

Anticoagulation in
Intracerebral
Hemorrhage (ICH)
Survivors for Stroke
Prevention and
REcovery

PROTOCOL TRAINING



ASPIRE

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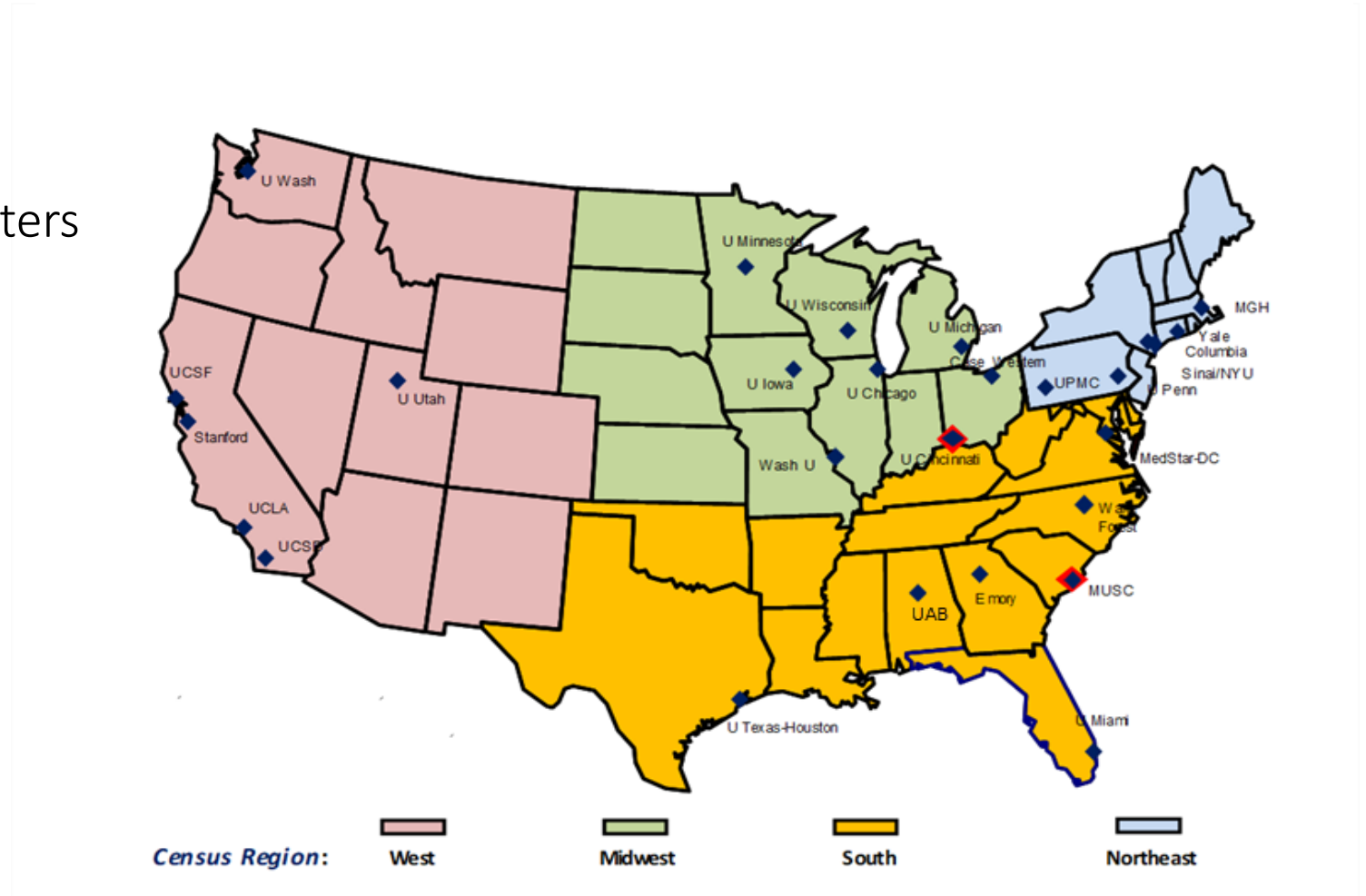
Trial Operations

Steering

ASPIRE Site Network

128 StrokeNet sites from
--27 Regional Coordinating Centers

4 non-StrokeNet sites



Background

- In patients with atrial fibrillation (AF) and CHA₂DS₂-VASc score ≥ 2, treatment with oral anticoagulants (OAC) is recommended by the AHA (IA-B evidence) for prevention of stroke/thromboembolism.
- Non-vitamin K oral anticoagulants (NOACs)* are recommended over warfarin for eligible patients with AF (IA evidence)
 - RCTs have shown NOACs to be consistently at least noninferior to warfarin for preventing stroke and systemic embolism with *lower risk for serious bleeding*.

