Measurement of the Anti-Xa Activity of Rivaroxaban
Submitted by:

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PURPOSE OF THE PROJECT

The purpose of the study is to assess the systemic factor Xa inhibition of a standard dose of rivaroxaban in a diverse cohort of patients with new onset atrial fibrillation at various time intervals.

INTRODUCTION:

In November of 2011, the US Food and Drug Administration approved rivaroxaban to reduce the risk of stroke in patients with non-valvular atrial fibrillation. This was based on the findings of the ROCKET-AF trial, where rivaroxaban was found to be non-inferior to warfarin for the prevention of stroke and systemic embolism. Unlike warfarin, rivaroxaban did not require laboratory monitoring because of its predictable pharmacokinetics and pharmacodynamics. Kubitza el.al. showed rivaroxaban’s peak plasma concentrations occurred within 3-4 hours of dosing, its maximal direct Xa inhibition was achieved after 3 hours and a the measured half life was 5-9 hours. However, closer investigation of the study reveals that analysis was only performed on 14 healthy male subjects, ages 18 to 55, with a body mass index (BMI) between 18 and 32 kg/m². The pharmacodynamics of rivaroxaban in patients who have atrial fibrillation and varying ages, sex, BMIs and medical conditions is largely unknown. Even though the efficacy of the drug has been proven in a large scale multinational trial, there was no objective measurement of anti Xa activity of rivaroxaban in a diverse population and the primary question regarding the magnitude of systemic Xa inhibition provided by standard dose of rivaroxaban remains unanswered.

GOAL:

Measure the Xa inhibition of Rivaroxaban in patients with newly diagnosed atrial fibrillation meeting anticoagulation criteria for stroke prophylaxis.

OBJECTIVES:

This is an open label, multicenter study. All adult patients with new onset atrial fibrillation meeting criteria for enrollment based on the criteria mentioned below will receive 20mg of rivaroxaban once daily by mouth. A total of 100 patients will be recruited. Anti Xa activity, inr, prothombin
time and thrombin generation will be assessed at 3 hours, 6 hours, 12 hours and 24 hours after starting the medication.

INCLUSION CRITERIA:

1. Men or women aged ≥ 18 years with newly diagnosed non-valvular atrial fibrillation.
2. Atrial fibrillation must be documented by ECG evidence (e.g. 12-lead ECG, Holter, Pacemaker Interrogation).
3. ECG evidence of atrial fibrillation must be present on 2 occasions, 24 hours apart.
4. Presence of 2 or more of the following risk factors
   - Heart failure and/or left ventricular ejection fraction less than 35%.
   - Hypertension (defined as use of anti-hypertensive medications or persistent systolic blood pressure more than 140mmHg or diastolic blood pressure above 90mmHg)
   - Age ≥ 65 years.
   - Diabetes (defined as history of Type 1 or 2 diabetes mellitus or use of anti-diabetic medications)
   - History of prior ischemic stroke or TIA
   - Female sex
   - Presence of vascular disease
5. Patients must have signed an informed consent.

EXCLUSION CRITERIA:

1. Hemodynamically significant mitral valve stenosis.
2. Prosthetic heart valves.
3. Known presence of atrial myxoma or left ventricular thrombus.
4. Active endocarditis.
5. Active internal bleeding.
6. History of/or conditions associated with increased bleeding risk but not limited to
   - Major surgical procedure or trauma within 30 days before enrollment visit.
   - Clinically significant gastrointestinal (GI) bleed within 6 months before enrollment.
   - History of intracranial, intraocular, spinal or atraumatic intra-articular bleeding.
   - Chronic hemorrhagic disorder.
   - Known intracranial neoplasm, arterio-venous malformation or aneurysm.
7. Planned invasive procedure with potential for uncontrolled bleeding including major surgery.
8. Platelet count less than 90,000/µL at screening visit.
9. Sustained uncontrolled hypertension: systolic blood pressure ≥180mm Hg or diastolic blood pressure ≥100mmHg.
10. Severe disabling stroke (Modified Rankin Score of 4 to 5, inclusive) within 3 months or any stroke within 14 days of enrollment.
11. Transient ischemic attack within 3 days before enrollment.
12. Indication for anticoagulant therapy other than atrial fibrillation.
13. Use of intravenous anti-platelets within 5 days of enrollment.
14. Fibrinolytics within 10 days before enrollment.
16. Treatment with a strong inducer or inhibitor of cytochrome P450 3A4 (carbamazepine, phenobarbital, rifampin, glitazones, clarithromycin, ketoconazole, protease inhibitors) within 4 days before enrollment.
17. Pregnancy or breast feeding.
18. Calculated CrCl (creatinine clearance) of <50ml/min
19. Known significant liver disease with Child-Pugh Score of B or C, or ALT > 3 times the upper limit of normal.
20. Currently receiving linezolid
21. Failure to sign the informed consent.
**BACKGROUND STUDIES**

