IRB APPROVED
AS MODIFIED
May 06, 2019

UF Institutional Review Board
UNIVERSITY of FLORIDA

University of Florida – Jacksonville

SUBJECT INFORMATION AND CONSENT FORM

TITLE: Pharmacodynamic effects of low-dose rivaroxaban in combination with antiplatelet therapies in patients with coronary and peripheral artery disease manifestations

PROTOCOL NO.: None
WIRB® Protocol #20180155
NCT03718429

SPONSOR: University of Florida

FUNDING: Janssen Scientific Affairs, LLC

INVESTIGATOR: Dominick J. Angiolillo, MD, PhD
655 West 8th Street
Jacksonville, Florida 32209
United States

STUDY-RELATED PHONE NUMBER(S): Dominick J. Angiolillo, MD, PhD
904-244-3933
904-244-0411 (24 hours)

Name of person seeking your consent: _____

Place of employment & position: _____

Name of Participant ("Study Subject")

_____

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

WHAT WILL BE DONE AS PART OF YOUR NORMAL CLINICAL CARE (EVEN IF YOU DID NOT PARTICIPATE IN THIS RESEARCH STUDY)?
If you choose not to participate in this study, you will be treated and followed by your primary care team per normal standard of care.

WHY IS THIS RESEARCH STUDY BEING DONE?
You are being asked to participate in this study because you have coronary artery disease or peripheral artery disease and you are taking blood thinning (antiplatelet) medications such as aspirin alone or in combination with either clopidogrel (Plavix) or ticagrelor (Brilinta). You may also be asked to participate in this study if you have atrial fibrillation and are currently being treated with 20mg of rivaroxaban (Xarelto). You must be informed so you can decide whether you want to participate.

Platelets are parts of your blood that stick together to help form a clot. The stickier your platelets are, the greater your chances of having heart attacks or strokes. Platelets from patients with heart disease tend to stick together more, increasing the risk of having further heart attacks or stroke. To prevent a heart attack, there are antiplatelet drugs (blood thinners) to keep your platelets from sticking together. Clopidogrel (Plavix®) and Ticagrelor (Brilinta) are two of the antiplatelet drugs used in the treatment of patients with artery disease like yours and is typically used in association with baby aspirin. Moreover, it is not uncommon that patients who had a heart attack or received a stent also have cardiac arrhythmias, such as atrial fibrillation, and receive an anticoagulant (which is also a blood thinner). The most common anticoagulant is warfarin and it helps to prevent clots from forming. However, treatment with aspirin plus clopidogrel and warfarin is associated with increased risk of bleeding. Another anticoagulant, called rivaroxaban (Xarelto), has been approved by the U.S. Food and Drug Administration (FDA) for use in place of warfarin, however the dose being used in this study is investigational. Rivaroxaban is able to reduce stroke as good as warfarin but it causes less bleeding. However, the effects on platelets of adding rivaroxaban to patients already taking aspirin and clopidogrel or ticagrelor is unknown.

The purpose of this study is to evaluate the effects of very low dose rivaroxaban used in combination with aspirin alone or with clopidogrel or ticagrelor (on a background of aspirin). In particular, subjects participating in this study will have a very low dose of rivaroxaban (2.5mg) added to their drug therapy regimen for 7-10 days. After 7-10 days the aspirin will be dropped. Afterwards you will receive your standard-of-care therapy. Patients taking rivaroxaban alone for atrial fibrillation will also be enrolled but will not receive any additional treatment.

The dose in which rivaroxaban is being used in this research has not been approved by the FDA. Moreover, patients taking part in this study do not have a clinical indication to be on rivaroxaban and its use is investigational.

HOW MANY PEOPLE ARE EXPECTED TO TAKE PART IN THIS RESEARCH STUDY?
Up to 80 people are expected to take part in this study.

HOW LONG WILL YOU BE IN THIS RESEARCH STUDY?
If you are eligible, you will be expected to take part in the research for up to 30 days.

