Date Initially Completed: 3/2/2016 **or Date Updated:** 06/16/2017		**IRB # (if known):** 4831
Protocol Title:	CAN RIVAROXABAN OR APIXABAN LEAD TO ANTICOAGULATION-RELATED NEPHROPATHY?	
Protocol Version/ Date:	06/16/2017	
Sponsor:	Albert Einstein Society	
Investigator:	Basma Abdulhadi, MD	**Email:** abdulhab@einstein.edu

Please carefully review and complete each section of this form. If your study already has a separate protocol (e.g. developed by a sponsor or submitted as part of a grant application), you have the option to reference the section and page numbers of that protocol where appropriate in this form. PLEASE NOTE: many of the questions below are looking specifically for what will be happening locally to protect participants. This information is generally not found in a protocol written for multiple sites.

NOTE: Depending on the nature of your research, certain sections below may not be applicable. Indicate "N/A" as appropriate. You must provide a response for each section. DO NOT DELETE SECTIONS OR LEAVE SECTIONS BLANK.

Keep an electronic copy of this form. You will need to modify this form when making changes to the protocol.

1) Protocol Abstract (*Briefly (in 250 words or less) describe the study in language understandable to a layperson. Include a brief description of the study purpose, target disease/condition if applicable, key eligibility criteria, and main study interventions*):

Anticoagulation-Related Nephropathy (ARN) is a side effect of treatment with blood thinners which leads to kidney dysfunction. ARN is diagnosed when there is a decline in kidney function after starting the blood thinner and other possible causes of this decline have been excluded. ARN has mainly been studied in relation to the common blood thinner - warfarin, where the prevalence is variable but can be as high as 37% (approximately 1 in 3) in the patients at highest risk. The risk factors that make this side effect more likely include the presence of pre-existing kidney disease, high blood pressure, older age and diabetes mellitus. Studies have shown that the occurence of ARN can lead to an accelerated progression of pre-existing kidney disease and a 65% increase in the risk of death (mortality).

The non-vitamin K oral anticoagulants (NOACs) are a new group of drugs which have been recently approved for use as blood thinners. They have a faster onset of action compared to warfarin and unlike warfarin, they do not need frequent monitoring. Apixaban and Rivaroxaban both have a similar mechanism of action. They inhibit Factor 10 which a clotting factor. They are the most commonly prescribed NOACs at Einstein Medical Center Philadelphia. We intend to serially monitor the kidney function by measuring the serum creatinine and urinalysis of 40 high risk patients who are recently started on either apixaban or rivaroxaban over a six month period. This will enable us to discover what proportion of patients actually develop ARN after starting a NOAC.

2) Project Objectives and Hypotheses:

Determine the incidence of ARN in high risk patients on rivaroxaban or apixaban (Factor 10 inhibitors).

Hypothesis - the incidence of ARN with apixaban or rivaroxaban is less than the previously reported incidence of ARN in warfarin.

- Describe demographic and urinalysis-associated predictors of ARN in patients on rivaroxaban or apixaban (Factor 10 inhibitors)

3) Background/Significance of Research (*Provide the scientific or scholarly background and rationale for the research based on the existing literature (include references). Describe relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data. Explain the significance of the research in terms of why it's important and how it will add to existing knowledge.*):

Anticoagulation-related nephropathy (ARN) is an understudied renal complication of anticoagulant therapy that is characterized by acute kidney injury (AKI) defined as an increase in baseline serum creatinine ≥ 0.3 mg/dL, without any alternate etiology, in the setting of a supra-therapeutic International Normalized Ratio (INR) greater than 3.0 [1-7]. ARN has mainly been studied in relation to warfarin, it usually occurs in the first two months of starting anticoagulant therapy and retrospective studies have estimated the prevalence to range from 16% to 37% [4-6]. The strongest risk factor for ARN is pre-existing chronic kidney disease (CKD); other risk factors include older age, diabetes mellitus and hypertension [1,4]. Patients with ARN have an accelerated progression of CKD and a retrospective study of more than 15,000 patients on warfarin showed a 65% increase in mortality in patients with ARN [4,6].

