Title: **A**pixaban for Early Prevention of **Re**current Embolic **S**troke and Hemorrhagic **T**ransformation (AREST)

Drug or Device Name(s):	Apixaban
FDA IND:	Exempt
BMS Protocol #	CV185-370
IRB Protocol #:	Pro00019754
NCT #	NCT02283294

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ABBREVIATIONS AND DEFINITIONS OF TERMS

°C	Degrees centigrade
AE	Adverse event
AF	Atrial Fibrillation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
aPTT	Activated Partial Thromboplastin Time
BMS	Bristol-Myers Squibb
CMP	Complete metabolic panel
CBC	Complete blood count
CK	Creatine kinase
CMB	Cerebral Microbleeds
CT	Computed Tomography
DSMB	Data and Safety Monitoring Board
E.G.	For Example
EKG	Electrocardiogram
EOS	End of Study
EW	Early Withdrawal
FDA	Food and Drug Administration
GRE	Gradient Recovery Echo
INR	International Normalization Ratio
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
NVAF	Non-Valvular Atrial Fibrillation
NSAE	Non Serious Adverse Event
PI	Principal Investigator
SS-QOL	Stroke Specific Quality of Life Scale
SACCO	Stroke Adjudication Committee for Classification and Organization
SWI	Susceptibiltiy Weighted Imaging
TEE	Trans-Esophageal Echocardiogram
TSH	Thyroid Stimulating Hormone
TIA	Transient Ischemic Attack
ULNS	Upper Limit of Normal
USF	University of South Florida
WOCBP	Women of Child Bearing Potential

Schedule of Study Procedures

TIA -Apixaban group	**Screen/ Baseline**	**Treatment Initiation**	**Maintenance‡**						**End of Study**	**30day PC**	**Early Withdrawal**	**Unsch**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Study Days (Visit Window)	**0**	β (See also table 2)	**14** (±3)	**30**(±5)	**60**(±10)	**90**(±10)	**120**(±10)	**150**(±10)	**180** (±10)	**210**±10)		
Informed Consent	✓											
Inclusion/Exclusion Criteria	✓											
General Medical History/Demographics	✓											
Physical Exam	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓
Vital Signs§	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓
mRS	✓		✓	✓	✓	✓	✓	✓	✓		✓	
NIHSS	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓
SS-QOL	✓			✓					✓		✓	✓
Urine pregnancy test‡	✓	✓‡	✓	✓	✓	✓	✓	✓	✓		✓	
12-lead ECG	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓
Clinical Lab Evaluation*	✓**			✓		✓			✓		✓	✓
PT/INR (Warfarin arm only)		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
TEE	✓†											
Event Monitor (prior to DC)		✓										
Carotid Ultrasound	✓											
MRI or CT scan	✓		✓						✓		✓	
Record AE/SAEs		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior and con. medications/procedures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Dispense Study Drug		✓	✓	✓	✓	✓	✓	✓				✓
Drug Compliance			✓	✓	✓	✓	✓	✓	✓		✓	✓
Non-study anticoagulation initiation									✓		✓	

β drug initatiation will be as follows: TIA: Apixaban arm day 0-3/Warfarin arm day 7(±5): Small stroke: Apixaban arm day 3-5/Warfarin arm day 14(±5): Medium stroke: Apixaban arm day 7-9/Warfarin arm day 14(±5)

* Results of existing tests will be obtained from subject's hospital chart to assess eligibility. If tests results are not available labs will be performed at the visit. See section 6 for a detailed description of what this entails.

§ Vitals: BP, HR,, weight, (RR and Temperature are optional, height obtained at baseline only)

** Labs for inclusion/exclusion criteria will include CMP, CBC with diff and platelets, Creatinine, PT/INR, LFTs and Lipid panel.

† performed prior to discharge

ǂ **All WOCBP MUST have a negative pregnancy test within 24 hours before receiving apixaban.** The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive apixaban and must not be enrolled in the study.[¥] **Study day at screening is day of event**

Dosing Category	**Apixaban dose initiation window**
TIA	Day 0-3
Small Stroke	Day 3-5
Medium Stroke	Day 7-9
Dosing Category	**Warfarin dose initiation window**
TIA	Day 7 (+/- 5)
Small Stroke	Day 14 (+/- 5)
Medium Stroke	Day 14 (+/- 5)

Table 2

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Non-Valvular Atrial Fibrillation (NVAF) is a growing problem with prevalence in the United States of approximately 5 million, up to half of whom are unaware that they have the most common cardiac arrhythmia. Patients with AF are at five time's greater risk for having a stroke than those in normal sinus rhythm[1, 2]. Current clinical practice prohibits early use of anticoagulation following stroke even when etiology is suspected as embolic[3, 4]. Furthermore, strokes in patients with atrial fibrillation have been shown to be associated with increased morbidity and mortality[1, 2].

Several recent trials with novel anticoagulation (table 3) have shown stroke prevention efficacy equal to or superior to warfarin with over a fifty percent reduction in intracranial bleed; however they excluded subjects with a stroke within seven or less days [5, 6, 7, 8, 9].

The results from these pivotal trials are listed below:

	Rely		**Rocket AF**		**Aristotle**		**Engage AF**	
	Warfarin	**Dabigatran 150mg**	**Warfarin**	**Rivaroxaban**	**Warfarin**	**Apixaban**	**Warfarin**	**Edoxaban 60mg**
Stroke Per year	1.69 %	1.11%	2.2 %	1.7%	1.6%	1.27%	1.50 %	1.18%
Hemorrhagic stroke per year	0.38%	0.10%	0.7 %	0.5 %	0.47%	0.24%	0.47%	0.26%
Major Bleed Per year	3.36 %	3.11 %	14.5% *	14.9% *	2.09%	2.13%	3.43 %	2.75 %
Intracranial Bleed Per Year	0.74%	0.30%	0.70 %	0.50 %	0.80 %.	0.33 %	0.85 %	0.39 %

Table3* total bleed rate accounted for not just major bleed

This study is being conducted to evaluate if anticoagulation treatment with Apixaban, initated earlier then the recommended guidelines of within 14 days after embolic stroke for patients with atrial fibrillation is associated with decreased risk for recurrent embolic stroke without increasing the risk of hemorrhagic transformation compared to conventional treatment (i.e. no anticoagulation treatment within 14 days of stroke[10, 11].

1.2 Findings from pre-clinical and clinical studies

Currently, there are limited data regarding the early start of anticoagulation therapy following embolic stroke.

In the review of our local stroke database from October 2011 until December 2013, we examined the records of 336 small to medium stroke patients admitted to Tampa General Hospital with an ischemic stroke secondary to atrial fibrillation. The average age in our study population was 75.3 ± 1.83 years of age. Stroke risk was similar to other AF groups in the literature, possessing an average CHADS2 score of 2.6 ± 0.26 on admission; average CHA2DS2-VASc score was 4.4 ± 0.4. Average hospital stay was 9.8 ± 1.49 days. We observed a 24.7% ± 6.2% mortality rate in our population prior to discharge. In addition, stroke survivors had a 5.1% recurrent non-fatal stroke risk. Patients with disabling or fatal

strokes were of a more advanced age than those who survived without severe disability (78.0 ± 1.96 years vs 69.7 ± 3.50 years, p <0.001).Our data indicate that the risk of fatal to recurrent stroke is approximately 25 % with standard treatment (initiating anticoagulation approximately seven to fourteen days after signs and symptoms) for this group of patients [12].

The HAEST trial indicated that low molecular weight heparin results in a reduction in mortality and disability when used early (30 hours post stroke)in the treatment of ischemic stroke; however, this benefit is offset by an increased risk of intracranial hemorrhage [3, 13, 14]

The previous studies on novel anticoagulation (NOAC) excluded subjects with a stroke/TIA within seven or less days; however, these randomized trials consistently demonstrated a lower risk of intracranial bleed compared to traditional anticoagulants (see table 2) [5, 6, 7, 8, 9].

