Study Title: A Mechanisic Study in Patients with Non-Dialysis CKD to investigate Altered Platelet Response to Antiplatelet Therapy
PI: Dr. Jain Nishank
Institution: UAMS
Support: ASN Foundation for Kidney Research

Place Medical Record Sticker Here

University of Arkansas for Medical Sciences Informed Consent Form

- **The word "you" means both the person who takes part in the research.**
- **We are asking you to be in a research study.**
- **You do not have to be in the study.**
- **If you say yes, even then you can quit the study at any time.**
- **Please take as much time as you need to make your choice.**

Why am I being asked to be in this research study?

- It is known that people with chronic kidney disease (CKD) are at higher risk to have heart and blood vessel problems like heart attack and stroke compared to people that do not have kidney problems.
- **Aspirin**, **clopidogrel** and **ticagrelor** are "antiplatelet drugs" that have been approved by the Food and Drug Administration (FDA) and they have been used by doctors for a long time to prevent blood clots building up in the vessels. If a blood clot is present in one vessel, it could stop oxygenated blood to get to a specific organ, and that could cause problems like heart attack or stroke. **Aspirin**, **clopidogrel** and **ticagrelor** will be called the "study drugs" and/or "antiplatelet medicines".
- There is very little knowledge about the way these "antiplatelet" medicines work in people with kidney problems. With your help, we want to learn how these "study drugs" can help patients with CKD and if these medicines work differently in people with normal kidneys.
- We are asking people like you to help us. We plan to enroll 54 people that have chronic kidney disease and 27 people without kidney problems.

What if I say yes, I want to be in this study?

Screening Visit	By phone or in person. It takes about 40 minutes
Baseline Visit	In person. It takes about 40 minutes
Final Visit	In person. It takes about 4 hours

✓ **SCREENING VISIT (Visit 1) could be done on the phone or in person**

- The study doctor will discuss with you about our study and the risks/benefits before you decide to be part in this study.
- If you decide to be part of our study, we will determine your eligibility (if you can be part of the study or not):
  - asking you about your medical problems, medicines that you are taking daily and collect demographic information (like date of birth, gender, race, ethnicity, education). Moreover, we will ask you some questions related to COVID-19 to understand if you could be potentially exposed.
  - If you are a CKD UAMS patient will collect some information about you and your health conditions from your medical records.
  - If you are a healthy control your eligibility will be determined after your first in person visit. During this visit we will evaluate how your kidney are working (blood draw and urine collection). A couple of days later we will call you to let you know if you are eligible or not.
- If you decide to be part of our study, we are going to ask you to stop taking any of the following medicines/supplements:
  - Aspirin
  - Vitamin E and herbal supplements
  - Nonsteroidal anti-inflammatory drugs (painkillers)
  - Fish oil
  - Proton pump inhibitors (a group of medicines for acid reflux)

  For at least 2 weeks before your baseline visit.

  If you are not taking aspirin, we can schedule your next visit when it is convenient for you (no need to wait 2 weeks).

  Moreover, we will ask you to stop drinking alcohol 12 hours before visit 2 and stop eating and smoking for at least 6 hours before the visit 2.

✓ **BASELINE VISIT (Visit 2):**

- Study drug dispensing
  - **If you have chronic kidney disease,** you will be randomly assigned (like flipping a coin) into one of these 2 study groups:
    - **Ticagrelor** (90 mg) one pill in the morning and one pill in the evening + Aspirin (81 mg) one pill in the morning.
    - **Clopidogrel** (75 mg) one pill in the morning + placebo one pill in the evening + **Aspirin** (81 mg) one pill in the morning. Placebo looks like the study drug but has no medicine in it.

  Neither you nor your study doctor will know whether you are in one or the other study group. The study drugs will look the same, except the Aspirin pill.

- **<u>If you do NOT have chronic kidney disease</u>**, you will receive:
  - **Ticagrelor** (90 mg) one pill in the morning and one pill in the afternoon + **Aspirin** (81 mg) one pill in the morning.

Total Time of the Treatment:
2 weeks (14 days plus one morning dose on the 15th day at the last visit)

We will give you the study drugs that you are supposed to take. The UAMS research pharmacist will prepare and package the study medicine.
You will bring the study drugs at home and you will take them for 2 weeks.

- We will ask you about the medications that you have been taking since the last visit.
- We will ask you about any medical problems you have had since the last visit.
- We will ask you to complete a questionnaires about your diet and your exercise habits.
- Draw about three tablespoons of blood from your arm. You cannot eat and smoke 6 hours before this blood draw. You cannot drink alcohol 12 hours before this blood draw.
- We will give you instructions about the next/last visit.

