VUMC Institutional Review Board
Informed Consent Document for Research

Study Title:	The Impact of Factor Xa Inhibition on Thrombosis, Platelet Activation, and Endothelial Function in Peripheral Artery Disease
Version Date:	06/10/25
PI:	Aaron Aday, MD, MSc

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.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:

The purpose of this study is to understand how the drug rivaroxaban improves outcomes among patients with peripheral artery disease (PAD). If you decide to be part of this study, you will have 3 total study visits. The screening visit will take about an hour, and the 2 additional study visits will take about 3 hours each. You will need to come fasting for both of the study visits. For this study you will be taking two FDA approved drugs, aspirin and rivaroxaban. You will be given aspirin to take once a day, and receive placebo or rivaroxaban to take twice daily. The primary risk associated with these medications is the increased risk of bleeding. The combination of rivaroxaban plus aspirin has been shown to reduce cardiovascular disease, stroke, and leg amputations in patients with PAD comparted to aspirin alone. As part of this study you will receive aspirin plus placebo for 1 month rather than the FDA-approved combination of both drugs, which may increase your risk for the above mentioned complications of your disease and/or for death.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you have peripheral artery disease.

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

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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:
Fasting: inconvenience and low fluid status in the body are both side effects of fasting. To minimize this risk, please drink plenty of water the day before the visits. Also, there is a potential risk of hypoglycemia (low blood sugar) while fasting. Signs of hypoglycemia include dizziness, lightheadedness, extreme sweating, and extreme hunger. Please let us know if you experience any of these symptoms.
Blood samples, IV placement, and wire insertion (for endothelial cell collection): You may feel bothered or pained from the needle stick or wire insertion. You may have a bruise, or rarely, the site may get infected. It is rare, but some people faint. Drawing blood from your arm may cause pain, bruising, lightheadedness and rarely, infection.
Flow mediated dilation: Subjects will feel some local discomfort when the cuff is applied. Some subjects may feel continued, mild muscle soreness afterwards (the delayed muscle soreness is temporary and should resolve within 1-2 days).
Drug Interaction: For your safety, you must tell the study doctor or research staff about all the drugs you are taking, including over-the-counter drugs and herbals, before you start the study and before taking any new drugs while you are on the study.
Aspirin: the most common side effect is an increased risk of bleeding,
Nitroglycerin: can lead to hypotension (low blood pressure), headache, dizziness, nausea, vomiting
Rivaroxaban: the most common side effect is an increased risk of bleeding

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: The combination of aspirin and low-dose rivaroxaban have been shown to reduce death from cardiovascular disease, stroke, and leg amputations. Although the length of the study may be too short to see a significant reduction in these risks, patients may receive some benefit from this medication.
The proposed study will provide a better understanding of the wide range of effects of low-dose rivaroxaban in patients with atherosclerotic disease. Specifically, it will provide information about the different biologic pathways impacted by this drug regimen. A better understanding of these pathways

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may serve as the basis of clinical trials of more targeted therapies in patients with atherosclerotic disease and, in particular, peripheral artery disease.

Procedures to be followed:

Screening Visit
During this visit, we will tell you about the study, have you sign the consent form, and perform tests and procedures to see if you qualify to take part in this research study. This visit will take approximately 1 hour.

At this visit, we will:

- Ask about your medical history and medications
- Conduct a physical examination, including measurement of height, weight, waist size, hip size and "vital signs" (blood pressure, heart rate, respiratory rate, and oxygen saturation).
- If you are a woman of childbearing potential, you will be asked to take a urine pregnancy test to confirm you are not pregnant.
- Draw a blood sample of about 4.5 mL to test your kidney function
- Perform an ankle-brachial index
  This test is done by measuring blood pressure at the ankles and in the arms while a person is at rest. The ankle-brachial index (ABI) result is used to determine the severity of PAD.
- You will receive a pill bottle with aspirin 81mg tablets. You will also be provided with a pill bottle containing either rivaroxaban tablets or matched placebo. You will have a 1 in 2 chance of receiving placebo (like flipping a coin). You will take your medication (or placebo) twice daily for 30 days. Neither you nor the doctor will know if you are receiving the actual drug or the placebo. In case of emergency, the study doctor can get this information for you.

Phone Call
48 – 72 hours after beginning the medication, study staff will contact you by phone to see if you are having any side effects.

Study Visit 1
You will be asked to return for an additional visit approximately one month after your screening visit. This visit will take approximately 3 hours. We ask that you not eat or drink anything (other than water) for at least 6 hours before your visit.