*also called direct oral anticoagulants or DOACs

Key Trial – Aristotle (2011)

Randomized, double-blind trial, comparing apixaban (5 mg twice daily) with warfarin (target INR, 2.0-3.0) in patients with AF and at least one additional risk factor for stroke, found **apixaban was superior to warfarin** in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

Outcome	Apixaban (n=9120) Event Rate (%/yr)	Warfarin (n=9081) Event Rate (%/yr)	HR (95% CI)	P
Primary outcome:				
Stroke or systemic embolism	1.27	1.60	0.79 (0.66–0.95)	0.01
Ischemic or uncertain type stroke	0.97	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	0.24	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	0.09	0.10	0.87 (0.44–1.75)	0.70
Key secondary outcome:				
Death from any cause	3.52	3.94	0.89 (0.80–0.998)	0.047
Stroke, systemic embolism, or death	4.49	5.04	0.89 (0.81–0.98)	0.02

Why ASPIRE?

- Approximately 20% of ICH survivors have or develop atrial fibrillation.
- Yet, these patients have been excluded from past studies of NOACs.
- Current ICH guidelines reflect the need for studies in this population by stating:
 - “Anticoagulation and antiplatelet therapy after non-lobar ICH might be considered” (IIb, B)
 - “The usefulness of dabigatran, rivaroxaban, or apixaban in patients with atrial fibrillation and past ICH is uncertain” (IIb, C)
 - “An important question to be addressed is the possible role of the newer direct OACs in patients at increased ICH risk and the identification of the subgroup that might derive the greatest benefit from the reduced tendency of these agents to trigger intracranial bleeding”

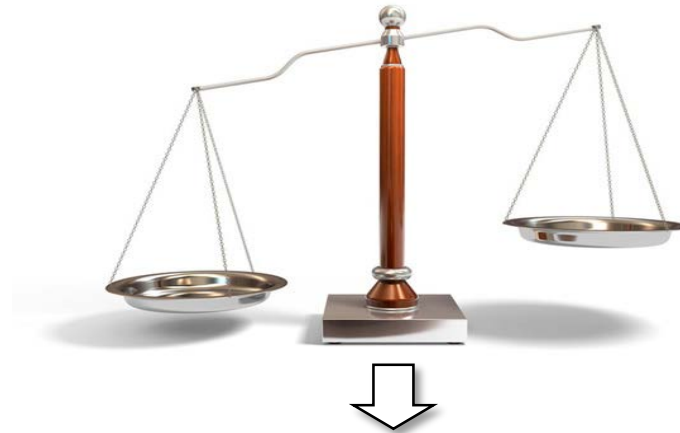
Stroke 2015;46:2032–2060

Use of oral anticoagulation is a major clinical dilemma in care of ICH patients with atrial fibrillation

Currently available evidence:

Thrombosis Risk

- Ischemic stroke
- Systemic Thromboembolism



Hemorrhage Risk

- Recurrent ICH
- Systemic Bleeding

Mortality

Oral Anticoagulation after ICH

Meta-analyses of observational studies have shown OAT resumption after ICH was associated with:

- Lower risk of thromboembolic complications (e.g., ischemic stroke, MI)
- Lower risk of death
- No significant association with risk of ICH recurrence

Limitations:

- Follow-up limited to one year
- Very few patients on DOACs
- Observational study framework – may be affected by indication bias