✓ **Mid-Treatment Phone call**

After about 7-10 days from the second visit we will call you to ask how is it going with the study drugs and to schedule your next /last visit.

✓ **LAST VISIT (Visit 3):**

- We will ask you about any symptoms you had during the treatment
- We will measure your body temperature, blood pressure, height and weight
- We will ask you if you have taken any medicines other than the study drugs since the last visit
- We will ask you to complete a questionnaires about your diet and your exercise habits.
- We will collect the empty/used/not used pill pockets
- **Two blood draws:**
  - **<u>FIRST BLOOD DRAW.</u>** We will draw about three tablespoons of blood.
  - We will ask you to take the last pill of your study treatment and wait for 3 hours. You can eat during these 3 hours.
  - **<u>SECOND BLOOD DRAW</u>.** We will draw one tablespoon of blood.

With your permission, we would like to use some of your blood for a genetic study. What is a genetic study? A genetic study is a study of your genes. Genes are passed from parents to their children. Genes are like a bar code that has all the information about the way you look, but also

about your risk for disease and how you respond to drugs. We want to study only your genes that carry information about how your body should respond to the study drugs. No other genes will be studied.

- ✓ **FOLLOW UP CALLS:**
  After 1, 6 and 12 months from your baseline visit (Visit 2), we will call you. We will ask you if you have been hospitalized and/or had procedure done due to heart and/or blood vessels problems and/or stroke. If you had any of the above we will ask you when and the hospital where you have been hospitalized.

What if I don't understand something?

- This form may have words you don't understand.
- You can ask as many questions as you like before you decide whether you want to be in this study. You can ask questions also during or after you are in the study.

How long will this study take?

- The study will take about 4 weeks. You will be required to make 2-3 visits to the UAMS. The first 2 visits will take about 40 minutes each. Last visit is going to take about 4 hours.
- We will also follow up on phone at 1-month, 6-months and 12-months. Each phone call will last about 20 minutes.

Where and for how long will my samples be stored for this study?

- Your information and samples will be stored for an indefinite period of time in the study doctor office and laboratory here at UAMS. Your information and samples will be labeled with a study number and they will not have any of your identifiable information (like name, date of birth etc.). The research staff only will maintain the key to re-identify this information and samples. No samples or information given to investigators outside the current research study will contain anything that could identify you.

What if I say no, I do not want to be in the study?

- Nothing will happen and you can still get your medical care at UAMS.

Can I stop being in the research?

- You can stop being in the study at any time. Contact the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. Please call Dr. Jain Nishank at 501-218-6714 or 501-686-5301.
- If you withdraw from the study, any information and sample collected before you withdraw will be retained in the study.
- You can still get your medical care at UAMS if you decide to drop out of the study early.

- The study doctor can take you out of the study at any time if he believes it is in your best interest; or if you do not follow study instructions; or if the study is stopped. This may happen without your consent.
- If there is new information about the study drugs or new information about alternative treatments which may benefit you, you will be contacted by your research doctor. We want you to know about anything that may change your mind about being in the study.

Will my information or samples be used for anything else, including future research?

- Yes. Your study information and biological samples (blood and urine) will be retained for specified and unspecified future research. Your biological samples will be labeled with a study number and they will be stored for an indefinite period of time here at UAMS. These samples will be retained for future analyses for which an IRB approval will be obtained at a later date. You can participate in the current study without allowing us to store your samples and information for future research projects. No future genetic research will be done on your genes.

What are the risks of being in this study?

- ✓ You will be asked to stop aspirin for 2 weeks prior to visit 2. This may potentially increase your risk of heart attack and stroke. However, these risks are minimal. Stopping dietary supplements such as Vitamin E has not been clarified to be risky for your health. Stopping fish oil may increase your blood cholesterol concentration temporarily.

  All "study drugs" have risks and cause side effects:

- ✓ **Aspirin** may cause some, all or none of the side-effects listed below: Common side effects (<10%) are ulcers and bleeding of the stomach and intestines, which could happen if you are taking aspirin for long time. You will be put on the medication for only 2 weeks' duration which limits your risk. Rare side effects (<1%) are ringing in the ears, breathing problems, swelling and allergic problems. Reye's syndrome (fever, rash, vomiting, headaches and lethargy-feeling tired and sleepy) is also reported, which however, occurs more commonly in children and those with a known allergy to aspirin.
- ✓ **Clopidogrel** in chronic kidney disease patients may cause some, all or none of the side-effects listed below: Common side effects (<10%) are bleeding. Less common side effects are bleeding from stomach in approximately 2% of the patients and 2.7% of the patients when combined with aspirin. Any bleeding requiring hospitalization and blood transfusion occurs in 0.8% of patients on clopidogrel. Rare side effects (<1%) are low blood counts (low white cell count, low red cell count, low platelets); damage to liver (hepatitis, liver failure), bleeding in brain; bleeding in the eyes (0.05%); breathing problems such as pneumonia, injury to lung and bleeding in lungs. In studies with healthy volunteers, clopidogrel use has been associated with nausea and flatulence.
- ✓ **Aspirin and clopidogrel** have been used together safely in some patients with chronic kidney disease in previous studies to reduce risk of heart attack. The risk of bleeding does

increase minimally as compared to using either drug alone. However, the risk remains small given that you will be treated with both drugs for only 2 weeks.

