Official Title: A Randomized Comparison of Platelet Inhibition Using a Low Maintenance Dose Ticagrelor Regimen Versus Standard Dose Clopidogrel in Diabetes Mellitus Patients Without Prior Major Cardiovascular Events Undergoing Elective Percutaneous Coronary Intervention: The OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus)-6 Study

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WIRB®

RESEARCH SUBJECT INFORMATION AND CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

TITLE:	A Randomized Comparison of Platelet Inhibition Using a Low Maintenance Dose Ticagrelor Regimen versus Standard Dose Clopidogrel in Diabetes Mellitus Patients without Prior Major Cardiovascular Events Undergoing Elective Percutaneous Coronary Intervention: The OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus)-6 Study
PROTOCOL NO.:	optvi_version3 WIRB® Protocol #20180124
SPONSOR:	University of Florida
FUNDING:	AstraZeneca
INVESTIGATOR:	Dominick J. Angiolillo, M.D., Ph.D. 655 W 8th St Jacksonville, Florida 32209 United States
SITE:	University of Florida Health Science Center / Jacksonville 655 W. 8th St Jacksonville, Florida 32209 United States
STUDY-RELATED PHONE NUMBERS:	Dominick J. Angiolillo, M.D., Ph.D. 904-244-3378 904-244-0411 (24 hours)

Name of person seeking your consent:_____

Place of employment & position:_____

Name of Participant ("Study Subject")

_____

Introduction

You are being asked to take part in a research study. Before you decide if you want to take part, it is important for you to understand the following:

- Why the research is being done
- How your information will be used
- What the study will involve, and
- The possible benefits, risks and discomforts to you.

Please take time to read the following information carefully and discuss it with your family doctor, if you wish. If you are in any other study receiving another study drug, you cannot take part in this study. If you do not sign this consent form, you cannot take part in this study.

Information about this study is made available on public websites around the world in accordance with AstraZeneca public commitment to transparency of the clinical research and with applicable law.

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.

Information on AstraZeneca-sponsored, new and ongoing clinical studies and results from these studies are also provided on http://www.astrazenecaclinicaltrials.com/.

Your study doctor is a researcher for this study. As a researcher, he is interested both in your health and how this study is carried out. The study doctor is receiving funding from AstraZeneca (the company paying for the study or 'the study sponsor') to carry out this study. You do not have to take part in any research study offered by any doctor. Whether or not you choose to take part in this study, you will still receive the medical care you already have been receiving. You may ask for a second opinion about your care at any time. You can get this opinion from a doctor who is not connected with this study.

The Western Institutional Review Board® (WIRB®) has approved the information in this consent document and has given approval for the study doctor to do the study. The Western Institutional Review Board® (WIRB®) is a group of people who perform independent review of research. This does not mean that WIRB has approved your participation in the study. You must think about the information in this consent document for yourself. You must then decide if you want to be in the study.

Read this information carefully and please ask the study doctor or the study staff if you have any questions.

Why is this research being done?

You are being asked to participate in a research study. The purpose of this consent form is to give you information about the study including its purpose, procedures, benefits, and risks. You should take part in the study only if you want to do so. You may refuse to take part in or withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled.

You are being asked to take part in this research study because you have diabetes and you are undergoing diagnostic angiography to define whether you have blockages in the arteries of the heart (known as coronary artery disease) that may require treatment with a balloon and a stent (also known as Percutaneous Coronary Intervention or PCI). If you undergo PCI, you will be asked to take either ticagrelor (BRILINTA™) or clopidogrel during this study. Ticagrelor and clopidogrel are routinely used in patients undergoing PCI, the choice of which is at the discretion of the treating physician. However, if you participate in this study, you will be randomly assigned (like a flip of a coin) to receive ticagrelor or clopidogrel.