The non-vitamin K oral anticoagulants (NOACs) are replacing warfarin in the clinical setting for long term anticoagulation because of the advantages of faster, reliable onset of action, and unlike warfarin, they do not require dose-response monitoring [8-10]. Apixaban and Rivaroxaban both have a similar mechanism of action. They inhibit Factor 10 which a clotting factor. They are the most commonly prescribed NOACs at Einstein Medical Center Philadelphia. A few animal models and case reports have shown that these NOACs (particularly dabigatran and apixaban) can lead to deterioration of kidney function, but there is limited epidemiologic data on ARN in NOACs and the incidence of ARN in NOACs is unknown [11-14]. A proposed guideline to diagnose ARN recommends that serum creatinine and urinalysis be checked monthly in the first few months of anticoagulation [1]. Clinical trials that compared warfarin to NOACs specifically studied stroke risk and bleeding outcomes and did not document the incidence of ARN because they did not make these regular creatinine and urinalysis measurements in the first few months of anticoagulation [15-20]. Our study intends to make these necessary measurements in a selected group of high risk patients started on rivaroxaban or apixaban and hence determine the incidence of ARN in this group.

This study will be the first epidemiological study using a prospective design to measure the incidence of ARN in a population receiving NOACs. Given the high morbidity and mortality associated with ARN, the findings will enhance patient safety, enabling patients and health providers to make informed decisions with their patients regarding the choice of anticoagulants. It will also establish baseline data that will serve as foundation for future studies.

SIGNIFICANCE

Anticoagulant-related nephropathy (ARN) is a relatively new and underdiagnosed complication of anticoagulant therapy with the potential to accelerate chronic kidney disease and lead to increased mortality [4,6]. Brodsky, et al, performed a retrospective study of more than 15,000 subjects and showed that the 5-year Kaplan-Meier survival rate was significantly lower in the ARN cohort compared to the patients without ARN with a 65% increased risk of mortality [4]. This dramatic increase in mortality that is attributable to an episode of ARN in a patient taking an anticoagulant is the reason why this study is very significant.

The clinical trials that compared the NOACs to warfarin did not specifically study ARN and did not repeat creatinine and urinalysis testing in the first two to three months of therapy to establish possible ARN diagnosis [15-20]. In most of these studies, only baseline creatinine and creatinine levels 6 to 12 months later were analyzed, hence it is possible that ARN was under-diagnosed as most cases of ARN are detected in the first eight weeks of therapy. Our study aims to accurately capture ARN cases by making these measurements monthly in the first three months of starting the anticoagulant.

This study is pivotal because it will for the first time, define the incidence of ARN in patients on rivaroxaban or apixaban therapy. If we find that ARN incidence in patients started on rivaroxaban or apixaban is less than that seen with warfarin, this can help support evidence that this NOAC is safer for the kidneys compared to warfarin and this data can enable us make evidence based decisions regarding the continued use of the medication to help our patients. If on the other hand we find that the medication leads to ARN, then we will be contributing important post-marketing surveillance data that can also help us make safety decisions about the use of the medication in the future.

INNOVATION

Previous studies on ARN have utilized retrospective study designs which have many epidemiological pitfalls including the cause versus effect bias and the inability to ascertain relative risk [1]. Our study is unique because we intend to utilize a prospective epidemiological design to study this renal complication, a first in the study of ARN. This is important because ARN is a diagnosis of exclusion and hence a prospective study is able to more accurately define cases of the condition compared to the assumptions that are made in retrospective studies where further work up cannot be done in retrospect.

This will be the first epidemiological study focused on ARN in a NOAC. Even though NOACs are new, they are becoming ubiquitous and a mainstay in clinical practice and not just an alternative to warfarin. For example, the recent CHEST guidelines recommend them as first line therapy in the treatment of venous thromboembolism [8]. Hence it will be important to clearly delineate their effects on the kidneys.

In summary, this is a proposal for a prospective study to investigate the incidence of anti-coagulant nephropathy, a dreaded renal complication of anticoagulation. Our literature search has shown that there are no prospective studies of this condition in the new oral anticoagulants and clinical trials did not perform the necessary testing in the appropriately timed interval to diagnose ARN. We chose to study rivaroxaban and apixaban, the most commonly prescribed NOACs in our academic medical center and we anticipate that the result of this study will contribute safety data that will lead to better care of our patients and great cost savings by avoiding the morbidity and mortality associated with renal disease.