- ✓ **Ticagrelor** in chronic kidney disease patients may cause some, all or none of the side-effects listed below: Common side effects are bleeding from any site that can occur in up to 4% of patients and difficult breathing (about 14%). About 1–10% of patients may have abnormal heart beat, dizziness, nausea, and problems with kidney function. Rare side effects (<1%) are serious allergic reaction which causes swelling of the face or throat; heart block; slower heart beat; gout resulting in joint pain; skin rash. If you have coagulation problems and liver disease you cannot be part of this study. In studies with healthy volunteers, ticagrelor use has been associated with nose bleeding, bruises, inflammation of the gums, headache, gum inflammation and bleeding, muscle pain and skin rush

- ✓ **Possible interactions of the study drugs with following medicine**:
  - Antithrombotic drugs (like Ranolazine, Aggrenox and Cilostazol) could potentially increase risk of bleeding. Given this possible risk, we are asking you to do not take any antithrombotic drugs during the study.
  - Painkillers called Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines known to reduce blood coagulation and can cause bleeding complications. Given this possible risk, we are asking you to not take any NSAIDs during the study.
  - Medicines for acid reflux called Proton pump inhibitors (PPIs), fish oil, Vitamin E and herbal supplements should be avoided.

  You should discuss these risks with the study doctor and your regular health care provider.

- ✓ The questions regarding your health condition or side effects of the side drug could make you sad or upset.
- ✓ Someone could find out that you were in the study and learn something about you that you did not want others to know.
- ✓ You could have a legal problem if you tell us about a crime such as child or adult abuse. We have to report this abuse.
- ✓ Risk and side effects for blood collection: pain or bruising at the injection site and infrequently infection.
- ✓ Genetic testing involves unique risks such as psychological and social risks and the risk of identification. Social risks include being stigmatized, discriminated against, labeled, or having difficulty obtaining employment or insurance. Because your genetic information is unique to you there is a chance that someone could identify you. In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. A new Federal Law called the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes

it illegal for group and individual health insurers from using your genetic information to set insurance eligibility, premiums, or contribution amounts. They cannot request or require that you take a genetic test. In addition, employers with 15 or more employees may not use your genetic information to make decisions regarding hiring, firing, job assignments, or promotions, nor can they request, require, or purchase your genetic information. GINA does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

Who will see the information about me that is collected?

- The only people allowed to see your information are the people who work on the study and people who make sure our study is run the right way. They are:
  - ✓ American Society of Nephrology
  - ✓ OHRP (Office for Human Research Protections)
  - ✓ UAMS IRB (Institutional Review Board)
  - ✓ And other institutional oversight offices
- Your health information and a copy of this form will be locked in our files. We will not put these into your medical record.
- When we share the results of the study in the national conferences, medical journals or social media, we will not include your name, date of birth, address or any other relevant information that may identify you as an individual. We will do our best to make sure no one outside the study knows you are part of the study.

Will it cost me anything to be in the study?

- The study will not cost you anything. You or your insurance company will be responsible for your regular medical care as usual.

Will being in this study help me in any way?

- Being in the study will not help you, but may help people with chronic kidney disease in the future.

Will I be paid? –YES

- **BASELINE VISIT (Visit 2)** we will give you a $25 Walmart gift card at the end of the baseline visit.
- **LAST VISIT (Visit 3)** you will get a $100 Walmart gift card at the end of the visit

You will not receive any compensation for the visit that you are not able to attend.

What if I get sick or hurt while I'm in this study?

- If you get hurt when you are here for the study, we will help you get the care you need.

- If you get hurt or sick when you are not here, you should call your doctor or call 911 for emergency. If your sickness could be related to the research study, tell the doctor or Emergency Room staff about the study, the name of the head of the study and give them a copy of the consent form if you have it. Call the study doctor Dr. Jain Nishank at 501-218-6714 or 501-686-5301 as soon as you can.
- If you get hurt the costs for your care will be billed to you or your insurance company. Some insurance companies, Medicare, and Medicaid may not pay your bills that are related to research.

Where can I find more information about this clinical trial?

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 website will include a summary of the results. You can search this website at any time.

What if I have questions?