An RCT is needed

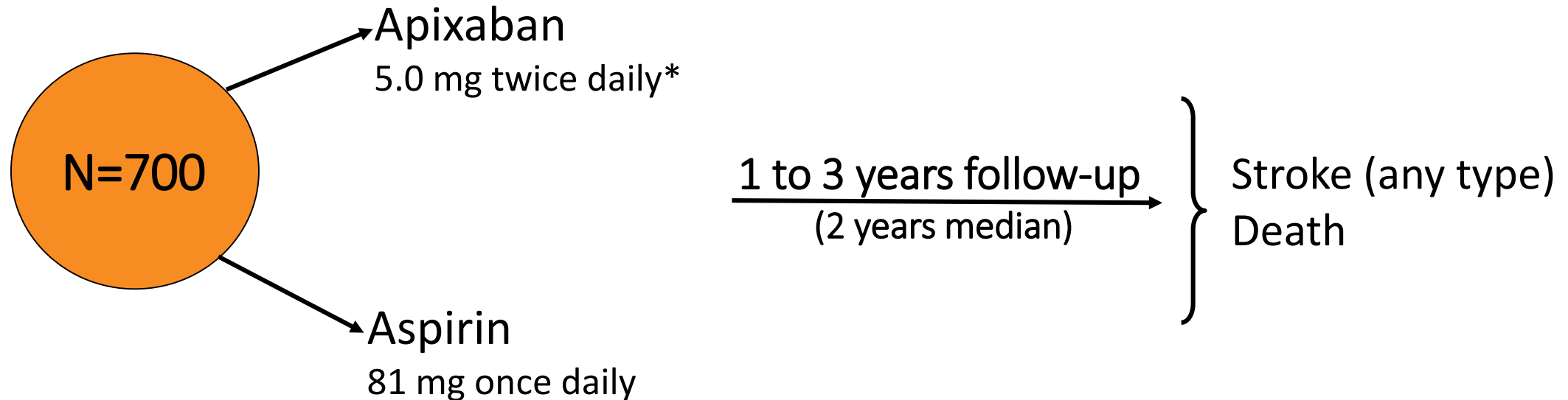
ASPIRE:

First ICH prevention study in recent NIH history

- Designed to answer an active clinical practice question

Study Design

Randomized, double-blinded, phase III clinical trial



Blinding is achieved through use of active and matching dummy medications for both aspirin and apixaban.

*Reduced 2.5 mg dose apixaban may be used following standard criteria.

Study Aims

Primary Aim

To determine if apixaban is superior to aspirin for prevention of the composite outcome of any stroke (hemorrhagic or ischemic) or death from any cause in patients with recent ICH and AF.

- *We hypothesize that apixaban is superior to aspirin for prevention of recurrent stroke/death in patients with prior ICH and AF.*

Secondary Aim

To determine if apixaban, compared with aspirin, results in better functional outcomes as measured by the modified Rankin Scale.

- *We hypothesize that the benefit of apixaban will result in improved functional outcomes.*
- *Patient centered outcome will complement hard traditional endpoints.*

Tertiary / Exploratory Aims

To assess the safety and efficacy of apixaban, compared with aspirin, for:

- Components of the primary outcome
- Major hemorrhage
- Thromboembolic events (MI, DVT, PE, SE),
- Measures of cognition and quality of life
 - MoCA
 - PROMIS (global health, anxiety, depression)

Why Apixaban?

- Selective Factor Xa inhibitor
 - Decreases thrombin generation
 - No direct antiplatelet effects
- Indications for use:
 - ↓risk of ischemic stroke and systemic embolism risk in patients with nonvalvular AF
 - DVT/PE prophylaxis for hip or knee replacement surgery
 - DVT/PE treatment and ↓risk of recurrence
- Only NOAC that has been compared with aspirin for AF in a randomized trial

Key Trial – Averroes

Randomized, double-blind trial comparing apixaban (5 mg twice daily) with aspirin (81 to 324 mg per day) in patients with AF who were at increased risk for stroke **found apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage.**

Outcome	Apixaban	Aspirin	HR (95% CI)	P
	(n=2808)	(n=2791)		
	Event Rate (%/yr)			
Stroke, systemic embolism, or death	4.6	7.2	0.64 (0.51–0.78)	<0.001
Stroke	1.6	3.4	0.46 (0.33–0.65)	<0.001
Ischemic	1.1	3.0	0.37 (0.25–0.55)	<0.001
Hemorrhagic	0.2	0.3	0.67 (0.24–1.88)	0.45
Unspecified	0.3	0.1	2.24 (0.69–7.27)	0.18
Systemic embolism	0.1	0.4	0.15 (0.03–0.68)	0.01
Death from any cause	3.5	4.4	0.79 (0.62–1.02)	0.07
Major bleeding event	1.4	1.2	1.13 (0.74–1.75)	0.57

Averroes-MRI

In sub-study of Averroes trial, apixaban treatment was associated with a nonsignificant trend toward reduction in the composite of clinical ischemic stroke and covert embolic-pattern infarction and **did not increase the number of microbleeds** in patients with atrial fibrillation compared with aspirin.