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4) Setting of the Human Research:

a. Indicate all AEHN locations where the human research will be conducted (check all that apply):

- ☒ Tabor Rd campus
- ☐ Elkins Park campus
- ☐ Belmont Center for Comprehensive Treatment
- ☐ Center One
- ☐ Montgomery campus
- ☐ Other: please specify -

b. Indicate if human research will be conducted at external location(s) overseen by the AEHN investigator (e.g. private physician office, collaborating hospital/university)

- ☐ Yes (Complete Appendix B: External Site Approvals on Application for Human Research)
- ☒ No

5) Resources available to conduct the Human Research:

a. Target population (e.g. Adult subjects with a diagnosis of Type II diabetes for greater than two years":
Elderly patients with CKD who have recently been started on Rivaroxaban or Apixaban

b. **For prospective studies:**

i.) Total number of subjects planned to be enrolled in the study at AEHN site(s): 40

ii) For multi-site projects, please indicate total number of subjects planned to be enrolled in the study at all sites: 0

iii) Describe access to a population that would allow recruitment of the targeted number of subjects (***i.e. how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?***) : We estimate that around 100 patients meeting our criteria are started on Apixaban or Rivaroxaban in a six-month period. We anticipate to recruit 40% (40) of them into the study

c. **For retrospective studies:**

i.) Estimated number of charts to be reviewed: N/A

ii.) Time period of interest for data being collected (**e.g. *Subjects who had XX procedure between 6/1/00 and 6/1/05***: N/A

d. Describe the number and qualifications of the study team members, their experience in conducting research, their knowledge of the local study site(s), culture, and society:

Principal Investigator: Dr. Basma Abdulhadi is a first year intern in Internal Medicine at Albert Einstein Medical Center. Dr. Abdulhadi completed her medical school training at the University of Jordan in Jordan where she graduated top of her class. She completed a graduate degree in Public Health at Thomas Jefferson University in Philadelphia and she is interested in population epidemeology and determinants of health. At Einstein, he has been very keen to work on research projects with collaboration with other colleagues on various projects

Co-Principal Investigator/Attending Mentor:Dr. Janani Rangaswami's training at Weill Cornell Medical Center stimulated her interest in studying biomarkers and in providing better understanding of the outcomes with transplant and dialysis patients. She worked in the lab of Dr.Manikkam Suthanthiran studying the molecular signature of interleukin-17 in allograft rejection. She also worked on a project studying VEGF inhibition and thrombotic angiopathies with renal injury from chemotherapy. She is currently working on several projects at Einstein including "the ARChIVED trial" and the study on the "Temporal Variation of Platelet Reactivity throughout the Hemodialysis Cycle" She is an assistant program director of the internal medicine program at Einstein Medical Center is very active in mentoring residents in research at Einstein.

Co-Principal Investigator/Attending Mentor: Dr. Vincent Figueredo is the associate chair of the division of cardiology at Einstein Medical Center Philadelphia. He has extensive experience in research which has produced more than 80 peer-reviewed publications and more than 20 book chapters and articles and more than 40 abstracts at national meetings. He has been involved in more than 20 clinical trials. He is very active in mentoring residents and fellows in research at Einstein.

Co-Investigator: Dr. Michael Jaecks is a primary day-shift decentralized pharmacist on Tower 5 (telemetry *unit) at* Einstein Medical Center Philadelphia. He is the primary individual verifying inpatient prescription orders for

patients in on the inpatient cardiology floor and he will work closely with the PI to help in recruitment of patients for the study. He has been involved in research and carried out a pharmacy residency research project with poster and verbal presentation. He has accredited pharmacy continuing education (CE) presentation, accredited respiratory care CE presentation and departmental drug information publications and presentations.

Research Coordinator: Rachel Murphy has 2 years of research experience and functioned as research coordinator on previous projects. She is CITI trained and aware of the research code of conduct.

Co-Investigator: Mario Naranjo, MD is a second year resident in Internal Medicine at Albert Einstein Medical Center. He has participated in clinical research projects and completed CITI research training.

Co-Investigator: Parasuram Krishnamoorthy, MD is a second year fellow in Cardiology at Albert Einstein Medical Center. Dr Krishnamoorthy completed his medical school training in India after which he spent his time studying the role of inflammation in the development of cardiovascular and metabolic diseases. He worked in the lab of Dr Nehal Mehta and Dr Dan Rader at the University of Pennsylvania studying patients with psoriasis as an inflammatory model and assessing CV risk in these patients. He completed his residency training at Mount Sinai Englewood Hospital in New Jersey after which he came to Einstein for his fellowship in Cardiovascular Diseases. He is also interested in population epidemiology and clinical outcomes research and is actively involved in multiple descriptive studies from the National registries and other large public databases.

e. Describe the time that the investigator and other study team members, if applicable, will devote to conducting and completing the study within the anticipated study period ***(e.g. 10% of PI's time and full-time coordinator)***: Dr Abdulhadi will dedicate approximately 10% of his time to this study. Dr. Krishnamoorthy and Dr. Naranjo will dedicate 3% each of their time to this study. Pharmacist Jaecks will dedicate 2% of his time, Drs Rangaswami, and Figueredo will dedicate 1% of their time and Ms Murphy will dedicate 3% of her time to this study.