WHO CAN PARTICIPATE IN THIS STUDY?
Your study doctor will determine if you are able to participate in this research study. Please feel free to ask the study doctor about the study requirements for participation.

WHAT WILL BE DONE ONLY BECAUSE YOU ARE IN THIS RESEARCH STUDY?
Your study doctor will fully explain the study, other possible treatments, and any known or possible side effects of participating in this study. If you consent to participate in this study, your study doctor will collect data from your medical records. You will be evaluated to see if you meet criteria to enter into the research protocol. If you are a woman of childbearing potential, a pregnancy test will be done prior to taking any study medication. If you are found to be pregnant, you will not be randomized and your participation in this study will end.

At the screening visit, if results from blood tests performed in the last 90 days are not available, blood will be collected for determination of complete blood count and renal function. After undergoing screening, if you are eligible to participate, you will come for a total of 3 visits and a total of 1 blood draw per visit. Approximately 20 cc (or one tablespoon) of blood will be collected at each visit from you by inserting a needle directly into your vein or from a catheter in your vein. Baseline platelet function tests (while you are taking your standard of care medications) will be done to see how sticky your platelets are.

After this baseline visit, you will have a very low dose of rivaroxaban 2.5 mg added. If you are currently taking 20mg of rivaroxaban for atrial fibrillation you will just have a one-time baseline blood draw and your participation will be completed. No changes to your medications will take place. During the first phase of the study, you will continue treatment for 7-10 days and then you will be asked to come to our clinical site in the morning, 12±4 hours after the last dose of rivaroxaban, to re-assess how sticky your platelets are. After completing this first phase you will start immediately the second phase of the study.

During this second phase, you will stop taking aspirin. Therefore, if your standard of care medication was aspirin alone, you will be taking rivaroxaban alone. If your standard of care medication was aspirin plus either clopidogrel or ticagrelor, you will be taking clopidogrel or ticagrelor and rivaroxaban. After approximately 7-10 days you will be asked to return to our clinical site in the morning, 12±4 hours after the last dose of rivaroxaban, to perform the last blood draw. After this blood draw, the study will be over and you will resume your standard of care therapy as instructed by your treating physician.

Most of your blood samples will be processed immediately. However, others will need to be stored and processed after the end of the study. Only laboratory staff will have access to these samples and your identity will be protected.

WHAT ARE THE POSSIBLE DISCOMFORTS AND RISKS?
Your study doctor will be responsible for reviewing and monitoring your well-being.

The following are potential risks:

i. Blood drawing. There is the discomfort of blood drawing and you may experience bruising, and/or bleeding where the needle is inserted. Occasionally some people become dizzy or feel faint.

ii. Since rivaroxaban is a blood thinner, it may make it more difficult for you to form blood clots that prevent you from bleeding too much. Therefore, there is a risk of bleeding from anywhere in your body whether or not you have a cut or injury. This may include bleeding that you can see like bruising (black and blue marks), or dark stool, or bleeding that you cannot see, like a low blood cell count. Bleeding signs may also include weakness, pallor (paleness or whitish skin color), dizziness, headache, chest pain or angina, shortness of breath, low blood pressure, or unexplained swelling. Bleeding if severe, may require transfusion. Bleeding from rivaroxaban is rarely fatal (seen in less frequently than 0.1%; less than 1 out of 1000 patients).

The following terms are used to describe how often side effects have been seen in patients:

- **Very common**: Means that it affects 1 in 10 or more patients (10% or more)
- **Common**: Means that it affects between 1 and 10 in 100 patients (between 1% and 10%)
- **Uncommon:** Means that affects between 1 and 10 in 1,000 patients (between 0.1% and 1%)
- **Rare**: Means that it affects between 1 and 10 in 10,000 patients (less than 0.1%)

COMMON: Seen in 1% (1 in 100 patients) to 10% (1 in 10 patients)
Internal bleedings which may occur in your stomach and intestines may result in a low blood count (anemia) or decrease in your blood pressure (hypotension). Other common bleeding sites include eye bleeds, bleeding from your gums, nose bleeds, dark urine, heavy menstrual bleedings, hematomas (collection of blood) on the skin and small bleeds under the skin, coughing up blood, bleedings from wounds and after surgical procedures.