The primary purpose of this study is to measure how sticky your platelets are at different time points after receiving ticagrelor or clopidogrel. This is the part of the research study that is under investigation. In particular, platelets are a type of blood cells. When you have a cut or break in your skin, platelets have an important job of traveling to the area and forming a clot or scab to stop the bleeding. The stickier your platelets are, the greater your chances of having heart attacks, strokes, or clots in your stents. Platelets from patients with diabetes tend to stick together more, increasing the risk of having further heart attacks or strokes. To prevent these, there are antiplatelet drugs (blood thinners) to keep your platelets from sticking together. Clopidogrel and ticagrelor are among the most common blood thinners used in the treatment of patients with coronary artery disease and are both approved by the U.S. Food and Drug Administration (FDA) for patients with unstable angina and acute coronary syndrome. However, it has been shown that platelets from patients with diabetes treated with clopidogrel still continue to stick together more than they should. On the contrary, ticagrelor is more effective for at least the first twelve months following acute coronary syndrome in preventing platelets from sticking together. Two maintenance doses of ticagrelor have been approved by the FDA. A higher dose (90 mg twice/day) is commonly used during the first year in patients undergoing PCI because of a heart attack, while a lower dose (60 mg twice/day) is commonly used once patients with heart attacks are more stable, in particular one year following when patients experienced a heart attack. In these more stable patients it is has been shown that the two doses of ticagrelor have very similar effects in preventing platelets from sticking together. Therefore, it has been suggested that the lower dose may be of potential value in stable patients (e.g., who never had a heart attack) with diabetes who undergo PCI. Preliminary studies, which have also included patients with diabetes, have already supported the feasibility of doing this and have also shown the lower dose of ticagrelor to be more effective than clopidogrel in preventing platelets from sticking together. In this study the goal is to investigate the effects of the low dose ticagrelor with standard dose clopidogrel exclusively in stable patients with diabetes undergoing PCI. Their use in this study is investigational.

How many people are expected to take part in this research study?

The study will include about 50 randomized subjects. Half of the subjects (25) will receive clopidogrel and the other half (25) will receive ticagrelor.

How long will you be in this research study?

You will be participating in the study for up to 33 days.

What will be done as part of your normal clinical care (even if you did not participate in this research study)?

You will undergo a diagnostic coronary angiography and receive a PCI if necessary. If you undergo PCI, you will receive a blood thinner (commonly clopidogrel or ticagrelor) in addition to aspirin. You will also receive an initial dose of aspirin (loading dose) that will be higher than the maintenance dose, if this has not been done, or if you are not already on aspirin every day, followed by a daily maintenance dose of aspirin 81mg. The loading dose of aspirin administered is 325 mg.

What will be done only because you are in this research study?

Once you have signed this consent form, you will be assigned a unique number to help protect your identity and personal health information. By participating in this study, you are agreeing to allow the study sponsor, its representatives, and the study manager to collect information about your health and treatment. Information about you will be reported directly from your study doctor to the research study personnel.

If you agree to participate in this study, your medical records will be reviewed and your information will be recorded onto case report forms for scientific, medical, and other research purposes. Depending on your study doctor's/institution's requirements, copies of the study forms may be included in your medical record. Your study doctor will use this information about you to complete this research.

Study Visits

The first visit with your study doctor, also known as the **Screening Visit**, will start with your study doctor and/or the study staff explaining the study to you. During this visit, you will receive a copy of this Research Subject Information Consent-Authorization Form, and you will be allowed to ask your study doctor any questions that you might have. You are welcome to take this form home to think about whether or not you want to participate. If you decide to participate in this study, you will need to sign this form at your study doctor's office. Your study doctor or an authorized study representative will sign this form as well. You will receive a signed copy of this form.

Once you have signed this form, your study doctor will perform a physical exam as well as check things like your heart rate, respiration rate, blood pressure, and body temperature. Your study doctor will also take a blood sample from you (about one half tablespoon of blood) to test for routine blood levels. If you are a woman, you may need to take a pregnancy blood test. Your study doctor may ask you some questions about your health during your exam, including asking you about your health history and any medications you are taking.

If you meet the requirements to be in the study, you will need to see your study doctor again to begin your treatment. This is known as the **Randomization/First Dose visit** and will occur at the time of coronary angiography. You will be randomly assigned to take either ticagrelor or clopidogrel, along with aspirin. If you are randomized to receive clopidogrel, you will receive a 600 mg loading dose followed by 75 mg daily dose and your daily 81 mg aspirin. If you are randomized to receive ticagrelor, you will receive a 180 mg loading dose followed by a 60 mg twice a day dose and your 81 mg aspirin. You will take the first dose of study drug in the

catheterization laboratory after the diagnostic angiography procedure is performed. After the diagnostic angiography procedure is over and it has been determined that a PCI is necessary as your standard of care, you will take either 180 mg of ticagrelor or 600 mg clopidogrel. If you are assigned to ticagrelor, you will start taking 60 mg of ticagrelor twice daily starting 12 hours after the first dose. If you are assigned to clopidogrel, you will start taking 75 mg of clopidogrel once daily starting 24 hours after the first dose.