f. Describe the plan for ensuring that all investigators/staff assisting in this research are adequately informed of: 1) the protocol, including revisions to protocol and other study specific changes, 2) investigational product information if applicable, and 3) study related duties and functions: Dr. Rangaswami's research team, including Dr. Abdulhadi, meets every 4 weeks to review the progress of all research projects. Any protocol changes, study difficulties and new written material will be discussed at those meetings.

g. Describe the facilities available to conduct this research: Recruitment at Telemetry floor and Cardiology clinic of Einstein Medical Center Philadelphia. Blood draws at Suite 110 at the Klein building.

h. If applicable, describe the availability of medical or psychological resources that subjects might need as a result of the anticipated consequences of this research: This research has no additional risk above and beyond that of a blood draw and urine collection. The patient will be followed by their primary care physician and cardiologist thoughout the duration of the entire study and receive usual care.

6) Study Design

a. Recruitment Methods:

i. Describe when, where, and how potential subjects will be recruited (***Describe the source of subjects. Describe the methods that will be used to identify potential subjects. Describe materials, such as advertisements, that will be used to recruit subjects (include these with submission materials. If study is a chart review, describe which records will be accessed to collect data and how you will access them*** :
Participants will be recruited from the telemetry inpatient service and the cardiology clinic at the Einstein Medical Center Philadelphia. Participants on the telemetry inpatient service who are started on rivaroxaban or apixaban will be identified by Michael Jaecks (co-investigator), a staff pharmacist who verifies new medication orders for telemetry inpatients, while participants in the cardiology clinic will be identified by the patient's cardiologist who initiates the anticoagulant in the clinic. The division of cardiology at Einstein Medical Center supports this study and all cardiologists will be informed about the study. Identified patients will be given a written description about the study and Dr. Mezue (principal investigator) will be notified. All identified patients will have their medical records/chart reviewed by Dr. Mezue to determine eligibility for the study. If appropriate, he will then contact them by phone and arrange a meeting to discuss the study protocol, answer any questions and complete the consent process

ii. Will payments to subjects be provided?
☒ Yes, amount and timing: 4 payments of $10 cash each at the point of each blood draw, totalling $40 cash
☐ No
☐ N/A

b. Inclusion and Exclusion Criteria:

i. Describe how you will screen for eligibility (**e.g. review charts, perform specific screening tests, etc.**):
Participants will be recruited from the telemetry inpatient service and the cardiology clinic at the Einstein Medical Center Philadelphia. Participants on the telemetry inpatient service who are started on rivaroxaban or apixaban will be identified by Michael Jaecks (co-investigator), a staff pharmacist who verifies new medication orders for telemetry inpatients.

Participants in the cardiology clinic will be identified by the patient's cardiologist who initiates the anticoagulant in the clinic. The division of cardiology at Einstein Medical Center supports this study and all cardiologists will be informed about the study.

Screening will be also be carried out by a query on the electronic medical record with a confidential report generated weekly by the Einstein's AECIS which will contain all rivaroxaban and apixaban prescriptions ordered by electronic scripts. Investigators and co-investigators will review the medical records of patients on the list to determine if they meet the inclusion criteria for the study.

Identified patients will be given a written description about the study and Dr. Mezue (principal investigator) will be notified. All identified patients will have their medical records/chart reviewed by Dr. Mezue to determine eligibility for the study. If appropriate, he will then contact them by phone and arrange a meeting to discuss the study protocol, answer any questions and complete the consent process

ii. Describe the criteria that define who will be included or excluded in your final study sample:

Inclusion Criteria

- Age ≥ 60 years
- GFR ≤ 90 ml/L based on creatinine clearance
- Participant has been initiated on long term anticoagulation with rivaroxaban or apixaban for atrial fibrillation within four weeks of recruitment
- Participant is willing to comply with all aspects of the protocol, including adherence to medical therapy and follow-up visit
- Participant is willing to give written informed consent

Exclusion Criteria

- History of blood dyscrasias or active bleeding,
- History of hematuria
- Patients on dialysis

c. Study Timelines:

i. Duration of an individual subject's participation in the study: 6 months

ii. Time period anticipated to enroll all study subjects or to complete chart review: 4 months

iii. Estimated overall study duration (***i.e. from initiation to completion of primary analyses***): 12 months

d. Study Endpoints:

i. Describe the primary and secondary study endpoints (***i.e. the outcome(s) that the study is designed to evaluate***):

Primary endpoint - Incidence of ARN is the primary outcome of this study and this is based on a documentation of AKI (defined as an increase in baseline serum creatinine ≥ 0.3 mg/dL), in the absence of any other obvious etiology for the AKI identified after a standard clinical evaluation and work up by the patient's primary care physician, cardiologist or nephrologist. This incidence will be expressed as a percentage.