- Abdominal and stomach pains
- Upset stomach
- Nausea
- Constipation
- Diarrhea
- Vomiting
- Fever
- Swelling (edema; swelling caused by a fluid build-up in the body)
- Decreased general strength and energy
- Bruises
- Some enzyme levels in blood may increase (such as liver enzymes called transaminases)
- Pain in limbs (arm or leg pain)
- Dizziness (feeling dizzy)
- Headache
- Kidney problems*
- Itching
- Rash (skin rash)

*this was observed after major orthopedic surgery of the lower limbs

UNCOMMON: Seen in 0.1 % (1 in 1,000 patients) to 1% (1 in 100 patients):

- Increased platelet count (increased number of platelets in your blood)
- Increase heart rate
- Dry mouth

- Feeling unwell
- Allergic reactions and skin allergic reactions
- Wound oozing
- Some enzyme levels in blood may increase (i.e. lipase, amylase, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl transpeptidase and bilirubin**)**
- Bleeding into your joints (intraarticular bleeding or hemarthrosis)
- Brain bleeding or intracranial bleeding (especially in patients with high blood pressure and the elderly)
- Fainting (syncope)
- Hives (urticaria)

RARE: Seen in less than 0.1% (less than 1 in 1,000 patients):

- Localized swelling
- Yellow skin (jaundice; liver problems that causes yellowing of the skin or eyes)
- Blood collection outside an arterial wall (vascular pseudoaneurysm)
- Elevation of bilirubin in the blood (break down blood product), with or without an elevation of a liver enzyme called alanine aminotransferase
- Hematomas (collection of blood) or bleeds in the muscle tissue

After marketing authorization, the following side effects for rivaroxaban have been reported. Their frequency cannot be estimated from post approval experience.

- Angioedema and allergic edema (swelling of the face, lips, mouth, tongue or throat)
- Cholestatis (decreased bile flow), hepatitis including hepatocellular injury (inflamed liver, including liver injury)
- Thrombocytopenia (low number of platelets which are cells that help blood to clot)

Rivaroxaban is not recommended for you if a doctor has told you that you have a severe form of antiphospholipid syndrome, a disease which can cause blood clots. Please discuss with your doctor if you have been told that you have this condition.

As rivaroxaban is still being studied in new indications, there may be side effects which are not yet known. It is important that you tell the study staff about any discomforts and health issues you may have during the study since these could be side effects of the study drug. If you have ever had an allergic reaction to rivaroxaban, you should not enroll in the study.

Sometimes during a study, the sponsor may learn new facts about the study drug. It is possible that this information might make you change your mind about being in the study. If new information is discovered your study doctor will tell you about it right away.

Tell your doctors or dentist that you are in a study and taking a blood thinner. This is very important if you have any planned or emergency surgery, dental procedures, or other procedures such as a colonoscopy.

Risks of antiplatelet therapies (Ticagrelor and Clopidogrel):

- Dyspnea (shortness of breath)
- Headache
- Cough
- Atrial fibrillation
- Mild to moderate diarrhea
- Nausea
- Hypotension (low blood pressure)
- Hypertension
- Dizziness
- Non-cardiac chest pain
- Back Pain
- Fatigue
- Cardiac (heart) chest pain

Risks of aspirin therapy:

- bruising,
- gastric irritation, and
- hypersensitivity reactions.

General Risk of Bleeding

- Medications that restrict platelet function including aspirin, ticagrelor and clopidogrel increase the risk of bleeding. Ticagrelor increased the overall risk of bleeding slightly more than clopidogrel.