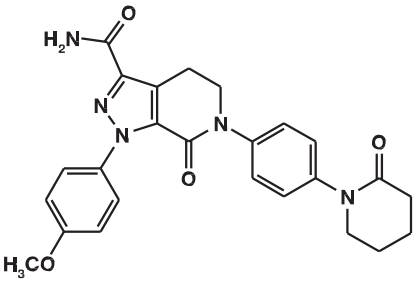
ARISTOTLE followed a limited number of subjects (44) who suffered a stroke/TIA, between 7 and 14 days prior to randomization to treatment with either Apixaban or warfarin. There was only 1 subject in the warfarin group who suffered a major bleed [5, 15]. There were no recurrent stroke or systemic embolism in any of the 44 patients.

Recently investigators have reported the use of Dabigatran given within 24 hours of a TIA/minor stroke onset in a population of non-AF patients and have found it to demonstrate no significant increase in hemorrhagic transformation in this population [16].

Based on these limited data, we propose to examine the potential advantage of a treatment regimen of Apixaban at 0-3 days after TIA, 3-5 days after small ischemic stroke and 7-9 days after medium stroke in patients with atrial fibrillation

1.3 Name and Description of Investigational Product or Description of Intervention [17]

Apixaban, a factor Xa (FXa) inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide. Its molecular formula is C25H25N5O4, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



Apixaban is a white to pale-yellow powder. At physiological pH (1.2–6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL [17].

This study is an open label, randomized, active controlled pilot study of Apixaban in subjects with NVAF who have, within 48 hours from signs and symptoms, been diagnosed with a TIA or a Small to Medium Ischemic Stroke as defined by the SACCO (see section 2.3) .

In this study 120 patients with NVAF who have had a recent small or medium stroke or TIA (within 0-48 hours) will receive Apixaban twice a day for 180 days with drug initiation day 0-3 (TIA), day 3-5(small stroke) or day 7- 9 (medium stroke) respectively or receive standard of care warfarin starting at day 7±5 (TIA) or day 14 ±5 (small to medium ischemic stroke).

1.4 Selection of Drugs and Dosages

1.4.1 Apixaban

The dosage of Apixaban is based on the clinical findings of studies in human subjects and its FDA approved dosage for patients with nonvalvular atrial fibrillation. Patients will receive 5mg dosage twice a day or 2.5 mg if they have any 2 of the following characteristics:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Coadministration with CYP3A4 and P-glycoprotein inhibitors: For patients receiving Apixaban 5 mg twice daily when Apixaban is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin), the recommended dose is 2.5 mg twice daily [patients already taking 2.5 mg twice daily, coadministration of Apixaban with strong dual inhibitors of CYP3A4 and P- glycoprotein should be avoided [17].

1.4.2 Warfarin

Standard of care arm will be on Warfarin which will be locally sourced and commercial drug supply provided by Primary Investigator. See appendix 13.4 for dosing guidelines.

1.5 Compliance Statement

This study will be conducted in full accordance with all applicable Institutional Policies of participating sites and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report adverse events in accordance with IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY GOVERNANCE

2.1 Executive Committee

The Executive Committee will be composed of a group of clinical experts responsible for ensuring that study design, execution and management are of the highest quality. The Executive Committee will monitor progress of study enrollment, make recommendations in collaboration with the sponsor based on the Stroke Adjudication Committee and DSMB Committee input, and oversee the presentation and publication of the trial results. The committee will convene regularly by teleconference and/or face-to-face meetings to discuss and report on the ongoing conduct of the study in collaboration with the sponsor.
The chairman of the Executive Committee will serve as the third member to both the stroke adjudication and atrial fibrillation committees to meet consensus if necessary.

2.2 Data and Safety Monitoring Board

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. The recommendations will be forwarded to the Executive Committee and the sponsor for final decision.
The DSMB is an independent group advisory to the executive board and is required to provide recommendations about continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, about the benefit/risk ratio of procedures and participant burden

The DSMB will convene annually and at the milestones of 40 and 80 patients enrolled as well as at study conclusion to review safety data.

Notification of and referral for abnormal findings Data will be collected by the research team. Study data will be entered into the data collection forms or recorded electronically as they are collected during the study visit. The PIs will monitor all data for any inconsistencies or irregularity. If unanticipated adverse events or SAE of importantce (symptomatic hemorrhagic transformation) are observed, they will be reported to the DSMB within 24 hours. All other AE's will be reported during scheduled meetings and to the IRB according to standard AE reporting policies. The Principal Investigator will forward all decisions to the regulatory authority as appropriate.

2.3 Stroke Adjudication Committee (SACCO)

The Stroke Adjudication Committee will review and adjudicate all stroke endpoints. The committee will not be blinded to patient and study medication arm during the review of each stroke endpoint case.

2.3.1 Adjudicators

W. Scott Burgin, MD
David Z. Rose, MD
Swetha Renati, MD
Department of Neurology
University of South Florida
Ryan Murtagh, MD
Department of Radiology
University of South Florida

2.3.2 Stroke/TIA Subtype Classification[18, 19]

2.3.2.1 Ischemic Stroke

Defined as an acute symptomatic focal cerebral or retinal dysfunction caused by an infarction of central nervous system tissue.

1. a. Acute infarcts are classified as small, medium or large based on size of the largest ischemic lesion:
    a. small = lesion in the anterior or posterior circulation <1.5 cm.
    b. medium = equal to or greater than 1.5cm but less than a complete territory infarct lesion in a cortical superficial branch of the anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), or in a branch of MCA or PCA, or lesion in internal border-zone territories.
    c. large posterior = lesion involving complete PCA territory, or lesion of cerebellum 1.5 cm or larger or any lesion of the brain stem.

d. large anterior = lesion involving complete ACA or MCA territory, or lesion involving >1 artery territory

e. All classifications are based of the measurement of the largest lesion size with preferred sequencing to be GRE on MRI (*but all effort should be used to maintain the same modality of sequencing and magnet strength used at baseline*

2.Subacute/chronic or 'old' infarcts (i.e. more than 2 weeks) are noted but not classified.

3.Transient Ischemic Attack (TIA)
defined as an acute symptomatic focal cerebral, spinal, or retinal dysfunction in which symptoms resolve (typically in less than 1 day) without acute damage on neuroimaging.

2.3.2.2 Hemorrhagic Stroke

Defined as an acute symptomatic focal or global cerebral dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage; or asymptomatic neuroimaging-positivity, including greater than three cerebral microbleeds found with GRE-sequenceing and/or CT hyperintensities

2.3.2.3 Undetermined Stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

2.3.3 Examination

Outpatient (in clinic) or Inpatient (in hospital) physical neuro-examination at day 14, 30, 60, 90, 120, 150 and 180

2.3.4 Stroke Disability

Stroke disability should be measured by a reliable and valid scale in all cases, modified Rankin Scale (mRS) and NIHSS at day 14, 30, 60, 90, 120, 150 and 180 (see appendix 13.1 and 13.2)

2.4 Atrial Fibrillation Review Committee

The Atrial Fibrillation Adjudication Committee will provide Atrial Fibrillation Classifications and Diagnosis prior to randomization on subjects with new onset atrial fibrillation if the local PI is in doubt of diagnosis. All patients will be reviewed by the Atrial Fibrillation Review Committee at the end of the study.