Secondary endpoint - Urinalysis measurements (particularly hematuria and proteinuria) will be analyzed for correlation with the incidence of ARN. Demographic variables including age and race will be analyzed in contingency tables using Fisher's exact test to ascertain if they are significant for the primary outcome.

ii. Describe any primary or secondary safety endpoints (***e.g. any disease or symptom that would result in the withdrawal of that subject from the study***): Subjects will be censored from the study if anticoagulation is withdrawn for any clinical reason

e. Human Research Methods:

i. Describe and explain the study design ***(e.g. randomized, double-blind, placebo-controlled clinical trial or retrospective chart review)***:

This is a prospective observational study designed to determine the incidence of ARN in 40 adult patients recently initiated on rivaroxaban or apixaban at Einstein Medical Center Philadelphia.

ii. Describe all research activities involved in this protocol, including a study visit timeline if appropriate:

Baseline demographic data, past medical history, current medication list and baseline laboratory records (taken within the last three months) will be obtained from the patient's hospital chart and the electronic medical record. Serum creatinine and urinalysis measurements will then be repeated at monthly intervals for the first three months and then at the six-month mark. These laboratory tests will be drawn at Einstein's Klein building Suite 100 by a trained phlebotomist.

If AKI, defined as an increase in baseline serum creatinine $\geq$ 0.3 mg/dL from baseline, is noted in any study participant, the patient and his primary care physician or cardiologist will be notified both verbally and through a detailed letter. A standard clinical evaluation and work up will then be performed by the patient's primary care physician or cardiologist as part of the patient's usual care with referral to a nephrologist if necessary. The research team will then be notified of the result of this work up.

Dr. Mezue will create a "study participant list" that contains the names and birth dates of all study subjects and assigns them a unique three digit identification number. This list will be password encrypted and stored on the Einstein computer network. A separate encrypted "study database" will be constructed and baseline data, laboratory results and work up data will be aggregated into this database using the identification numbers. Following the completion of the study, the initial study participant list will be deleted. All data will be checked twice upon entering it into the database to ensure accuracy.

iii. Identify which tests/procedures are being administered solely for research purposes and which are being conducted as part of standard of care (i.e. procedures that would be done even if the participant were not involved in research):

Serum creatinine and urinalysis measurements monitored in the first six months after starting anti-coagulation will be test done for research purposes.

If AKI, defined as an increase in baseline serum creatinine $\geq$ 0.3 mg/dL from baseline, is noted in any study participant, the patient and his primary care physician or cardiologist will be notified both verbally and through a detailed letter. A standard clinical evaluation and work up will then be performed by the patient's primary care physician or cardiologist as part of the patient's usual care with referral to a nephrologist if necessary.

iv. Describe steps taken to lessen the probability or magnitude of risks associated with tests/procedures being done for research purposes only (***e.g. only appropriately trained personnel involved in procedures, extra tests being done for safety purposes***):

The tests proposed for the study subjects are serum creatinine assay and urinalysis. Obtaining a smple for urinalysis is not an invasive test and dost not portend any major risk to participants. Serum creatinine assay will involve four blood draws during the course of the study. Blood draws involve using a needle to obtain blood from a peripheral vein. This procedure is a low risk procedure however, it may cause pain, bleeding or bruising. To minimize this risk, we will employ a phlebotomist who has been trained to do blood draws using standard techniques that cause the least discomfort.

v. Describe alternative treatments that are available to subjects if they choose not to participate in research: No new treatment is started in this study. Patients will be observed in on-going treatment that is started before the observation. Patients who do not participate will continue to receive standard clinical care.

vi. Describe the source records that will be used to collect data: AECIS records for background demographic data. Laboratory results from the Einstein laboratory after serum creatinine and urinalysis are assayed.

vii. Describe what data (variables) will be collected for this research: Baseline demographic data(age, sex, height, weight, race), past medical history, current medication list and baseline laboratory records (basic metabolic panel, serum creatinine, urinalysis) will be obtained from the patient's hospital chart and the electronic medical record. Serum creatinine and urinalysis measurements will then be repeated at monthly intervals for the first three months and then at the six-month mark.

viii. Describe any plans to conduct audio or video recording of research participants during the conduct of the research. Specify whether recording is optional or not and how information on how recordings will be used and how long they will be retained is being shared with subject: N/A

f. Specimen Management:

i. Will any type of specimen (e.g. blood or tissue) be collected for this study?