Outcome	Apixaban	Aspirin	HR 95% CI
Primary outcome			
Covert “embolic” infarction and symptomatic ischemic stroke	12/601 (2.0%)	19/579 (3.3%)	0.55 (0.27-1.14)
Microbleeds			
New/increased no. of microbleeds	26/377 (7.0%)	24/334 (7.2%)	0.92 (0.53-1.60)
Reduced no. of microbleeds	21/377 (5.6%)	17/334 (5.1%)	1.07 (0.56-2.03)
Net change in microbleeds			P = .47

Am Heart J 2016;178:145-50

Target Population for ASPIRE

Patients with a first-ever, qualifying ICH and high-risk, non-valvular atrial fibrillation/flutter

Tips for Finding Patients

- Use EPIC clinical trial search function periodically
- “Hot pursuit” ID – scan ICU and stroke service lists daily
- Reach out to cardiology, stroke and NSG clinics

Major Eligibility Criteria

Inclusion

- Age \geq 18 years
- Qualifying intracerebral hemorrhage (ICH)
- Ability to be randomized 14-120 days after index ICH
- Non-valvular AF and CHA2DS2-VASc score \geq 2

Exclusion

- History of ICH before index event
- Lobar ICH with “high-risk” cerebral amyloid angiopathy (CAA)
- Clear indication for (or unwilling to stop) antithrombotic therapy
- Left atrial appendage closure – previous or planned

Temporary Exclusions (can randomize once resolved)

- Persistent, uncontrolled systolic blood pressure (\geq 180 mmHg)
- ICH caused by AVM that has not been secured

Qualifying Intracerebral Hemorrhage (ICH)

ICH is defined as a focal collection of blood within the brain parenchyma or ventricular system documented on CT or MRI.

Brain hemorrhages that are *not eligible*:

- Hemorrhages due to brain infarction (i.e., hemorrhagic transformation)
- Hemorrhages caused primarily by a tumor
- Subdural hemorrhages
- Non-cortical subarachnoid hemorrhages
- Hemorrhage due to AVM unless the AVM has been secured
- Lobar ICH with evidence of “high-risk” CAA

A radiologist or stroke specialist who is experienced in brain imaging interpretation must review brain imaging to confirm the presence of a qualifying ICH, location (*lobar vs. non-lobar*), and, for lobar ICH, if criteria for “high-risk” CAA are met.

Non-valvular Atrial Fibrillation/Flutter (AF)

Diagnosis of AF (whether paroxysmal or permanent) requires one of the following:

- 12-lead ECG or heart-rhythm monitoring documenting AF of any duration
- Patient is taking anticoagulant medication at time of admission for index ICH *and*
 - AF history noted in medical records or is confirmed by PCP
- Patient is *not* taking anticoagulant medication at time of admission for index ICH *but*
 - AF history noted in medical records and is confirmed by PCP

Patients with valvular AF are not eligible for ASPIRE

- AF in patient with mechanical heart valve or moderate-to-severe mitral stenosis will be considered valvular.

CHAD₂DS₂-VASc Score ≥2

- Identifies patients with AF at high risk for ischemic stroke
- Score components and points are shown below.

Component	Definition	Points
Congestive heart failure/ left ventricular dysfunction	Presence of signs and symptoms of either right (elevated central venous pressure, hepatomegaly, dependent edema) ventricular failure <i>or</i> left ventricular failure (exertional dyspnea, cough, fatigue, orthopnea, paroxysmal nocturnal dyspnea, cardiac enlargement, rales, gallop rhythm, pulmonary venous congestion) <i>or</i> both, or other credible evidence of a history of congestive heart failure as judged by the site PI	1
Hypertension	Credible evidence of a history of hypertension as judged by the site PI	1
Age	≥75 years	2
Diabetes	Fasting plasma glucose level ≥7.0 mmol/L (126 mg/dL), hemoglobin A1c ≥7.0%, or treatment with oral hypoglycemic agent and/or insulin for diagnosis of diabetes	1
Ischemic Stroke/TIA/TE	Prior ischemic stroke, TIA or thromboembolism	2
Vascular disease	Prior myocardial infarction, angina pectoris, percutaneous coronary intervention or coronary artery bypass surgery <i>or</i> Presence of any the following: intermittent claudication, previous surgery or percutaneous intervention on the abdominal aorta or the lower extremity vessels, abdominal or thoracic surgery, arterial and venous thrombosis	1
Age	65-74 years	1
Sex category	Female	1

“High-Risk” CAA-related Lobar ICH

Patients with lobar ICH *and* evidence of “high-risk” cerebral amyloid angiopathy (CAA) are excluded due to very high risk for ICH recurrence.