If you are a woman:

- The risks of rivaroxaban to the human embryo, fetus, or breastfed infant are unknown. Use of rivaroxaban during pregnancy could cause serious bleeding resulting in emergency delivery
- You cannot take part in this study if you are pregnant or breastfeeding a child
- You must agree not to become pregnant while you are in this study
- If you are heterosexually active and able to get pregnant you must use birth control during the study. The type of birth control you use must be discussed with the study doctor before you begin the study. The study doctor must approve the method you use before you can enter the study
- If you get pregnant during the study, you must tell the study doctor immediately. You will have to stop taking the study drug. The study doctor will advise you about your medical care and will ask you to allow him/her to collect information about your pregnancy, your delivery and the health of your baby

If you are a man:

- If your partner becomes pregnant in the time between when you start taking the study drug until your last dose of study drug, you must tell the study doctor immediately. The sponsor may ask you and your partner to allow them to collect information about her pregnancy, delivery, and the health of the baby

i. You have the theoretically increased risk of forming a clot from stopping your aspirin.
ii. **Loss of confidentiality**.

To protect you from above concerns:
i. The blood tests will be drawn by experienced personnel.
ii. Patients who are known to have bleeding problems will not participate in this study to reduce this risk.
iii. The data will be stored as secured coded access.

This study may include risks that are unknown at this time.

Taking part in more than one research study or project may further increase the risks to you. If you are currently enrolled or have recently taken part in another research study, you must tell the person reviewing this consent form with you.

Throughout the study, the researchers will notify you of new information that may become available and might affect your decision to remain in the study.

If you wish to discuss the information above or any discomforts you may experience, you may ask questions now or call the Principal Investigator or contact person listed on the front page of this form.

WHAT ARE THE POSSIBLE BENEFITS TO YOU?
Participation in this study will not help to improve your condition. It is also possible that your condition may worsen. There is no guarantee that you will personally benefit by participating in this research study.

HOW COULD OTHERS POSSIBLY BENEFIT FROM THIS RESEARCH STUDY?
Your participation in this study may help the investigators to learn more about the effects of administering rivaroxaban (Xarelto) in addition to clopidogrel/ticagrelor with and without aspirin, or aspirin alone, and may help other people in the future.

HOW COULD THE RESEARCHERS BENEFIT FROM THIS RESEARCH STUDY?
The sponsor is paying the University of Florida for conducting this research study. In general, presenting research results helps the career of a scientist. Therefore, the study doctor may benefit if the results of this study are presented at scientific meetings or in scientific journals.

CONFLICT OF INTEREST
Dr. Angiolillo is a paid consultant for Bayer pharmaceuticals the maker of rivaroxaban (Xarelto) which is used in the study. Jannsen co-markets the drug and is funding the study. Please feel free to ask any questions you may have about this matter.

IF YOU CHOOSE TO TAKE PART IN THIS STUDY, WILL IT COST YOU ANYTHING?

The Sponsor will pay for the medical services that you receive as part of your participation in this study which are described in the section of the consent form headed by the question "What Will Be Done Only Because You Are In This Research Study". This may include some medical services that you would have received if you were not in this study. All other medical services will be billed to you or your insurance company. You will be responsible for paying any deductible, co-insurance, or co-payments for those services, and for any non-covered or out-of-network services. Some insurance companies may not cover costs associated with research studies. Please contact your insurance company for additional information.

WILL YOU BE PAID FOR TAKING PART IN THIS RESEARCH STUDY?

You will be paid $30.00 in Visa debit cards for each completed study visit to help cover time and travel. It may take up to 48 hours to process your debit card. If you do not complete all of your visits you will be paid for the visits that were completed.

If you are paid more than $75 for taking part in this study, your name and social security number will be reported to the appropriate University employees for purposes of making and recording the payment as required by law. You are responsible for paying income taxes on any payments provided by the study. Payments to nonresident aliens must be processed through the University of Florida Payroll and Tax Services department. If the payments total $600 or more in a calendar year, the University must report the amount you received to the Internal Revenue Service (IRS). The IRS is not provided with the study name or its purpose. If you have questions about the collection and use of your Social Security Number, please visit: http://privacy.ufl.edu/SSNPrivacy.html.