2.4.1 Members

Michael Fradley, MD
Department of Cardiovascular Sciences
University of South Florida

2.4.2 Atrial Fibrillation Classifications and Diagnosis [10]

2.4.2.1 Definition

a. **Non Valvular Atrial fibrillation (NVAF**) is defined as a supraventricular tachyarrhythmia with rapid, uncoordinated atrial electrical activity and irregular ventricular responses in the presence of intact atrioventricular (AV) conduction. ECG, Holter, telemetry, or event monitor characteristics include:

1) irregular R-R intervals (when AV conduction is present), 2) absence of distinct repeating P waves, and 3) irregular atrial activity**.**

b. **Premature atrial contractions (PACs)** with underlying sinus rhythm or organized atrial supraventricular tachyarrhythmias such as atrial tachycardia or atrial flutter will not constitute a diagnosis of AF

2.4.2.2 Classification

a. **Paroxysmal** – Atrial fibrillation that terminates spontaneously or with intervention within seven days of onset. Episodes may recur with variable frequency.
b. **Persistent** – Atrial fibrillation that is sustained for more than 7 days. Episodes often require pharmacologic or electrical cardioversion to restore sinus rhythm.
c. **Long-standing persistent** – Atrial fibrillation that has lasted for more than 12 months.
d. **Permanent** – Persistent atrial fibrillation where a joint decision by the patient and clinician has been made to no longer pursue a rhythm control strategy.

e. **Non valvular Atrial fibrillation** – AF in the absence of rheumatic mitral stenosis, a mechanical valve

2.4.2.3 Atrial Fibrillation Diagnosis

a. Known past medical history of atrial fibrillation (as documented in patient's medical record)
b. Newly diagnosed atrial fibrillation lasting at least 10 seconds as documented by 12-lead electrocardiogram, rhythm strip, telemetry monitoring, Holter/event recorder monitoring.
c. Pacemaker/ICD/implantable loop recorder interrogation – Electrograms must be used to make the diagnosis (marker channels and mode switch episodes are not sufficient or appropriate). Electrograms should be reviewed by a member of the Atrial Fibrillation Adjudication Committee

3 STUDY OBJECTIVES

3.1 Research Hypothesis

Early anticoagulation treatment regimen with Apixaban at 0-3 days after TIA, 3-5 days after small ischemic stroke and 7 to 9days after medium ischemic stroke for patients with atrial fibrillation will result in a decreased incidence for recurrent ischemic stroke and without significant increase in risk of intracranial hemorrhage compared to conventional treatment for TIA, small and medium sized strokes.

3.2 Primary Objective

In patients with atrial fibrillation with recent cerebral ischemic symptoms (0-48 hours), to evaluate whether the treatment regimen with Apixaban (Three subgroups: TIA: day 0-3; small stroke: day 3-5; medium stroke: day 7-9) compared with standard of care treatment regimen with warfarin (Three subgroups: TIA: day 7±5; Small or medium stroke: day 14±5) reduces the composite endpoint of fatal stroke, recurrent ischemic stroke or TIA at 30 and 180 days. (See figure 1)

3.3 Secondary Objectives

In patients with atrial fibrillation with recent cerebral ischemic symptoms (0-48 hours), to evaluate whether the treatment regimen of early Apixaban (Three subgroups: TIA: day 0-3; small stroke: day 3-5; medium stroke: day 7-9) compared with standard of care treatment with warfarin (three subgroups: TIA: day 7±5; Small or medium stroke: day 14±5) does not increase the number of intracranial hemorrhage assessed by MRI/CT by 30 and 180 days.

Additional information will be collected on:

- Quality of Life
- Modified Rankin Score
- NIH Stroke Scale
- Echocardiography
- AF Burden (Event Monitor data).

4 INVESTIGATIONAL PLAN

4.1 General Schema of Study Design

This will be a multi-center, open label, randomized, active control, parallel-group pilot trial to examine the effect of initiation of APIXABAN at days 0-3 (TIA), days 3-5 (small stroke) and days 7-9 (medium stroke) to decrease fatal and/or recurrent stroke/TIA in 120 subjects who have suffered a recent(0 to 48 hours from symptoms) TIA, or small to medium ischemic stroke as defined by appendix 13.1 compared to standard of care warfarin treatment regimen. Subjects will be randomly assigned in a 1:1 ratio to one of two treatment arms (apixaban or warfarin). Subjects will be followed for a total of 180 days from screening through follow-up.

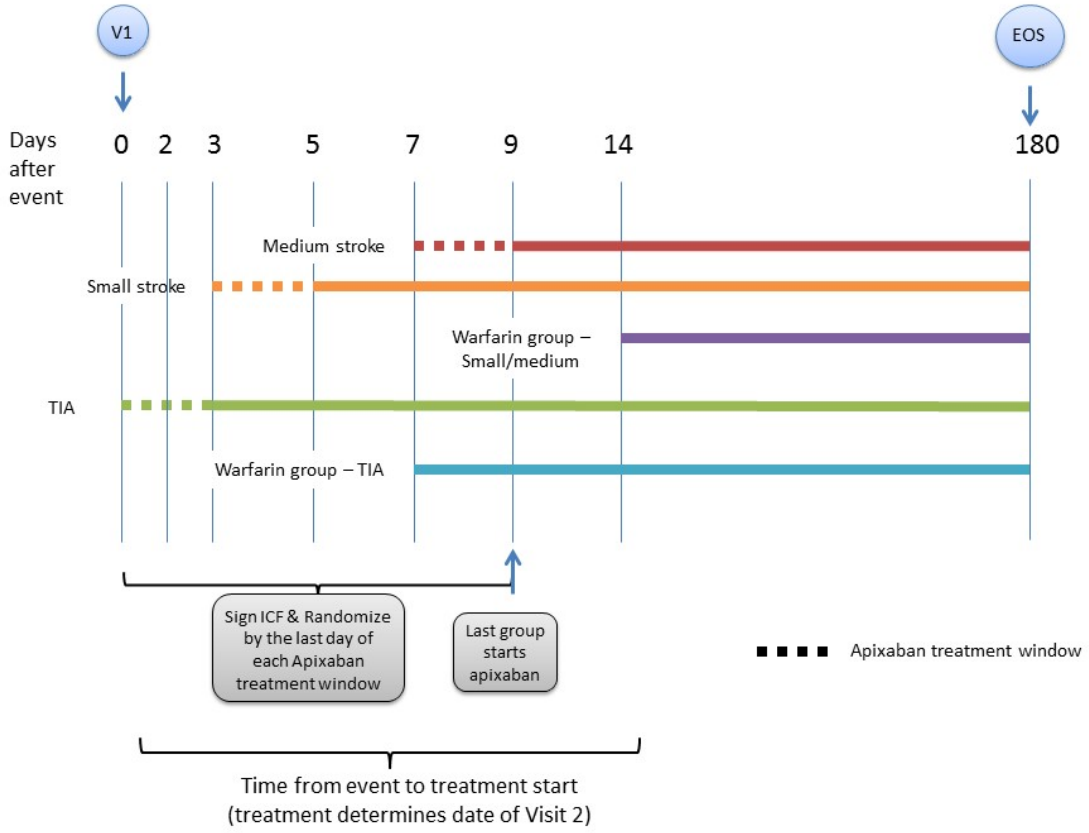


Figure 1

4.1.1 Screening Phase

Potential subjects will be screened using the protocol inclusion and exclusion criteria. All subjects will have a diagnosis of NVAF with TIA or small to moderate embolic stroke.

Subject consent will be obtained prior to any study related procedures being performed, including discontinuation of current therapy. All females of child bearing age will have a urine pregnancy test. Labs to assess liver and kidney function and an EKG will be obtained from the patients' hospital record or obtained at screening if not available at time of consent. A physical exam will be obtained at screening and at various points throughout the study.

The screening and baseline/randomization visit may be combined as long as all inclusion/exclusion criteria have been met prior to randomization. Otherwise, if these reports are not available at the time of screening then randomization and study initiation can be combined into one visit.

4.2 Study Duration, Enrollment and Number of Sites

4.2.1 Duration of Study

The study duration per subject will be approximately 180 days. The active treatment phase is dependent on the dosing category (TIA, small or medium ischemic stroke) that the subject is placed in and which treatment regimen the patient is randomized into.

4.2.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at University of South Florida (USF Health's South Center for Advanced Health Care, USF Health's Morsani Center for Advance Health Care , Tampa General Hospital), University of Louisville (hospital and clinic), University of California Los Angeles (hospital and clinic), and Bayfront Cardiovascular Sciences for a total of 4 enrolling sites.

Recruitment will stop when approximately 120 subjects meeting eligibility criteria are enrolled. To account for drop-outs as well as screen-failures up to 125 subjects will be consented and randomized.

4.3 Study Population

Adult patients with the diagnosis of atrial fibrillation and recent TIA or ischemic small to medium stroke . Recent TIA will be defined as up to 3 days from signs and symptoms, recent small stroke will be up to 5 days from signs and symptoms and recent medium stroke will up to 9 days from signs and symptoms.

4.3.1 Inclusion Criteria

1. Signed Written Informed Consent
    - Before any study procedures are performed, subjects will have the details of the study described to them, and they will be given a written informed consent document to read. Then, if subjects consent to participate in the study, they will indicate that consent by signing and dating the informed consent document in the presence of study personnel.