- Please call the head of the study Dr. Jain at 501-218-6714 or 501-686-5301, if you:
  - ✓ Have any questions about this study and about your rights.
  - ✓ Feel you have been injured in any way by being in this study.
- Please call the office that supervises research (UAMS IRB) at 501-686-5667, if you:
  - ✓ Have questions about this study and your rights.

Can't reach the study team or you need to speak to someone not directly involved with this study.

What should I do if I want to be in the study? Sign this form. We will give you a copy of the form to keep.

HIPAA Research Authorization Form

What is HIPAA?

HIPAA is the Health Insurance Portability and Accountability Act of 1996. It helps to keep your health information private and secure. When we say "you" or "your", we are talking about the person who takes part in the research and the person who gives the permission to be in the research.

What is the purpose of this form?

We are asking you to take part in the research described in the consent form. To do this research, we need to collect health information that tells who you are. We may collect the following information about you:

- Information such as age, gender, race/ethnicity,

- Information related to your health such as laboratory data, vital signs and current medication you are taking,
- Information about known medical conditions or diseases that you have (like diabetes, high blood pressure etc.),
- Discharge summary of any hospitalization, procedure notes/operative report for any medical procedure or death report you may have after the end of the study treatment (up to 1 year) to explain unexpected adverse events.

We will only ask for information we need for the research. Being part of this study will create the following new health information:

- Information about how "antiplatelet medicines" work in chronic kidney disease patients in comparison people that do not have kidney problems
- Vital sign (blood pressure, pulse, body weight etc.)
- Blood count and platelet function before and after treatment
- Your side effects to "study drugs" and how this medicines are processed by your body
- Inflammation markers present in your blood

To be in this study, we need your permission to collect, create and share your information.

What will happen with my health information?

If you sign this form, we may share your health information with people at the University of Arkansas for Medical Sciences (UAMS). These are people who help with the research or things related to research, such as:

- the research staff
- the office that supervises research {UAMS IRB (Institutional Review Board)}
- the UAMS research compliance office
- Organizations/companies that pay for all or part of the research or who work with us on the research, such as: the Sponsor listed above; their legally authorized contact; anyone who might purchase those companies at a later date.

We may also need to share your health information with people outside of UAMS who make sure we do the research the right way, OHRP (Office for Human Research Protections). Some of the people outside of UAMS may share your health information with someone else. We cannot protect your health information once it leaves UAMS.

What happens if I sign this form?

Signing this form means you are agreeing to be in this research study. You are giving us permission to create, collect, use and share your health information as described in this form. The permission you give us will be in effect until the end of the research study or until you tell us

to stop. If you give us permission to store your samples for future research, this authorization does not expire with this study (samples and information will be stored for undefined time).

What if I don't sign this form?

If you decide not to sign this form, you cannot be in the research study. This decision will not affect your current or future medical care or benefits at UAMS.

What if I sign this form but change my mind later?

You can change your mind at any time. This will not affect your current or future medical care or benefits at UAMS. If you want to leave this study and/or later you do not want your information/sample stored for future study, follow these steps:

- Write a letter saying you have changed your mind and that you are "revoking your HIPAA Research Authorization" and/or "revoking your permission to store samples and information for future research"
- List the "Study Title" listed on this form in your letter and sign the letter
- Send the letter to the Principal Investigator Dr. Jain Nishank (University of Arkansas for Medical Sciences. Internal Medicine, Nephrology. 4301 W. Markham Street #501. Little Rock, AR 72205).
- We may still use and share your information that was collected before you sent the letter asking to leave the study.

If you report any possible side effects from the drug in this study over the next 12 months, we would like your permission to obtain your medical records from any clinic visit or hospitalization that may have been related to the side effects:

YES _____ NO _____

Will my information or samples from be used for future research?

Please initial below to give us your permission to use your study information and biological samples in future research: YES _____ NO _____

No future genetic studies will be done in your genes.

Please notify Dr. Jain if your current address/telephone number or legal name changes.

By signing the document, I am saying:

- I understand that joining this study is voluntary and I agree to be in the study.

- Someone talked with me about the information in this document and answered all my questions. I have been asked if I wish to talk directly to the research study doctor.
- I agree to provide blood sample for genetic study.

I know that:

- I can stop answering your questions at any time and nothing will happen to me.
- I can call the office that supervises research (UAMS IRB) at 501-686-5667 if I have any questions about the study or about my rights, or if I cannot reach the study team or want to talk to someone not directly involved in the study.
- My decision will not change my medical care at UAMS.
- I do not give up any of my rights by signing this form.

I agree to be part of this study:

_____ _____

Your name (please print) Your signature

_____

Date

_____ _____

Name of person obtaining consent (print) Signature of person obtaining consent

Date _____