Rivaroxaban established its efficacy and safety in a large multinational trial involving more than 14,000 patients\(^1\). It has been recommended that rivaroxaban does not need any laboratory monitoring as the pharmacodynamics and pharmacokinetics of the drug are predictable over a wide range of dosage\(^2\). Preliminary studies have shown that there is very little inter and intra- individual variability among normal healthy populations as most of the pharmacokinetic properties of rivaroxaban were studied in healthy young subjects\(^3\). However, the patients who are at risk of developing vascular thromboembolic complications based on the CHADS2VASC score and qualify to receive Rivaroxaban have unfortunately never been studied in a systematic manner. Although the efficacy of the drug in that subgroup of patients is known, the degree of Factor Xa inhibition is largely unknown, despite the availability of accurate anti-factor Xa assays\(^6\). This knowledge may be especially helpful in sub-groups of patients who have variation from the medication’s normal pharmacokinetics or pharmacodynamics\(^4\). The level of Xa inhibition may be important, specifically when there are complications like bleeding or in pre-operative settings. Inhibition monitoring may be a clinically effective means of optimizing a particular individual’s drug regimen. Moreover, because of the lack of data regarding the magnitude of anti-Xa in patients receiving rivaroxaban, it is difficult to justify its use in the setting of acute coronary syndrome where other Factor Xa inhibitors like enoxaparin and fondaparinux have been proved to be efficacious and safe\(^5\), but rivaroxaban has been associated with increased risk of non fatal bleeding\(^7\).

Our study will be the first post marketing evaluation of the hematological properties of rivaroxaban. We will we be able to assess the activity of rivaroxaban in different subgroups of patients in hope it may provide us answers to make the drug safer and perhaps pave the pathway for the use of the medications in conditions like acute coronary syndrome and PCI.
REFERENCES:

EVALUATION METHODS

Investigation Site:
Geisinger Community Medical Center, Scranton, PA
Regional Hospital of Scranton, Scranton, PA
Moses Taylor Hospital, Scranton, PA
Dr. Samir Pancholy’s Office, S Abington Twp, PA
Dr. Michael Kondash’s Office, S Abington Twp, PA
Dr. Stephen Voyce’s Office, Scranton, PA

Inclusion and Exclusion Criteria:

INCLUSION CRITERIA:

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**Anticipated Number of Subjects:**

A total of 100 patients will be enrolled in the study.

**Randomized Procedures if single or double-blind:**
This is an open label study.

Parameters to be Measured:

1. Anti Xa activity of rivaroxaban and Fondaparinux at baseline and 3, 6 hour, 12 hour and 24 hour after drug administration*
2. PT/inr at each time interval*
3. Thrombin Generation at each time interval*
4. Age
5. Sex
6. Body Mass Index
7. Presence/ Absence of hypertension
8. Presence/ Absence of diabetes
9. Presence/ Absence of TIA or Stroke
10. Presence/ Absence of vascular disease
11. Type of atrial fibrillation: Paroxysmal, Persistent or Permanent
12. ALT
13. Creatinine Clearance
14. Use of non-steroidal anti-inflammatory drugs
15. Complications (if any)

*Xa inhibition, PT/inr and Thrombin Generation will be analyzed at each time interval using a single 3.2 ml blood sample collected into a trisodium citrate anticoagulant non-wettable tube.

Anticipated Length of Study:

1(One) Year
PROPOSAL EVALUATION CRITERIA

Qualifications of those doing the work, especially the Principal Investigator (P.I.):

Samir B Pancholy. MD.FACC. FSCAI. (Principal Investigator). Program Director, Cardiology, WCGME.

Michael Kondash. D.O. Director of Osteopathic Medical Education, WCGME

Stephen Voyce MD FACC, FACP, FSCAI. Associate Program Director, Cardiology, WCGME

Pranjal Kumar Boruah. M.D. Cardiology Fellow, WCGME

Nicholas Ierovante D.O. Internal Medicine Resident, WCGME

Fred Leri, PharmD, Pharmacist, Geisinger Community Medical Center

Commitments and Support:

The Wright Center will be providing administrative space as necessary for the accomplishment of the project deliverables. Geisinger Community Medical Center will be providing us the laboratory support for the anti Xa levels. Basic research support like screening and recruitment of patients will have support from the Internal Medicine residents.