2. Males and Females 18 years of age and over.

3. History of Nonvalvular Atrial Fibrillation (NVAF) by documentation in the medical history or newly diagnosed nonvalvular Atrial Fibrillation at time of study randomization by ECG, device or telemetry (see section 2.4.2)

4. Diagnosis of a recent TIA or small or medium ischemic stroke . Recent TIA is defined as up to 3 days from signs and symptoms, recent small stroke will be up to 5 days from signs and symptoms and recent medium stroke will up to 9 days from signs and symptoms. (See section 2.3.2)

5. Women of child-bearing potential must use a reliable method of contraception and must provide a negative pregnancy test at entry into the study and within 24 hours of study treatment initiation.

6. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug Apixaban plus 5 half-lives (approximately 3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion.

7. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with Apixaban plus 5 half-lives (approximately 3 days) plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion.

8. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena by WOCBP subject or male subject's WOCBP partner Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard™
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

4.3.2 Exclusion Criteria

1. Hemorrhagic stroke
2. Large ischemic stroke
3. History of major bleeding within the last 6 months from time of subject enrollment (e.g. GI bleed).
4. History of intracranial bleed
    a. Traumatic intracranial bleed within one year of randomization. (Traumatic ICH greater than one year of randomization is not an exclusion).
5. Current or history of bleeding disorders (e.g. blood dycrasias)
6. Blood Pressure of 180/100 mmHg on hypertensive therapy day of randomization per PI discretion [20].
7. Current illicit drug use and/or chronic alcohol use per PI discretion.
8. Severe liver disease (AST/ALT 2x upper limit).
9. Patients with kidney disease meeting criteria to take 2.5 mg twice daily who are taking strong dual inhibitors of CYP3A4 and P-glycoprotein (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin) .
10. Any other suspected etiology for stroke (e.g. ipsilateral carotid disease).
11. Greater than 3 Cerebral Micro-bleeds (CMB) on gradient recovery echo (GRE) or evidence of intracranial hemorrhage on CT at time of randomization. (SWI sequencing may be used if GRE sequencing is not obtainable)
12. Therapeutically anti-coagulated at time of admission (INR at admission greater than 2.0 on warfarin or took two consecutive doses of NOAC).
13. Absolute indication for use of warfarin only.(e.g. Mechanical Valve)
14. Absolute indication for anticoagulation prior to randomization window. (e.g. DVT)
15. Hemoglobin less than 9 gm/dl and/or platelet count less than 100 K/uL.
16. Requires dual antiplatelet therapy.

17. Daily use of NSAIDS

18. Pregnancy or lactation.

19. Any use of an investigational product within the past 30 days.

20. Prisoners or subjects who are involuntarily incarcerated.

21. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

22. Concurrent participation in another clinical study where use of an investigational product is used

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria will be reported in accordance with IRB Policies and Procedures.

4.3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal :

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

5 STUDY DESIGN AND INTERVENTION

5.1 Screening Visit

Potential subjects will be screened using the protocol inclusion and exclusion criteria. All subjects will have a diagnosis of AF with TIA or small to medium ischemic stroke.

Subject consent will be obtained prior to any study related procedures being performed. All females of child bearing age will have a urine pregnancy test within 24 hours of starting study drug. Labs to assess liver and kidney function and an EKG will be obtained from the patients' hospital record or obtained at screening. A physical exam will be obtained at screening. The screening and baseline/randomization may be combined as long as all inclusion/exclusion criteria have been met prior to randomization. Otherwise, if these reports are not available at the time of screening, patients

will be required to return for a separate assessment visit after these items are obtained. Drug initiation visit may take place in hospital or as a clinic visit.

5.2 Baseline Visit/Randomization

The baseline/randomization visit will be performed up to 48 hours after signs and symptoms of stroke or TIA, and will be combined with the screening visit as long as all inclusion/exclusion criteria have met prior to randomization.

After subjects have been screened and enrolled in the study, baseline assessments will be performed. Patients will be stratified according to their type of stroke (TIA, small or medium stroke) and randomized 1:1 in each group to ensure for equal number of subjects for each three types. Treatment with APIXABAN 5mg or 2.5mg based on clinical characteristics defined in section 1.4 or Warfarin (target INR 2-3) will begin based on the randomization treatment regimen. Study treatment regimen is initiated based off of TIA or stroke size. Subjects in the Warfarin arm will return to clinic with unscheduled INR checks until they reached the standard INR of 2.0 to 3.0.

Hypertension will be treated per the AHA/ASA guidelines and are described below:

Goals for target blood pressure level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure less than 140 mm Hg and a diastolic pressure less than 90 mm Hg. For patients with a recent lacunar stroke, it might be reasonable to target a systolic blood pressure of less than 130 mm Hg. [20]

Resumption of Blood Pressure therapy is indicated for previously treated patients with hypertension.

5.3 Treatment Phase

A study visit for the initiation of treatment will be conducted based on dosing category of TIA, Small stroke or medium stroke. See table 2 below and figure 1:

Dosing Category	**Apixaban dose initiation window**
TIA	Day 0-3
Small Stroke	Day 3-5
Medium Stroke	Day 7-9
Dosing Category	**Warfarin dose initiation window**
TIA	Day 7 (+/-5)
Small Stroke	Day 14 (+/-5)
Medium Stroke	Day 14(+/-5)

Table 2

Subjects will maintain the maximum dose for approximately 180 days (depending on dosing category) with study visits at drug initiation, day 14, 30, 60, 90, 120, 150 and 180. Patients will undergo drug accountability, AE/SAE assessment, and any concomitant medication changes.

5.4 End of Study

A final visit will be conducted at day 180 in person. Study medication will be collected at this visit and the patient will be started on standard of care therapy. Decisions regarding anticoagulation will be based off the subject's individual needs as assessed by the Principal Investigator or Sub-Investigator.

30 days after the EOS a phone call will be made to assess for AE's or SAE's that may have occurred during that time frame.

5.5 Study Assessments (See figure 1)

The NIHSS and mRS Stroke will be obtained at screening and days 14, 30, 60, 90, 120, 150 and 180. MRI (or CT for subjects with contraindication to MRI) will be obtained at day 14 and EOS or Early Withdrawal (EW).

The Stroke Specific Quality of Life Scale (SS-QOL) will be conducted on screening day and again on day 30 and at EOS or EW.

5.6 Unscheduled Visits

5.6.1 Super-therapeutic/Sub-therapeutic INR

If the subject is not within therapeutic range they will be expected to return to clinic for an unscheduled visit to check the INR value until therapeutic range is met per the warfarin dosing protocol. These visits will be scheduled per PI discretion.

5.6.2 Adverse Events

If the subject reports an adverse event that requires medical investigation an unscheduled visit will be arranged. This can be arranged through the site coordinator. All medically relevant diagnostic tests will be performed at that time.

5.7 Subject Completion/Early Withdrawal

It will be documented whether or not each subject completed the clinical study. A subject is considered to have completed the study if he/she has taken all study medications for 6 months and has completed 6 month study assessments or withdrew from the study due to the occurrence of a recurrent embolic stroke , hemorrhagic transformation or death. If a subject does not complete the treatment phase, their data will be used for efficacy and for any safety analysis.

It is understood that withdrawals may occur during a trial. Each subject has the right to withdraw from the trial at any time for any reason without affecting the right to treatment by the investigator. Subjects who do not complete the treatment phase for other reasons then mentioned above , should be followed at day 14 and EOS visits, if possible. At minimum these patients should have a monthly phone call to asses AE/SAE and vital status if they are unable to continue follow-up in clinic.

Subjects needing to withdraw prior to the completion of the study and who do not agree to continue in follow-up should return to the clinic for completion of early withdrawal procedures, as outlined in table 1.