Your payment for participation in this research study is handled through the University of Florida's Human Subject Payment (HSP) Program. Your information which will include your name, address, date of birth, and SSN (depending on amount of money you are paid) is protected. Access to the (HSP) Program site is limited to certain staff with the assigned security role. You will be randomly assigned a specific identification (ID) number to protect your identity.

The study team will provide you with an informational form called the Prepaid Card Facts document. If you have any problems regarding your payment call the HSP Office (352) 392-9057.

WHAT IF YOU ARE INJURED BECAUSE OF THE RESEARCH STUDY?

The Principal Investigator will determine whether your injury is related to your participation in this study.

If you are injured as a direct result of your participation in this study, only professional medical care that you receive at the University of Florida Health Science Center will be provided without charge. Hospital expenses will be billed to you or your insurance.

You will be responsible for any deductible, co-insurance, or co-payments. Some insurance companies may not cover costs associated with research studies. Please contact your insurance company for additional information.

No additional compensation is routinely offered.

The Principal Investigator and others involved in this study may be University of Florida employees. As employees of the University, they are protected under state law, which limits financial recovery for negligence.

Please contact the Principal Investigator Dominick J. Angiolillo M.D. at (904) 244-3933 weekdays between the hours of 8:00 a.m. and 5:00 p.m., after regular business hours, you may call (904) 244-0411 if you experience an injury or have questions about any discomforts that you experience while participating in this study.

WHAT OTHER CHOICES DO YOU HAVE IF YOU DO NOT WANT TO BE IN THIS RESEARCH STUDY?
If you choose not to participate in this study, you will still continue receiving your medical care just as you normally do.

Aspirin, clopidogrel, ticagerol, and rivaroxaban are all marketed drugs. You might be able to receive the rivaroxaban as add-on treatment without being in this study.

DO YOU HAVE TO BE IN THIS STUDY?
Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

If you leave this study for any reason, please contact Dominick J. Angiolillo, M.D., Ph.D. at 904-244-3933 or 904-244-0411 (24 hours). They will tell you how to stop your participation safely.

CAN YOU BE WITHDRAWN FROM THIS RESEARCH STUDY?
The FDA, your study doctor, your local institution, has the right to stop your participation in the study, or cancel the study, without your consent at any time. Your study doctor may take you off the study at any time for any of the following reasons:

- if he/she decides it is in your best interest.
- if you do not consent to continue in the study after being told of changes in the research that may affect you;
- or for any reason.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

If you agree to participate in this study, the study doctor will create, collect, and use private information about you and your health. This information is called protected health information or PHI. In order to do this, the study doctor needs your authorization. The following section describes what PHI will be collected, used and shared, how it will be collected, used, and shared, who will collect, use or share it, who will have access to it, how it will be secured, and what your rights are to revoke this authorization.

Your protected health information may be collected, used, and shared with others to determine if you can participate in the study, and then as part of your participation in the study. This information can be gathered from you or your past, current or future health records, from procedures such as physical examinations, x-rays, blood or urine tests or from other procedures or tests. This information will be created by receiving study treatments or participating in study procedures, or from your study visits and telephone calls. More specifically, the following information may be collected, used, and shared with others:

- Complete past medical history to determine eligibility criteria
- Records of physical exams
- Laboratory, x-ray, MRI, and other test results
- Records about study medications or drugs

This information will be stored in locked filing cabinets or in computers with security passwords.

Some of the information collected could be included in a "limited data set" to be used for other research purposes. If so, the limited data set will include only information that does not directly identify you. For example, the limited data set cannot include your name, address, telephone number, social security number, or any other photographs, numbers, codes, or so forth that link you to the information in the limited data set. If limited data sets are created and used, agreements between the parties creating and receiving the limited data set are required in order to protect your identity and confidentiality and privacy.

Your PHI may be collected, used, and shared with others to make sure you can participate in the research, throughout your participation in the research, and to evaluate the results of the research study. More specifically, your PHI may be collected, used, and shared with others for the following study-related purpose(s):

- to determine the effectiveness of the study drug in treating coronary or peripheral artery disease and atrial fibrillation
- to evaluate a possible new use for the study drug

Once this information is collected, it becomes part of the research record for this study.