☒ Yes

☐ No , skip to section on Data Management

ii. What information will be associated with the specimens collected for this study? Each sample will be labeled with the patient's unique identification number.

iii. If specimens will be banked for future use, describe where and how the specimens will be stored: N/A

iv. Specify how long specimens will be stored locally: N/A

v. Specify who will have access to the specimens locally: N/A

vi. Will specimens be sent out or received: ☒ No ☐ Yes

a. Who is responsible for receipt or transmission of the specimens? N/A

b. How will specimens be transported? N/A

c. Describe the procedures to release specimens, including: the process to request a release, approvals required for release, who can obtain specimens, and the data to be provided with specimens: N/A

g. Data Management

i. Describe steps that will be taken to secure the data (e.g. training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality and separation of identifiers and data) during storage, use and transmission: As stated above, a study participant list containing identifiable data will be password protected and stored on the Einstein system. This list will only be able to be accessed by members of the research team. All other data will be stored in a separate database with unqiue but unidentifiable identification numbers. At the termination of the study the initial study participant list will be deleted.

ii. Describe the data analysis plan, including any statistical procedures and method for determining the sample size for the study:

Incidence of ARN is the primary outcome of this study and this is based on a documentation of AKI (defined as an increase in baseline serum creatinine $\geq$ 0.3 mg/dL), in the absence of any other obvious etiology for the AKI identified after a standard clinical evaluation and work up by the patient's primary care physician, cardiologist or nephrologist. This incidence will be expressed as a percentage.

Urinalysis measurements (particularly hematuria and proteinuria) will be analyzed for correlation with the incidence of ARN. Demographic variables including age and race will be analyzed in contingency tables using Fisher's exact test to ascertain if they are significant for the primary outcome.

There is no data at all in the literature for the incidence of ARN with rivaroxaban or apixaban and we short-listed that number (40) based on the reported incidence for warfarin (17-37%). We are selecting the patients at highest risk (elderly, CKD) for anticoagulation-related nephropathy (ARN) and we expect that the incidence we obtain will be the highest for the population we are studying.

In terms of precision, we will calculate confidence intervals of the proportional incidence using Stata (command line cii 40 (incidence)). If the incidence is zero, Stata calculates the 95% confidence interval based on our sample size as 0-9%. If we only find 2 cases of ARN, Stata calculates the point estimate incidence at 5% with 95% confidence interval as 0.6% - 17%, If we find 10 cases of ARN, Stata calculates the point estimate incidence as 25% with 95%

confidence interval as 13% to 41%, etc. Our sample is elderly, CKD subjects at higher risk hence we expect a higher incidence than in the normal population, hence a negative result will suggest very low risk in the general population.

iii. Describe where and how data will be stored locally: Data will be stored in password protected spreadsheets on the Einsetin computer network.

iv. Specify how long data will be stored locally: 6 years after publication of the study

v. Specify who will have access to the data locally: The research team members.

vi. Describe process that will be followed to ensure accuracy of collected data: All data will be checked twice upon entering it into the database to ensure accurancy. All calculations and statistical tests will be confirmed by both members of the team.

vii. Will data be sent out or received: ☒ No ☐ Yes

a. Who is responsible for receipt or transmission of the data? N/A

b. How will the data be transported? N/A

h. Provisions to monitor the data for the safety of subjects (Required only when Human Research involves more than minimal risk):

i. Describe plans to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. Include what data will be reviewed, who will review the data and when the data will be reviewed:

This research has no additional risk above and beyond that of a blood draw and urine collection. Blood draws for serum creatinine assay will be performed by a trained phlebotomist using standard techniques. Any problems encountered during blood draws will be reported to the research staff and will be reviewed by the entire research study team as soon as they occur to determine if and when the event needs to be reported to the IRB, and if the protocol and/or consent document require modification. Each safety data will be reviewed by at least 2 members of the research team and all events will be reviewed after every 10 patients are recruited.

i. Withdrawal of Subjects:

i. Describe the anticipated circumstances under which subjects will be withdrawn from the research without their consent: Subjects will be censored from the study if anticoagulation is withdrawn for any clinical reason

ii. Describe the procedures that will be followed when subjects withdraw from the research (or request that their data be withdrawn), including partial withdrawal from procedures with continued data collection: If a patient is censored from the study, all of their data will be removed from the study participant list and study database.