Reasons that a subject may discontinue the study include the following:
- Adverse events including recurrent stroke or hemorrhagic transformation
- Intercurrent illnesses
- Any significant new medical condition
- Protocol violation
- Non-compliance to study medication regimen

- Use of any investigational drug other than the study medication
- Intake of prohibited medication
- Pregnancy
- Subject withdrew consent or lost to follow-up
- Other (reason to be documented)

Withdrawals due to intercurrent illnesses or AEs will be fully documented in the CRF with the addition of supplementary information if available and/or appropriate. Withdrawals due to non-attendance will be followed-up by the investigator to obtain the reason for non-attendance.

5.8 Concomitant Medication

Concomitant medication documentation will begin as soon as the subject takes the first dose of study medication. All concomitant medications used through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included. Subjects will be allowed to continue on concomitant medications. Any study related side effect (e.g., nausea) requiring medication management must be approved by the investigator prior to consumption.

6 STUDY PROCEDURES

6.1 Visit 1 Screening Visit/Baseline/Randomization (can occur on same day)

- Signing an informed consent form prior to any study related activities
- Confirmation of Atrial Fibrillation either at admission or in subjects medical history
- Physical exam including vitals
- Body weight and height
- Review MRI results to determine diagnosis of TIA or determine size of Ischemic stroke
- Review of labs, echocardiogram, and EKG reports or draw labs and conduct EKG/ECHO if needed.
- Obtain medical history with demographics
- Schedule carotid ultrasound or CTA angiogram of the neck if not done at admission
- Schedule TEE if not done at admission (optional)
- Review of concomitant medications and procedures
- Obtain mRS, NIHSS and SS-QOL scales
- Urine pregnancy test (for women of childbearing potential)
- Review of all inclusion/exclusion criteria
- Treat any patient with hypertension according the current guidelines. (see section 5.2)

6.2 Randomization

- Confirm subject group selection based of the SACC recommendations, (TIA, Small ischemic stroke, Medium ischemic stroke) and must confirm subjects meets all inclusion criteria and no exclusion criteria prior to randomization.
- Randomize Subject
- Discuss treatment arm with patient

6.3 Drug Initiation (may be same as randomization depending on group and study arm)

- Urine pregnancy test if not done within 24 hours of this visit
- Dispense study medication

- Provide patient education regarding treatment regimen.
- Apply event monitor within 14 days from randomization
- Assess AE/SAE's
- Assess concomitant medication changes
- Schedule next visit
- INR for Warfarin arm

6.4 Treatment visits

Visit day 14 (+/-3)

- Physical exam
- Vital Signs
- Urine pregnancy test if required
- ECG
- NIHSS, mRS
- MRI or CT scan
- INR for Warfarin arm
- Assess Drug Compliance
- Dispense study medication
- Provide patient education
- Assess AE/SAE's
- Assess concomitant medication /procedure changes
- Schedule next visit

Visit day 30 (+/-5) and 90 (+/- 10)

- Physical exam
- Vital Signs
- Collect Laboratory assessments including INR for Warfarin arm
- Urine pregnancy test if required
- ECG
- NIHSS and mRS
- SS-QOL only at day 30
- Assess Drug Compliance
- Dispense study medication
- Provide patient education
- Assess concomitant medication /procedure changes
- Assess AE/SAE's
- Schedule next visit

Visit day 60, 120, 150 (+/- 10)

- Physical exam
- Vital Signs
- Collect INR for Warfarin arm
- Urine pregnancy test if required
- ECG
- NIHSS , mRS

- Assess Drug Compliance
- Dispense study medication
- Provide patient education
- Assess concomitant medication /procedure changes
- Assess AE/SAE's
- Schedule next visit

6.5 End of Study (+/- 10)

- Physical exam
- Vital Signs
- Collect Laboratory assessments including INR for Warfarin arm
- Urine pregnancy test if required
- MRI or CT scan
- ECG
- NIHSS ,mRS and SS-QOL
- Assess Drug Compliance
- Provide patient education
- Assess concomitant medication /procedure changes
- Assess AE/SAE's
- Start on non-study Anticoagulation therapy

6.6 Early Withdrawal (EW)

- Physical exam
- Vital Signs
- Collect Laboratory assessments including INR for Warfarin arm
- Urine pregnancy test if required
- MRI or CT scan
- ECG
- NIHSS ,mRS and SS-QOL
- Assess Drug Compliance
- Provide patient education
- Assess concomitant medication /procedure changes
- Assess AE/SAE's
- Start on non-study Anticoagulation therapy

7 STUDY ENDPOINTS AND EVALUATIONS

7.1 Primary Endpoint

Endpoint data will start at randomization up to 180 days. These composite endpoints include:

- Fatal stroke
- Recurrent Ischemic stroke
- New hemorrhagic stroke

7.2 Secondary Endpoints

- Any intracranial bleeds assessed by MRI/CT scan at day 14 and EOS or at outcome event.
- Any major bleeds defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that was fatal. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.[2]

7.3 Other Endpoints of Interest

- Understanding the natural progression of ischemic stroke patients with NVAF within the first 14 days status post initial stroke event (i.e. stroke or TIA)
- Effect of the addition of anti-epileptic medications during hospital admission on outcomes in patients with embolic stroke secondary to AF
- Factors attributing to the addition of anti-epileptic medications during hospital admission in patients with embolic stroke secondary to AF
- Factors affecting stroke specific quality of life in patients with embolic stroke secondary to AF

7.4 Baseline Evaluation (see also schedule of events)

7.4.1 Physical Examination

A complete medical history including demographic characteristics (age, gender, and race/ethnicity) will be collected at screening. Complete physical and neurologic examinations will be performed at screening

7.4.2 Vital Signs

Heart rate, blood pressure will be performed at every study visit (temperature, and respirations are optional)

7.4.3 Laboratory Evaluations

Evidence of clinical laboratory evaluation within 72 hours of hospital admission will be required at screening. This will include Creatinine (CPT 82575), complete metabolic panel (CPT 80053), complete blood count with differential and platelets (CPT 85025),, Lipid Panel (CPT 80061) and PT/INR (CPT 85730), urine HCG (CPT 81025) if indicated, aPTT (CPT 85730), TSH (CPT 84443)

All WOCBP MUST have a negative pregnancy test within 24 hours before receiving apixaban. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive apixaban and must not be enrolled in the study. In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

See schedule of events

7.5 Efficacy and Safety Evaluations (see also schedule of events)

7.5.1 Diagnostic Tests, Scales, Measures, etc.

MRI w/o contrast (GRE sequencing preferred but all effort should be used to maintain the same modality of sequencing and magnet strength from baseline or CT w/o contrast –
Will be performed, along with the NIHSS, to measure the size of ischemic stroke at screening. It will also be used for follow-up assessments to indicate any early hemorrhagic transformation or micro-embolic strokes. Patients who are unable to have a MRI due to contraindication (i.e. implantable pacemaker) will have be allowed to use CT with the NIHSS.

- TIA- will have no ischemic changes
- Acute infarcts are classified as small, medium or large based on size of the largest ischemic lesion:
    - small = lesion in the anterior or posterior circulation <1.5 cm.
    - medium = equal to or greater than 1.5cm but less than a complete territory infarct lesion in a cortical superficial branch of the anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), or in a branch of MCA or PCA, or lesion in internal border-zone territories.
    - large posterior = lesion involving complete PCA territory, or lesion of cerebellum 1.5 cm or larger or any lesion of the brain stem.
    - large anterior = lesion involving complete ACA or MCA territory, or lesion involving >1 artery territory

- All classifications are based of the measurement of the largest lesion size.

TEE-
Will be obtained or scheduled prior to discharge on all patients or will be scheduled as part of their evaluation for potential cardiac sources of emboli. In addition to imaging specifically of left atrium thrombus; measurements will be obtained for left atrial size, left atrium appendage, velocity, left ventricle size and function and other significant myocardial or valvular heart disease.

Carotid ultrasound-
Will be performed on all patients to rule out ipsilateral carotid disease during the screening visit.

Laboratory evaluations-
Will be obtained from all patients at screening, day 30, day 90 and day 180. Additional lab measurements for the warfarin group will be obtained monthly and at unscheduled visits if warranted by the warfarin dosing protocol.

Event Monitor-
Will be obtained on all patients in order to characterize the atrial fibrillation burden to assess potential relationship to outcome events. The event monitor be started within 14 days (+3) from randomization and maintained for 30 days.