Only certain people have the legal right to collect, use and share your research records, and they will protect the privacy and security of these records to the extent the law allows. These people include:

- the study doctor, and research staff associated with this project
- other professionals at the University of Florida or Shands Hospital that provide study-related treatment or procedures
- The University of Florida Institutional Review Board

Your PHI may be shared with:

- the study sponsor University of Florida.
- United States and foreign governmental agencies who are responsible for overseeing research, such as the Food and Drug Administration, the Department of Health and Human Services, and the Office of Human Research Protections
- Government agencies who are responsible for overseeing public health concerns such as the Centers for Disease Control and federal, state and local health departments
- Western Institutional Review Board
- Your insurance company for purposes of obtaining payment

Otherwise, your research records will not be released without your permission unless required by law or a court order. It is possible that once this information is shared with authorized persons, it could be shared by the persons or agencies who receive it and it would no longer be protected by the federal medical privacy law.

Your PHI will be used and shared with others until the end of study.

This information will be destroyed 2 years after research is conducted or longer per University of Florida and/or FDA requirements.

You may not be allowed to see or copy certain information in your medical records collected in connection with your participation with this study while the research is in progress if the research includes treatment. When the research study is completed you will have access to inspect or copy your records with certain exceptions under applicable law.

You are not required to sign this consent and authorization or allow researchers to collect, use and share your PHI. Your refusal to sign will not affect your treatment, payment, enrollment, or eligibility for any benefits outside this research study. However, you cannot participate in this research unless you allow the collection, use and sharing of your protected health information by signing this consent and authorization.

You have the right to review and copy your protected health information. However, we can make this available only after the study is finished.

You can revoke your authorization at any time before, during, or after your participation in this study. If you revoke it, no new information will be collected about you. However, information that was already collected may still be used and shared with others if the researchers have relied on it to complete the research. You can revoke your authorization by giving a written request with your signature on it to the study doctor.

Your withdrawal must be made in writing and sent to Dominick J. Angiolillo, M.D. Ph.D., 655 West 8th Street, Jacksonville, Florida 32209.

NEW INFORMATION ON THE STUDY DRUG
You will be informed about any new information, such as adverse reactions (side effects) that could affect your decision to continue in this study. You may be asked to sign a new consent form if that should occur.

WHAT IF I BECOME PREGNANT DURING THE STUDY?
If you are pregnant or nursing before you enroll in the study, you may not participate in the study.

WHERE CAN I FIND INFORMATION ABOUT THE STUDY?
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.

WHO WOULD YOU CALL IF YOU HAVE ANY QUESTIONS?
If you have questions about the study, please ask us before signing this form. If you require further general information regarding the research study, if at any time you feel you have had a research-related injury or reaction to the study drug, or if you have questions, concerns or complaints about the research please contact:

Dominick J. Angiolillo, M.D., Ph.D. at 904-244-3933 or 904-244-0411 (24 hours).

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

or

The University of Florida in Jacksonville at (904) 244-9478.

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

CONSENT TO PARTICIPATE IN THIS RESEARCH STUDY

I have been informed about this study's purpose, procedures, possible benefits and risks. I have also been told alternatives to being in the study and how my protected health information will be collected, used, and shared with others. I have been given the opportunity to ask questions. My questions have all been answered satisfactorily. I agree to be in this research study. I have received a copy of this form.

By signing this consent form, I have not given up any of my legal rights.

I authorize the release of my medical records for research or regulatory purposes to those agencies listed under the Authorization section of this consent form.

Name of Participant (Print) Date

Signature of Participant

As an investigator or the investigator's representative, I have explained to the participant the purpose, the procedures, the possible benefits, and the risks of this research study, the alternative to being in the study; and how the subject's protected health information will be collected, used, and shared with others:

Printed name of person conducting informed consent discussion Position

Signature of person conducting informed consent discussion Date