You will be taking the assigned study medication for up to 33 days. You will need to provide blood samples on the first two days. This may happen more than once per day, depending on the study visit day. You will have blood samples taken up to 8 hours after the first dose administration. You will be asked to come to our clinical site after 30±3 days from your PCI in the morning, before your morning dose of clopidogrel or ticagrelor, to re-assess how sticky your platelets are. After this blood draw, the study will be over and you will resume your standard of care therapy as instructed by your treating physician.

During your study participation, blood samples will be taken from you at different times:

- Before angiography (screening):
    - A total of 15 mL of blood (about 1 tablespoon) may be collected at the screening visit

- After angiography/randomization:
    - 30 ml of blood (about 2 tablespoons) will be drawn from you before you take your study drug for the day to measure your platelet response to the study drug
    - 30 ml of blood (about 2 tablespoons) will be drawn from you 0.5 hours after you take the study drug to measure your platelet response to the study drug
    - 30 ml of blood (about 2 tablespoons) will be drawn from you at the end of the PCI procedure to measure your platelet response to the study drug
    - 30 ml of blood (about 2 tablespoons) will be drawn from you 2 hours after the PCI procedure to measure your platelet response to the study drug
    - 30 ml of blood (about 2 tablespoons) will be drawn from you 8 hours after the PCI procedure to measure your platelet response to the study drug
    - 30 ml of blood (about 2 tablespoons) will be drawn from you 24 hours after the PCI procedure to measure your platelet response to the study drug before taking your dose of medication
    - 30 ml of blood (about 2 tablespoons) will be drawn from you 24 hours after the PCI procedure to measure your platelet response to the study drug 2 hours after taking your dose of medication
    - 30 ml of blood (about 2 tablespoons) will be drawn from you at 30 days after the PCI procedure to measure your platelet response to the study drug before taking your morning dose of medication
    - 30 of blood (about 2 tablespoons) will be drawn from you at 30 days after the PCI procedure to measure your platelet response to the study drug 2 hours after taking your dose of medication

You must also be willing to do the following:

- Attend the scheduled visits
- Take the study drug(s) as directed, and
- Tell the study staff about any other medicines that you are taking.

What are the possible discomforts and risks?

Either study drug may cause some side effects. You may experience none, some or all of those listed below.

The risks and discomforts associated with the collection of a blood sample from a vein include faintness, inflammation of the vein, pain, bruising, or bleeding at the site where the needle enters the vein. There is also a slight possibility of infection.

Percentage of subjects reporting adverse events not associated with bleeding at least 3% or more in each group

	Ticagrelor (9235 patients)	Clopidogrel (9186 patients)
• Dyspnea (shortness of breath)	13.8	7.8
• Headache	6.5	5.8
• Cough	4.9	4.6
• Atrial fibrillation	4.2	4.6
• Mild to moderate diarrhea	3.7	3.3
• Nausea	4.3	3.8
• Hypotension (low blood pressure)	3.2	3.3
• Hypertension	3.8	4.0
• Dizziness	4.5	3.9
• Non-cardiac chest pain	3.7	3.3
• Back Pain	3.6	3.3
• Fatigue	3.2	3.2
• Cardiac (heart) chest pain	3.1	3.5

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.

The study drug used in this study may involve other risks that are not known at this time, including possible life-threatening reactions.

The most important non-medical risk involved in a research study such as this is loss of confidentiality; however, the study will strive to conform to all applicable privacy and confidentiality laws.

New Information

Your study doctor may receive new information about the study drug. If the study doctor believes it may affect your decision to take part in the study, you will be told. If this changes your decision to take part in the study, please talk with your study doctor about your decision.