NIH Stroke Scale (NIHSS)- see appendix 13.2
Will be used with all patients to provide a rate of worsening, i.e., progression of the index stroke event assessed by deterioration in clinical symptoms and/or an increase in the score on the NIHSS. The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. The total score can range from 0-42. The breakdown of the scoring is described below:

0 = no stroke
1-4 = minor stroke
5-15 = moderate stroke
15-20 = moderate/severe stroke
21-42 = severe stroke

This scale will be administered at screening/baseline, day 14, 30, 60, 90, 120, 150, 180, and early withdrawal.

Modified Rankin Scale (mRS)- see appendix 13.1
Will be used with all patients to measure severity of stroke and overall disability of patients, this scale will also administered on screening/baseline, day 14, 30, 60, 90, 120, 150, 180, and early withdrawal. The breakdown of scoring is described below:

Scale	Disability
0	**No** symptoms at all
1	No significant disability despite **symptoms**; able to carry out all usual duties and activities
2	**Slight** disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	**Moderate** disability; requiring some help, but **able to walk without assistance**
4	**Moderately severe** disability; **unable to walk** without assistance **and** unable to attend to bodily needs without assistance
5	**Severe** disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Stoke Specific Quality of Life Scale (SS-QOL)-See appendix 13.3
The SS-QOL is a self-report questionnaire consisting of 49 items in the 12 domains of energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, upper extremity function, vision, and work/productivity. The domains are scored separately, and a total score is also provided. The psychometric properties of the SS-QOL have been validated in patients with ischemic stroke and intracerebral hemorrhage.

Physical
Weight will be recorded in pounds (lb) and height in inches (in).
Physical examination will include assessment of the head, eyes, ears, nose, throat, heart, chest, lungs, abdomen, extremities, peripheral pulses, skin and any other physical conditions of note.

Vital Signs
Blood pressure will be measured in all subjects in either the sitting or supine position.

Pregnancy Testing
Sexually active Women of Child-Bearing Potential (WOCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

Electrocardiogram (ECG)
12-lead ECG recordings will be obtained from primary care or performed at screening and examined for gross abnormalities. ECGs will be conducted at various points throughout the study as shown in section 5

Clinical Laboratory Evaluations
The following labs will be obtained at varies time points in the study as shown in section 6.

Complete metabolic panel which includes liver enzymes and creatinine, complete blood count with differential and platelets, PT/INR and if indicated urine HCG

7.5.2 Safety criteria for suspension of dosing

For subjects experiences adverse events the following criteria will be used to determine whether the individual or the entire trial should be discontinued.

For individual patients
In the event of a Grade 3 or higher adverse event attributable to treatment with APIXABAN and not related to the underlying disease, administration of APIXABAN will be suspended in the patient to allow analysis and determination whether to continue the treatment, alter dosing regimen or to exclude the patient from further participation in the study; if there is any increase in cerebral microbleeds (CMB) at day 14, in either arm, all study medication will be suspended until a repeat MRI is performed 48 hours from day 14 MRI. Study medication will be restarted in clinically stable individuals. In subjects who have a CT scan at day 14 and have a asymptomatic intracranial hemorrhage, all study medication will be suspended until a repeat CT is performed at 48 hours from the day 14 scan. Sstudy medication will be restarted in clinically stable individuals. If subjects experience any symptomatic hemorrhagic transformation in either arm, study medication will be suspended. All subjects will continued to be followed up monthly either by phone or clinic contact until the end of study.

For all patients
In the event of five or more patients experiencing a symptomatic hemorrhagic transformation in the APIXABAN arm and not related to the underlying disease, dosing will be suspended in all patients to allow analysis and determination whether to continue the treatment, alter dose regimen or to terminate the study.

8 STATISTICAL CONSIDERATIONS

8.1 Statistical Methods

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8.1.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). Non-parametric analyses will be used in situations where the variables are not normally distributed. Baseline comparisons will be performed to test if there is any residual unbalance between the treatment and the control groups on demographic and other influential clinical variables. ANOVA or nonparametric ANOVA will be used to test continuous variables such as AGE. Chi-square or Fisher's Exact test will be used to test categorical variables such as GENDER. If a covariate is unbalanced, it will be included in the regression model for the multivariable analysis as a control variable

8.1.2 Efficacy Analysis/Primary Aim

For the main outcomes, the proportion of patients with any primary outcome (fatal stroke, recurrent ischemic stroke, transient ischemic attack) will be computed along with the 95% confidence interval for the differences in treatment arms.

The primary outcome is defined as any component of the composite primary outcome occurred within 30 and 180 days or otherwise had adequate follow-up. Logistic regression models will be fitted with the primary outcome as the dependent variable and the SUBGROUP: (1) Apixaban TIA: day 0-3; (2). Apixaban small stroke: day 3-5; (3). Apixaban medium stroke: day 7-9; (4) warfarin TIA: day 7±5; (5) warfarin small stroke: day 14±5; (6) warfarin medium stroke: day 14±5 as the primary independent variable. The overall treatment effect will be assessed by the ESTIMATE and LSMEANS of all the Apixaban groups to all the warfarin groups. Comparison between individual subgroups will be assessed by constructing different ESTIMATE. For example, (1) Apixaban TIA versus (5) warfarin Small stroke: day 14±5. These analyses will be implemented by using SAS 9.2 PROC LOGISTIC which has the ESTIMATE and the LSMEANS statements for the group comparisons. $P<0.05$ is used for the overall treatment effects. All other subsequent subgroup testing will be adjusted for multiple comparisons by using PROC PLM.

8.1.3 Safety Analysis/Secondary Aim

The outcome will be measured at 30 and 180 days for all 6 subgroups: all coded as 0 or 1 at both follow-up points.

The analysis plan for this aim is very similar to that for the Primary Aim except the outcome here is defined as intracranial hemorrhage (which is coded as a 0 and 1 variable), and (2) the hypotheses for the outcomes are directional and therefore one-sided tests will be performed. AE incidence will be summarized along with the corresponding 95% confidence intervals.

8.1.4 Potential Confounders

Age and sex as well as a variety of clinical variables (e.g. $CHADS_2$-VASc, CHA_2DS_2) that are risk factors for embolic stroke, and their associations with fatal or recurrent embolic stroke or hemorrhagic cerebral bleed will be examined. Other clinically relevant variables that are shown to differ between treatment regimens at enrollment will also be examined as potential confounders.

For missing data, both an intent-to-treat analysis (in which subjects are analyzed according to their randomized assignment) and a per-protocol analysis (in which subjects not treated according to their randomized assignment and/or with other major protocol violations are removed from this analysis) will be conducted. Sensitivity analyses to assess the effect of missing outcome data on the primary result will be conducted

8.1.5 Sample Size and Power

As a pilot, open-label study, this project is intended to generate data to be used in the development of future, larger studies. A total of 120 patients are expected to be available and eligible to participate in this study and up to 125 may be screened in order to yield 120 randomized participants.

Review of our database indicates the risk of fatal or recurrent stroke in patients with atrial fibrillation is approximately 20% with standard treatment [9]. To calculate expected power in this study, this established risk was used as the basis for estimates that could be expected with this treatment if it is successful. Given the parameters of conducting a 2-sided test with alpha = .05, and equal allocation to treatment and control groups (50 patients per group), power calculations were conducted using various ratios of outcomes (i.e. fatal or recurrent stroke) in the control group compared to the experimental group. The following results were obtained:

Power	**Detectable outcome Risk in control / Risk in experimental**
80% power	2.30

90% power	2.52
99% power	3.00

8.1.6 Randomization

Randomization of treatment was calculated in SAS 9.4 using a stratified, blocked PLAN procedure. For the 120 subjects to be randomized to either apixaban or warfarin, a random seed number was generated. Each subgroup of stroke type (small stroke, medium stroke and TIA) was randomized implementing block randomization using four blocks of 10. The treatment allocation was created by an unblinded statistician and given to the TGH research pharmacy. Blinded study envelopes are provided to study team members for randomization.

8.2 Interim Analysis

Due the small size and brief duration of the study no interim analyses are planned.

9 STUDY MEDICATION

Apixaban is a white to pale-yellow powder. At physiological pH (1.2–6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL [17].

