARB, having had nothing to eat or drink since midnight. We will ask you to empty your bladder, and we will weigh you. Then we will ask you to lie down. You will remain lying down except to use the bathroom until the end of the study day.

We will put a small tube in the vein of each arm – one to give you medicine and one to take blood.

We will place a cuff on your arm to measure your blood pressure and heart rate every 5 minutes for the rest of the study day. After this, you will rest for at least 30 minutes.

We will begin to give you the drugs para-aminohippurate (PAH) and iohexol through the tube in your arm. PAH is investigational, meaning not approved by the FDA.

Ninety minutes later, we will take a blood sample (two teaspoons). We will then give you a pill of Entresto to take by mouth with a small amount of water. Entresto is a drug approved by the Food and Drug Administration to treat heart failure. At the same time, we will begin giving you either a medication called Firazyr, a drug that is FDA approved to treat swelling caused by drugs that increase the chemical bradykinin, or a small amount of saline (salt water) through the tube in your vein. Neither you nor the study doctors will know which you are getting, but we can find out if there is a need.

This medication will continue for one hour. We will continue to measure your heart rate and blood pressure for 6 hours after we start the medication. We will collect urine and blood (1 tablespoon) at 1, 2, 4, and 6 hours from the start of the IV medication. Before the 4-hour blood draw, we will have you stand so we can check your blood pressure and heart rate while you are standing. We will take a total of 7 tablespoons of blood during each study day.

You will then be finished with the study day.

Study Day 2
Four days later, you will again come to the CRC in the morning, having had nothing to eat or drink after midnight. All the procedures will be the same as for Study Day 1. The only difference will be the medication you are given in the vein. You will get either Firazyr or saline, whichever you did not get on Study Day 1.

You will then be finished with the study day.

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We will give you Entresto to take twice daily for the next 2 weeks. We will give you a blood pressure cuff and tell you how to monitor your blood pressure at home. We will have you take your blood pressure every day. If the top number is below 85 or you have symptoms of low blood pressure such as light-headedness, we will stop the Entresto.

At the end of the 2 weeks, we will have you come to the CRC for measurement of your blood pressure and blood potassium and creatinine. If these are within range, we will give you a higher dose of Entresto to take twice daily for the next 3 weeks. If it looks like increasing the dose will reduce your blood pressure too much or increase your potassium and creatinine too much, we will instead continue the original dose. We will again have you check your blood pressure during these three weeks to make sure it does not get too low.

At the end of the 3 weeks, we will have you come to the CRC for measurement of your blood pressure and blood potassium and creatinine. If these are within range, we will give you a third dose of Entresto to take for the next 10 days. Alternatively, we will continue the dose you were already taking.

After you have been taking the highest dose of Entresto you can tolerate for 7 days, and again three days later, we will ask you begin to collect all the urine you produce for 24 hours in jugs that we will provide for you.

Study Day 3
You will come to the CRC in the morning after the first 24-hour urine collection, having had nothing to eat or drink since midnight. We will ask you to empty your bladder, and we will weigh you. Then we will ask you to lie down. You will remain lying down until the end of the study day.

We will put a small tube in the vein of each arm – one to give you medicine and one to take blood.

We will place a cuff on your arm to measure your blood pressure and heart rate every 5 minutes for the rest of the study. After this, you will rest for at least 30 minutes.

We will begin to give you para-aminohippurate (PAH) and iohexol through the tube in your arm.

Ninety minutes later, we will take a blood sample (two teaspoons). We will then give you a pill of Entresto to take by mouth with a small amount of water. Entresto is a drug approved by the Food and Drug Administration to treat heart failure and under study for the treatment of blood pressure. At the same time, we will begin giving you either a medication called Firazyr, a drug that is FDA approved to

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treat swelling caused by drugs that increase the chemical bradykinin, or a small amount of saline (salt water) through the tube in your vein. Neither you nor the study doctors will know which you are getting, but we can find out if there is a need.

This medication will continue for one hour. We will continue to measure your heart rate and blood pressure for 6 hours after we start the medication. We will collect urine and blood (1 tablespoon) at 1, 2, 4, and 6 hours from the start of the IV medication.

You will then be finished with the study day.

Study Day 4
On morning after the second 24-hour urine collection, you will again come to the CRC in the morning, having had nothing to eat or drink after midnight. All the procedures will be the same as for Study Day 3. The only difference will be the medication you are giving in the vein. You will get either Firazyr or saline, whichever you did not get on Study Day 3.

You will then be finished with the study. After the study, you will continue to take Entresto at the highest tolerated dose.

Your samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, and/or others. If this happens, there are no plans to provide money to you.

Payments for your time spent taking part in this study or expenses:
If you complete the entire study, you will be paid $1,200 for your time. If you do not complete the study, you will be paid $300 for each study day that you complete.

We may ask you for your Social Security number and address before you are compensated for taking part in this study. You may receive up to $1,200 for taking part in this study. This amount may be taxable and will be reported to the Internal Revenue Service (IRS).

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Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt [or the Sponsor] to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Lynne Stevenson at **615-936-8187**. If you cannot reach the research staff, please page the study doctor at615-835-8325.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:

You may be removed from this study without your consent if:

- Staying in the study would be harmful to you
- You no longer meet the requirements of the study
- The study is stopped.

If you are removed from the study, you will be told the reason.

What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

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Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Confidentiality:
All efforts, within reason, will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. Information that could identify you will be kept in a locked cabinet or a password-protected computer and your samples and data will be coded. Only members of Dr. Stevenson's study team will have access to this information.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Stevenson and her staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

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Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you. Indicate if the research will include whole genome sequencing (human germline or somatic specimen with the intent to generate genome or exome sequencing).

Study Results:
At the end of the study, we will publish a paper in a medical journal, summarizing the final results. If you would like, we will send you a copy of the paper that is published.

Authorization to Use/Disclose Protected Health Information

What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this authorization?
You do not have to sign this authorization, but if you do not, you may not join the study.

How long will your information be used or shared?

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Your authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this authorization at any time. If you cancel, you must contact the principal investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

You have the right to see and copy the PHI we gather on you for as long as the study doctor or research site holds this data. To ensure the scientific quality of the research study, you will not be able to review some of your research data until after the research study is finished.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____

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Printed Name and Title

Time: _____

Consent for Genetic Research

The purpose of part of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood sample for genetic research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results.

A single blood sample will be taken at the same time we are taking blood for your lab tests. This will not take any extra time.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Stevenson and members of her study team will have access to your name.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Your sample will be used to make DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples and information about you may be shared with others to use for research. To protect your privacy, we will not release your name.

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You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for gene research.

At any time, you may ask to have your sample destroyed. You should contact Dr. Stevenson at

Dr. Lynne Stevenson
Vanderbilt Heart
1215 21st Ave South, 5th floor
Suite 5037
Nashville, TN 37232

to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples.

Please check Yes or No to the questions below:

My blood/tissue sample may be used for gene research in this study.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research in heart failure.

☐ Yes ☐ No

My blood/tissue sample may be stored/shared for future gene research for other health problems (such as cancer, heart disease, etc).

☐ Yes ☐ No

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