At this visit, we will:

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- Review changes in your medications
- Review any medical events that happened since your last visit
- Conduct a limited physical examination
- Flow-mediated dilation (FMD)
  Brachial artery diameter is first measured at rest. Then a blood pressure cuff will be placed around your upper arm and inflated until blood flow stops temporarily. The blood pressure cuff will be inflated for 5 minutes. Repeat brachial artery measurements are recorded one minute after the cuff is deflated. The measurements will be repeated at rest and after you are given a sublingual nitroglycerin tablet.
- Perform an ankle-brachial index
  This test is done by measuring blood pressure at the ankles and in the arms while a person is at rest. The ankle-brachial index (ABI) result is used to predict the severity of peripheral arterial disease.
- You will receive a pill bottle with aspirin 81mg tablet. You will also be provided with a pill bottle containing either rivaroxaban tablets or matched placebo. You will take your medication (or placebo) twice daily for 30 days. If you received placebo the first time, you will be given rivaroxaban. Those that were given rivaroxaban will receive placebo. Neither you nor the doctor will know if you are receiving the actual drug or the placebo.
- Draw a fasting blood sample of about 33 mL for lab testing
- Fill out a Walking Impairment Questionnaire

At this visit, we may:

- Perform endothelial cell sample collection
  A thin, short plastic tube may be placed into a vein (an 'IV') in the forearm. Then a sterile, thin wire would be put through the IV and into the vein about 4 inches. The wire would be moved up and down for about 30 seconds. We would then take the wire and IV out.

Phone Call

48 – 72 hours after beginning the medication, study staff will contact you by phone to see if you are having any side effects.

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Study Visit 2

You will be asked to return for an additional visit approximately one month after Study Visit 1. This visit will take approximately 3 hours. We ask that you not eat or drink anything (other than water) for at least 6 hours before your visit.

At this visit, we will:

- Review changes in your medications
- Review any medical events that happened since your last visit
- Conduct a limited physical examination
- Flow-mediated dilation (FMD)
  Brachial artery diameter is first measured at rest. Then a blood pressure cuff will be placed around your upper arm and inflated until blood flow stops temporarily. The blood pressure cuff will be inflated for 5 minutes. Repeat brachial artery measurements are recorded one minute after the cuff is deflated. The measurements will be repeated at rest and after you are given a sublingual nitroglycerin tablet.
- Perform an ankle-brachial index
  This test is done by measuring blood pressure at the ankles and in the arms while a person is at rest. The ankle-brachial index (ABI) result is used to predict the severity of peripheral arterial disease.
- Draw a fasting blood sample of about 33 mL for lab testing
- Fill out a Walking Impairment Questionnaire

At this visit, we may:

- Perform endothelial cell sample collection
  A thin, short plastic tube may be placed into a vein (an 'IV') in the forearm. Then a sterile, thin wire would be put through the IV and into the vein about 4 inches. The wire would be moved up and down for about 30 seconds. We would then take the wire and IV out.

Payments for your time spent taking part in this study or expenses:

You will receive $125 when you complete each study visit, excluding the screening, for a possible total of $250. This compensation is meant to help cover the costs of time and travel.

Costs to you if you take part in this study:

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

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If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

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 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 **Aaron Aday, MD** at **615-322-2318** or his research coordinator, **Caroline Crush at 615-322-5000.** If you cannot reach the research staff, please page the study doctor at **615-835-9311**.

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:
The study doctor may remove you from this study for any justified reason. Examples why you may have to stop some or all study-related activities, including study treatment are:

- Staying in the study would be harmful
- You need other treatment

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- You become pregnant
- You fail to follow instructions
- The study is cancelled

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.

Clinical Trials Registry:
A description of this clinical trial is available on www.clinicaltrials.gov (NCT05009862), 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 at this following link: https://clinicaltrials.gov/ct2/show/NCT05009862

Confidentiality:
Your study records and data will be stored in a secure database. The database will reside in a password protected secure web site supported by Vanderbilt. Only study personnel will have access to the database. Information in the database that will identify you will only be available to study personnel.

Your biological samples will be stored with a barcode. This barcode will not include any identifying information. Only study staff will have access to these barcodes. A list will be kept by study staff that will be able to link your barcode to your identifying information. Only study staff will have access to your identifying 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.

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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.

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. The research done on your samples will include RNA sequencing.

Study Results:
Your individual test results will not be shared with you. Results of this study will not be shared with participants.

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.

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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?
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.

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.

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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

_____ _____
Time Printed Name and Title

Consent for endothelial cell sample:

I agree to the optional endothelial sample that may be collected.

☐ Yes ☐ No

Signature: _____ Date: _____

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Consent for Genetic Research

The purpose of this study is to look at RNA and how it may affect health and disease. RNA is part of the instruction manual for your body and may help tell how individuals will respond to treatment.

You are being asked to give a sample of blood 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 of 2 tablespoons will be drawn from a vein in your arm using a needle.* This will take about *5 minutes* of your time.

Blood samples – You may feel bothered or pained from the needle stick. You may have a bruise or the site may get infected. It is rare, but some people faint.

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. Aday and designated research staff 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 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 may be used to make new products, tests or findings. 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.

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.

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.

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Date of Expiration: 09/09/2026

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At any time, you may ask to have your sample destroyed. You should contact Dr. Aday in writing to have your sample destroyed and no longer used for research. His mailing address is:
Dr. Aaron Aday
2525 West End Ave.
Suite 300
Nashville, TN 37203

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. You will not be paid for the use of 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 cardiovascular disease.

☐ 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

Signature: _____ Date: _____

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