Crystalline warfarin sodium occurs as a white, odorless, crystalline powder that is discolored by light. It is very soluble in water, freely soluble in alcohol, and very slightly soluble in chloroform and ether [21].

9.1 Packaging

9.1.1 Warfarin

Will be purchased by the Principal Investigator in and packaging will be based on manufacturer**.**

9.1.2 Apixaban

Formulation and packaging details are below:

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Appearance	Storage Conditions (per label)
Apixaban Tablet	2.5 mg	Bottles of 60/ Marketed label	yellow, round, biconvex, film-coated tablets with “893” debossed on one side and “2½” on the other side.	Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F)

Apixaban Tablet	5 mg	Bottles of 60/ Marketed label	pink, oval-shaped, biconvex, film-coated tablets with "894" debossed on one side and "5" on the other side.	Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F)

9.2 Labeling

Apixaban and Warfarin bottles will be labeled by the PI with subject number, visit number at which they are to be dispensed, the medication name, pill strength and directions detailing dosing for study subjects.

9.3 Dosing

9.3.1 Warfarin

Warfarin will be dosed per the Dosage protocol found in appendix 13.4.

9.3.2 Apixaban.

The dosage of Apixaban is based on the clinical findings of studies in human subjects and its FDA approved dosage for patients with non-valvular atrial fibrillation. Patients will receive 5mg dosage twice a day or 2.5 mg if they have any 2 of the following characteristics:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Coadministration with CYP3A4 and P- glycoprotein inhibitors: For patients receiving Apixaban 5 mg twice daily when Apixaban is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin), the recommended dose is 2.5 mg twice daily [patients already taking 2.5 mg twice daily, coadministration of Apixaban with strongdual inhibitors of CYP3A4 and P- glycoprotein should be avoided

If a dose of Apixaban is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

9.4 Treatment Compliance and Adherence

Subjects will be instructed to return all medication bottles (empty or partially used) at each study visit. The number of pills used will be counted and compared to the expected use to track treatment compliance.

Study medication will be counted to assess compliance at each clinic visit starting at day 14. Subjects who take between 75% and 125% of the prescribed dose will be considered compliant. Subjects who fall outside this range will be counseled and re-instructed on dosing procedures. Dose modifications along with the reasons for the modifications will be recorded on the CRF for each visit.

9.5 Drug Accountability

Records of study drug receipt and disposition will be maintained by the study sites including records of receipts, investigational drug orders, dispensing records, and disposition forms. These records will

be used to ensure that the investigational drug will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. The study medication is to be prescribed by the Investigator or designee and may not be used for any purpose other than that described in this protocol.

10 SAFETY MANAGEMENT

10.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

10.2 Adverse Event Reporting

All AEs that occur will be reported to the IRB. All SAEs will be reported to the IRB in accordance with IRB policies. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

10.3 Definition of an Adverse Event

An Adverse Event

[AE] is defined as any new untoward medical occurrence or worsening of a pre existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

- The causal relationship to study drug is determined by a physician and should be used to assess
- all adverse events (AEs). The causal relationship can be one of the following:
    - **Related**: There is a reasonable causal relationship between study drug administration and the AE.
    - **Not Related**: There is not a reasonable causal relationship between study drug administration and the AE.

- The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.
- Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events).

10.4 Definition of a Serious Adverse Event (SAE)

Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see ***NOTE****: below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific

judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

- Potential drug-induced liver injury (DILI) is also considered an important medical event--see the DILI section below for a definition of a potential DILI event.

Suspected transmission of an infectious agent (eg, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs

***NOTE:** The following hospitalizations are not considered SAEs:*

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

10.4.1 Serious Adverse Event Collecting and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on the SAE Report Form; Pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Fax Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

10.4.2 Relationship of SAE to study drug or other intervention

Assessment of Severity
The severity of each SAE will be assessed as described in the following table:

Assessment Definition
1 = Mild: Discomfort noted, but no disruption of normal daily activities; slightly bothersome; relieved with or without symptomatic treatment

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity to some degree; bothersome; interferes with activities, only partially relieved with symptomatic treatment

3 = Severe: Discomfort sufficient to reduce or affect normal daily activity considerably; prevents regular activities; not relieved with symptomatic treatment

For each solicited symptom, the subject will be asked if they sought medical advice (i.e. contact with a member of medical personnel) for this symptom.

Assessment of Causality
The investigator will attempt to explain each SAE and assess its causal relationship, if any, to the Study Medication . The degree of certainty with which an SAE can be attributed to Study Medication (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

-Reaction of similar nature having previously been observed with this type of medication.
-The event having often been reported in literature for similar types of medication.

The investigator will assess causality of all AEs, using the following method:

In your opinion, is there a reasonable possibility that the AE may have been caused by the study medication?

- No.
  - **Unrelated**: there is no suspicion that there is a relationship between Study Medication and AE, there are other more likely causes and the Study Medication is not suspected to have contributed to the AE.

- Yes.
  - **Related**: there is suspicion of a relationship between the study medication and AE (without determining the extent of probability); there are no other more likely causes and study medication is suspected to have contributed to the AE.

Events considered related to the study medication will be further classified as follows:

Probable-- AE cannot be reasonably explained by other factors (i.e. clinical condition, environmental/toxic factors or other treatments)
Possible-- AE can be reasonably explained by other factors (as mentioned above)
Unlikely-- AE occurs within an unusual time frame of administration of study medication and can also be reasonably explained by other factors (as mentioned above)

Non-serious and serious AEs will be evaluated as 2 distinct types of events given their different medical nature. If an event meets the criteria to be determined "serious", it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each SAE.

Other possible contributors include:
-Underlying disease
-Other medication
-Protocol required procedure
-Other cause (specify)

10.4.3 Definition of Severity

All AEs will be graded if possible by the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). The severity of AEs that cannot be graded by CTCAE version 4.0 will be categorized as follows:

Grade 1 – Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Grade 2 – Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

Grade 3 – Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.

Grade 4 – Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required hospitalization or hospice care probable.

Grade 5 – Death.

10.5 IRB/IEC Notification of SAEs

The investigator will promptly notify the IRB of all SAEs and other unanticipated problems related to research using the applicable IRB reporting form(s). External SAEs that are unexpected and related to the study intervention will be reported as they are received, within 24 hours of receipt, using the External SAE form (if applicable).
All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety.

10.5.1 SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will beevery three months and once once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be

used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately

10.5.2 Follow-up report

If an SAE has not resolved at the time of the initial report, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. All SAE will be followed until either resolved or stable.

10.5.3 Non-Serious Adverse Events

A nonserious adverse event is an AE not classified as serious.

10.5.4 Non-Serious Event Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Nonserious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

Nonserious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

10.6 Health Authority Reporting (US FDA IND)

Investigators must adhere to local Health Authority Reporting Requirements. For studies conducted under an investigator sponsored US FDA IND, provide details of the following:

Any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information.

BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at:
http://www.accessdata.fda.gov/scripts/medwatch/

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/
All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology

Bristol-Myers Squibb Company

Fax Number: 609-818-3804

Email: Worldwide.safety@bms.com

10.7 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.
- It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (eg, use the term anemia rather than low hemoglobin value).
- Laboratory test abnormalities are provided to BMS via annual safety reports (if applicable), and interim or final study reports

10.8 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).
The investigator must immediately notify WorldwideSafety@BMS.com of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.
Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.
Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form**.**
Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

10.9 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

10.10 Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

10.11 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious adverse event, as appropriate, and reported accordingly

10.12 Medical Emergencies

If medical emergencies arise during the study, the subject will contact the Doctor on call for the study. This individual will then triage the situation and direct the subject to a local hospital or appropriate site for immediate medical care, or arrange for urgent care for the next day when medically appropriate.

11 STUDY ADMINISTRATION

11.1 Treatment Assignment Methods

Subjects will be randomized at a 1:1 ratio for each treatment arm.

11.2 Data Collection and Management

The biostatistician will be responsible for design of the randomization scheme, creation of analytical databases, and the statistical analysis plan. The PI and study staff will be blinded to the randomization scheme.

Data review, coding and query processing will be done through interaction with USF and site personnel. Queries will be generated in real-time as the data are entered.