7) Risks to Subjects:

a) List the reasonably foreseeable risks, discomforts, hazards or inconveniences to the subjects. For each indicate the probability, magnitude, and duration when possible (consider physical, psychological, social, legal and economic risks as well as risks related to confidentiality): This research has no additional risk above and beyond that of a blood draw and urine collection. Blood draws may rarely cause pain, bleeding and bruising. Blood draws for serum creatinine assay will be performed by a trained phlebotomist using standard techniques.

b) If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable: None

c) If applicable, indicate which procedures may have risks to an embryo or fetus should the subject or the subject's partner be or become pregnant: None

d) Describe, if applicable, the process that will be followed if a subject or the subjects' partner becomes pregnant while participating in the study: None

e) If applicable, describe risks to others who are not subjects: None

8) Potential Benefits to Subjects

a) Describe the benefits that individual subjects may experience (include when possible the probability, magnitude and duration of the potential benefits) or indicate if there is no direct benefit: If a patient develops ARN, this study ensures that the condition will be detected and the patient will receive a comprehensive work up in standard care. The benefit to the patient is that they are receiving extra monitoring for this condition.

9) Medical care and compensation for injury (Required for Greater than Minimal Risk Studies Only):

a) Describe any provisions for medical care and available compensation in the event of a research related injury: N/A

b) Provide the contract language, if any, relevant to compensation for research-related injury: N/A

10) Cost to participants:

a) Describe any actual or potential cost that subjects may incur through participation: There are no costs that the subject may incur.

11) Provisions to Protect the Privacy Interests of Subjects:

a) Describe the steps that will be taken to protect the subjects' privacy interests and make them feel at ease. In this case, "privacy interest" refers to a person's desire to control access of others to themselves (*e.g. has consideration been made to having same gender interviewers, the disclosing of cameras, conducting physical exams in private rooms, discussing study health concerns of subjects in private rooms instead of public waiting areas, etc.*): In order to protect the privacy of the subjects, consent discussion will be held in a private room. Only the study team and phlebotomist will know if the patient is enrolled in the study.

12) Subject Authorization

Are you planning to obtain written HIPAA authorization from study subjects?

☒ Yes
☐ No (if checked, written approval for waiver from Privacy Officer is required)

13) Consent process:

a) Indicate the type of informed consent you propose to utilize in this research project:

☐ Requesting Waiver of Consent Process

Provide justification for why it would not be practicable (feasible) to conduct this research without a waiver: N/A

Explain whether or not subjects will be provided with additional pertinent information after their participation and if yes, describe what information will be provided and how it will be communicated (*e.g. a summary of study results will be provided to subjects in a newsletter*): N/A

SKIP TO SECTION 14

☐ Requesting an Alteration to the Consent Process (i.e. no documentation in writing)

Provide details on alteration requested (***e.g. only verbal consent will be obtained, required information will not be disclosed or the research involves deception***) and why it is necessary:

☒ Consent process with Documentation in Writing

b) Describe when and where the consent discussion will take place: Identified patients will be given a written description about the study and Dr. Mezue (principal investigator) will be notified. All identified patients will have their medical records/chart reviewed by Dr. Mezue to determine eligibility for the study. If appropriate, he will then contact them by phone and arrange a meeting to discuss the

study protocol, answer any questions and complete the consent process. The consent document will be reviewed and signed.

c) Describe the role of the individual(s) involved in obtaining consent from study subjects **(e.g. investigator, study coordinator, recruiter, etc.)**: Dr. Mezue and Ms Murphy will be actively involved in the recruiting process and obtaining informed consent.

d) Specify the time that will be devoted to the consent discussion: The team will dedicate whatever time is necessary to explain the study to the subject.

e) Will subjects be given the opportunity to think about the information provided as part of the consent discussion, ask questions, and discuss the research with family or friends if desired?

☒ Yes
☐ No

f) Describe the steps that will be taken to minimize the possibility of coercion or undue influence:
It will be made clear to the subject that participation in this study is completely optional and will not influence their care in any wa

g) From whom will consent or permission for research participation be sought (i.e. subject, parent, legally authorized representative): The subject themselves will consent for inclusion in the study.

h) Describe process to ensure subject/parent/LAR's understanding: In order to ensure the subject's understanding, they will be given the opportunity to ask as many questions as necessary. Furthermore, the consenting team will use "teach back" to assess the subjects understanding of the study's purpose and protocol.

i) Do you plan to consent subjects or their legally authorized representatives when the subject does not speak English?