Women Of Child-Bearing Potential

There might be unknown risks to the unborn baby if you are or if you become pregnant during the study. Due to these risks, you must not take part in this study if you are pregnant, plan to become pregnant during the research study period, or are breast-feeding a baby. Women must be post-menopausal or surgically sterile or have a negative serum pregnancy test and use reliable birth-control strategies during the study.

If you are a woman:

- By signing this consent form, you confirm to the best of your knowledge that you are not pregnant now and you do not intend to become pregnant during this study.
- A serum pregnancy test will be done to check for pregnancy before you take part in this study.
- If at any time during this study you think you might be pregnant, or later learn that you were pregnant during the study, you must contact the study doctor immediately for further instructions about your participation in this study and follow-up.

What are the possible benefits to you?

It is possible that either one of these treatments will help you; however, this cannot be guaranteed. The intent of this study is to better understand how ticagrelor and clopidogrel work in people with diabetes who are undergoing PCI immediately after having an angiogram.

How could others possibly benefit from this research study?

The information we get from this study may help us to better understand how patients with diabetes respond to these drugs after a PCI.

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.

What other choices do you have if you do not want to be in this research study?

You do not have to take part in this study to be treated for your heart disease. There are other approved treatments available for this condition. You might be able to get the Ticagrelor or Clopidogrel without being in the study. Your family doctor or the study doctor can explain the other treatments that are available.

What if you are injured because of the research study?

If you are injured as a direct result of your participation in this study, the sponsor will pay for all reasonable and necessary medical expenses required to treat your injury, so long as:

1. The injury occurs during your participation in the study.
2. The injury results directly from the study drug or study-required procedures [that you would not have received as part of your routine medical care]

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

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 Angiolillo, MD, PhD at 904-244-0411 if you experience an injury or have questions about any discomforts that you experience while participating in this study.

Will you be paid for taking part in this research study?

You will be paid a total of $50 in a Visa debit card for your complete participation in the study.

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. If the payments total $600 or more or you are a nonresident alien, payment will be processed through the University of Florida Accounts Payable department and 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.

If you choose to take part in this study, will it cost you anything?

The study drug will be provided at no cost to you while you are participating in this study.

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.

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, MD, PhD at 904-244-3933 or 904-244-0411 (24 hours). He will tell you how to stop your participation safely.

How is my Health Information Collected, Used, and Disclosed (Shared)?

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. 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 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 Artery Disease
- to evaluate a possible new use for the study drug
- to determine the causes or effects of the study condition Coronary Artery Disease

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 Dominick J. Angiolillo, MD, PhD and AstraZeneca LP
- 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 25 years after the study ends.

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. If you revoke your authorization, you can no longer participate in this research study.

Who would you call if you have any questions?

You have the right to ask questions about this study at any time and are encouraged to do so.

Contact Dominick J. Angiolillo, M.D., Ph.D. at 904-244-3933 or 904-244-0411 (24 hours) for any of the following reasons:

- if you have any questions about your participation in this study,
- if at any time you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research

If you have any questions about your rights as a research subject, or if you have questions, concerns or complaints regarding this research study, 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

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.

or

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

Can you be withdrawn from this research study?

You have the right to withdraw from this study at any time and still receive the same standard of care. There are no consequences if you decide to withdraw except you cannot be in the study anymore.

The study doctor or sponsor may choose to end your participation in this study without your consent at any time for any of the following reasons:

- You are unable to continue in the study
- You do not follow the instructions of the study doctor
- You experience an injury related to the study
- It is in your best interest
- You do not consent to continue in the study after being told of changes in the research that may affect you
- For any other reason.

If you stop taking part in the study completely, it is recommended that you go through study withdrawal procedures that the Study Doctor considers necessary for your safety. No further study related contacts or data collection will then occur except as described in this informed consent.

If you have an Adverse Event at your final study visit or withdrawal visit then your study doctor may wish to contact you and ask you about this, until it has completely resolved. The sponsoring company may also ask the study doctor for this information.

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 information and consent form, I have not given up any of the legal rights that I otherwise would have as a subject in a research study.

I authorize the collection, use and disclosure of my health information in accordance with this form, including transfer to countries outside of the United States.

_____ _____

Signature of Subject Date of Signature

_____

Printed Name of Subject

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:

_____ _____

Signature of person conducting informed consent discussion Date of signature