The cycle of data entry, review, query identification/resolution, and correction occurs over the course of the study period until all subjects have completed the study.

Forms and data collection

Study personnel will enter subject information and data into source document worksheets that correspond to an electronic database containing all subject study data.

It is the investigator's responsibility to ensure that entries are proper and complete.

11.2.1 Sources of Materials

Data from study visits will be recorded on clinical research forms (CRF) and entered into a secure electronic database. All study records will be kept confidential and each subject will be assigned a unique study identification number which will be used on all research records. The identity of patients will only be known to site personnel and the PI. Original records will be kept in locked files at each site and copies of these records will be kept in a locked drawer in a secure office at the PI's site. Subject information will not be released without the subject's written consent except to the IRB, FDA and other regulatory monitoring bodies as necessary.

Data to be recorded for this study include CT/MRI confirmation of stroke; EKG, physical exams; vital signs; copies of baseline labs and EKG reports (if available within previous 6 months); medical history; concomitant medications; Records will be retained in secure storage for 7 years after the study concludes.

11.3 Confidentiality

Enrollment or non-enrollment in the study will not affect the subject's clinical care in any way. All participation is voluntary. All data will be kept confidential except as required by law and kept in a secure data at each study site. All source documents will be stored in locked cabinets with access only for the principal investigator and co-investigators. Subjects will be identified by identification numbers not by personal identifiers. Subject information will be anonymized in publications and only the personnel involved in the studies may be able to link results with actual subjects.

11.4 Regulatory and Ethical Considerations

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to Bristol Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure; debarment).

11.4.1 Risks to subjects

<u>Human Subjects Involvement and Characteristics</u>

This pilot study will enroll 120 patients with NVAF and TIA or small to moderate strokes. The diagnosis of Atrial Fibrillation must be confirmed either by EKG at admission or past medical history. The diagnosis of TIA or Embolic stroke is will be confirmed with CT or MRI reads at time of admission. Adult patients of any race and ethnicity age 18 years and older will be included for this study.

<u>Inclusion of Women and Minorities</u>

Both male and female subjects will participate in the study.

There are no existing data supporting or negating significant differences in the effects of the study interventions among race/ethnicity subgroups.

<u>Inclusion of Children</u>

This study will not be including children as the diagnosis of non-valvular atrial fibrillation with TIA or embolic stoke does not usually occur in this population.

11.4.2 Potential Risks

The risks of anticoagulation have been well documented with the risk benefit ratios of anticoagulation in the treatment of atrial fibrillation being in favor for using these agents. [15, 20]

11.4.3 Risk Assessment

In the present study, the risk of serious side effects will be minimized by close follow-up of the subject during followup phase and at study visits after starting APIXABAN and warfarin treatment arms.

The risks of the other study procedures are generally small. Clinical outcome measures questionnaires (mRS, NIHSS, SS-QOL) are non-invasive and are very similar to standard clinical evaluation.

A standard venous blood draw is of minimal risk. There is a risk of pain at the insertion of the needle; this is only for a short time. There are low risks of fainting and infection. All venipunctures will be performed by a trained phlebotomist. All precautions will be taken to reduce the risks. No adverse events are expected.

11.4.4 Potential Benefits of Trial Participation

The principal objective of this study is to examine the effects of APIXABAN as an early treatment for recurrent embolic stroke prevention for subjects with NVAF after a TIA or small to moderate stroke. Study medication will be provided to patients free of charge for the duration of the study. It is possible, however, that a subject may not derive any benefit at all from participation in the study. Participation may help future patients by yielding important information on risks of Apixaban as an early prevention for embolic stroke.

11.5 Informed Consent

Informed consent will be obtained from all patients prior to the initiation of any study procedures. The consent will be obtained by the institution investigator and research coordinator. The study purpose, protocol and potential risks and benefits will be presented to the patient by the investigator and the patient will be permitted time to ask questions. The patient will have the opportunity to take the consent form home and discuss it with a friend or family member before signing the consent form. All subjects will be given a copy of the informed consent form and a signed copy will also be retained on site as part of the study files. One copy of the signed and dated consent will be retained by the investigator and one will be provided to the subject. The protocol and model informed consent will be reviewed by the University of South Florida IRB prior to distribution to each investigative site for IRB submission.

In some cases the subject may not be able to provide inform consent and a Legal Authorized Representative (LAR) will be used. The PI or Co-PI will determine the cognitive impairment of participants and when the use of the LAR is necessary. The signed consent form will be kept on file at the originating site and each subject will receive a copy of this document as well. Consent will be obtained prior to the initiation of any study related procedures.

11.6 Payment to Subjects/Families

In the present study there will be no payment to subjects. A small travel stipend will be given to subjects as appropriate.

11.7 Publication

It is expected that the Principal Investigators will submit the data for publication when the study is complete and has been evaluated.

12 REFERENCES

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13 APPENDICES

13.1 Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

13.2 NIHSS

NIH Stroke Scale (NIHSS) score is available at:
http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf

13.3 SS- QOL

Scoring: each item shall be scored with the following key

Total help - Couldn't do it at all - Strongly agree	1
A lot of help - A lot of trouble - Moderately agree	2
Some help - Some trouble - Neither agree nor disagree	3
A little help - A little trouble - Moderately disagree	4
No help needed - No trouble at all - Strongly disagree	5

Energy

1. I felt tired most of the time. ____
2. I had to stop and rest during the day. ____
3. I was too tired to do what I wanted to do. ____

Family Roles

1. I didn't join in activities just for fun with my family. ____
2. I felt I was a burden to my family. ____
3. My physical condition interfered with my personal life. ____

Language

1. Did you have trouble speaking? For example, get stuck, stutter, stammer, or slur your words? ____
2. Did you have trouble speaking clearly enough to use the telephone? ____
3. Did other people have trouble in understanding what you said? ____
4. Did you have trouble finding the word you wanted to say? ____
5. Did you have to repeat yourself so others could understand you? ____

Mobility

1. Did you have trouble walking? (If patient can't walk, go to question 4 and score questions 2-3 as 1.) ____

2. Did you lose your balance when bending over to or reaching for something? ____
3. Did you have trouble climbing stairs? ____
4. Did you have to stop and rest more than you would like when walking or using a wheelchair? ____
5. Did you have trouble with standing? ____
6. Did you have trouble getting out of a chair? ____

Mood

1. I was discouraged about my future. ____
2. I wasn't interested in other people or activities. ____
3. I felt withdrawn from other people. ____
4. I had little confidence in myself. ____
5. I was not interested in food. ____

Personality

1. I was irritable. ____
2. I was inpatient with others. ____
3. My personality has changed. ____

Self Care

1. Did you need help preparing food? ____
2. Did you need help eating? For example, cutting food or preparing food? ____
3. Did you need help getting dressed? For example, putting on socks or shoes, buttoning buttons, or zipping? ____
4. Did you need help taking a bath or a shower? ____
5. Did you need help to use the toilet? ____

Social Roles

1. I didn't go out as often as I would like. ____
2. I did my hobbies and recreation for shorter periods of time than I would like. ____
3. I didn't see as many of my friends as I would like. ____
4. I had sex less often than I would like. ____
5. My physical condition interfered with my social life. ____

Thinking

1. It was hard for me to concentrate. ____

2. I had trouble remembering things.

3. I had to write things down to remember them. ____
____

Upper Extremity Function

1. Did you have trouble writing or typing? ____
2. Did you have trouble putting on socks? ____
3. Did you have trouble buttoning buttons? ____
4. Did you have trouble zipping a zipper? ____
5. Did you have trouble opening a jar? ____

Vision

1. Did you have trouble seeing the television well enough to enjoy a show? ____
2. Did you have trouble reaching things because of poor eyesight? ____
3. Did you have trouble seeing things off to one side? ____

Work/Productivity

1. Did you have trouble doing daily work around the house? ____
2. Did you have trouble finishing jobs that you started? ____
3. Did you have trouble doing the work you used to do? ____

TOTAL SCORE ____

Reference

Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a stroke-specific quality of life scale. Stroke 1999 Jul;30(7):1362-9.

13.4 Warfarin Dosing Protocol