☐ Yes
☒ No

If yes, select one of the two options below that best describes your study:

☐ The research targets a specific population that is non-English speaking OR a significant proportion of subjects are anticipated to be non-English speaking (*if this is true, translations of the standard (i.e. IRB-approved, full-description) informed consent documents must be reviewed and approved by the IRB prior to enrollment of any non-English speaking subjects*).

☐ The research does not target a non-English speaking population, AND only a small proportion of subjects are anticipated to be non-English speaking (*if this is true and a translated study consent form is not available, the short form consent process must be used. For more information, see the Investigator Manual.*)

Describe your plan for conducting study visits and long-term follow-up with these subjects: N/A

j) Does the study allow for and do you plan to enroll adult participants with diminished decision making capacity?

☐ Yes
☒ No

If yes, select one of the two statements in each group below that is most appropriate for your study (if neither statement applies in one or both groups, your study does not meet the regulatory criteria for enrollment of these subjects):

Criterion 1(*must select one box below if you plan to enroll adults who are unable to consent for themselves*):

- ☐ The aims of the research cannot be accomplished if the subjects were limited to adults capable of consent.
- ☐ The research is intended to be beneficial to the subjects in a manner that is not available outside the research context.

Criterion 2 (*must select one box below if you plan to enroll adults who are unable to consent for themselves*):

- ☐ The research involves no more than minimal risk to subjects. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life of normal persons or during the performance of routine physical or psychological examinations or tests in normal persons [45 CFR 46.102(i)].
- ☐ The research involves more than minimal risk to subjects, but the research holds out the prospect of direct benefit to the individual subjects.
- ☐ The research involves more than minimal risk to subjects, there is no anticipated direct benefit to the individual subjects, but: (1) the subjects have a disease or condition for which the procedures involved in the research are intended, (2) foreseeable risks to the subjects are low AND (3) the negative impact on the subject's well-being is minimized and low.

Describe your plan for assessing a potential subject's ability to provide informed consent (e.g. clinical interview, standardized psychological or neuropsychological test, specially developed capacity assessment instrument, etc.): N/A

14) Vulnerable populations:

a) Indicate if any individuals who are potentially vulnerable to coercion or undue influence will be included in the study:

- ☐ Children (if checked, must complete Appendix C. Children on Application for Human Research)
- ☐ Pregnant Women
- ☐ Neonates of Uncertain Viability or Non-viable Neonates
- ☐ Prisoners
- ☐ Adults with Diminished Decision Making Capacity
- ☒ Students/ Employees

***You may not include members of the above populations as subjects in your research unless it is indicated in the inclusion criteria of the protocol and approved by the IRB.**

b) If vulnerable populations will be participating in the study, describe the rationale for including this population and the additional safeguards to protect their rights and welfare: Students are unlikely to be part of the study population given the age restriction and we estimate that very few employees of the hospital will be enrolled in the study. In the unlikley situation that an employee is started on rivaroxaban or apixaban and meets criteria for inclusion in the study, they will be offered entrance into the study.

Appropriate steps in informed consent will be taken to make sure that they do not feel coercion or any undue influence to participate.

c) If research involves children, describe the following:
   i. Will parental permission be obtained from either both parents or just one parent: N/A

   ii. Will assent be obtained from all, some, or none of the children? If assent will be obtained from some children, indicate which children will be required to assent: N/A

   iii. When assent of children is obtained, describe whether and how it will be documented: N/A

15) Is this Community-Based Participatory Research (*i.e. research conducted in communities in which community members, persons affected by condition or issue under study and other key stakeholders in the community's health have the opportunity to be full participants in each phase of the work including conception, design, conduct, analysis, interpretation, conclusions, and communication of results*):

☐ Yes
☒ No, go to section 16)

Describe involvement of the community in the design and conduct of the research: N/A

16) Sharing of results with participants:

a) Describe any plans for sharing results with participants: The results of this project will be reported to both the participants and the scientific community. A one-page handout with all of the study results and conclusions written in patient friendly language will be distributed to all study participants. Individual patient data will not be revealed to any participant. If any study participant wishes to discuss the results further, Dr. Mezue or Rangaswami will be available to meet with them. The results will be presented at national scientific meeting and then published in a peer-reviewed journal.

If separate protocol is not included, please attach list of references for background section etc. to this form.