For ASPIRE, evidence of “high-risk” CAA is defined as:

- ≥ 5 lobar microbleeds on brain MRI, or
- Disseminated cortical superficial siderosis (cSS) on T2*-GRE or other susceptibility-weighted imaging (SWI) MRI.

For details on how to apply criteria for ‘high-risk’ CAA, see *Cerebral Microbleeds and CSS Assessment Field Guide* (in ASPIRE Toolbox in WebDCU).

If brain MRI cannot be performed (*e.g., due to pacemaker*): ‘High-risk’ CAA will be considered present if patient meets any of the following at time of the lobar ICH:

- Age > 75 years
- No history of hypertension
- Dementia present

Consent Procedures

- Patients who meet all inclusion and no exclusion criteria can be consented for the study.
- Consent must be obtained in-person (*e-consent is not yet permitted by cIRB*).
- Surrogate consent is permitted if the local study investigator determines that the patient *lacks capacity* to give consent due to neurological deficits.
 - In this case, consent may be obtained from a legally authorized representative (LAR), health care proxy, or other surrogate as permitted by institutional and state regulations.

If Consent is Not Obtained

- A **Screen Failure form** should be completed for any patient age ≥ 18 years who presents with a confirmed ICH within 120 days of onset who is not consented.
 - Records reason for not obtaining consent, including inclusion criteria that are not met or excluded conditions that are present.
- Completion of these forms will permit tracking of each site's ICH volume, eligible ICH events, and consent rates for eligible patients.

After Consent is Obtained

- Blood samples for Biobank storage may be drawn any time after consent.
- Arrange location, logistics, and timing of baseline/randomization visit.
 - To minimize risk of hematoma expansion, randomization cannot occur until at least 14 days post ICH, *and*
 - Randomization cannot occur more than 120 days post ICH.

Post ICH Day 0: Calendar day (12:00am through 11:59pm) of ICH onset
or, if onset day unclear, day of 1st presentation for medical care.

- For a patient going to (or residing at) a rehabilitation or nursing facility, the following must be confirmed prior to the baseline visit:
 - Study drug can be administered at the facility, *and*
 - Facility agrees to not administer any open-label anticoagulant therapy.

Baseline Visit and Randomization

- At Baseline visit, eligibility criteria must be confirmed
 - including blood pressure measurement documenting systolic <180 mmHg
 - patient is not taking anticoagulants or antiplatelets
- Complete baseline assessments for risk factors, functional status, cognitive and quality of life measures
- Randomize and start study drug

Study Medications

- At randomization, participants will be assigned to either apixaban (5mg or 2.5 mg twice a day) or aspirin (81mg once a day).
 - Randomization algorithm is designed to ensure balance between treatment groups in ICH location (lobar/non-lobar) and CHA₂DS₂-VASc score.
- Because apixaban and aspirin tablets differ in appearance, a double-dummy method is being used to maintain blinding.
- Apixaban, aspirin and matching placebo for each is being provided by Biomedical Research Institute of New Mexico (BRINM).
- Central Pharmacy at the University of Cincinnati (NCC) will repackage study drugs and ship study drug kits to sites.

Apixaban

- Therapeutic half-life is 12 hours → requires twice daily dosing
- Available in 2.5 mg and 5 mg tablets
 - 2.5 mg dose is recommended for patients who meet at least 2 of the following:
 - Age \geq 80 years
 - Weight \leq 60 kg
 - Serum creatinine $>$ 1.5 mg/dL
- At therapeutic dose, prolongation of clotting tests (e.g., PT, INR, aPTT) are small and not useful in monitoring anticoagulation effect of apixaban

Study Drug Kits

- Each study drug kit will contain:
 - 1 bottle of 100 count aspirin (81mg tablets) or aspirin placebo tablets, *and*
 - 1 bottle of 200 count apixaban (5mg or 2.5mg tablets) or apixaban placebo tablets

Aspirin OR
aspirin placebo



ONCE a day from Bottle 1



Apixaban
OR
apixaban
placebo

TWICE a day from Bottle 2

- Subjects who meet clinical criteria for reduced dose of apixaban will be dispensed 2.5 mg apixaban or 2.5 mg apixaban placebo tablets.

Study Drug Supplies at Site

- Initially, all sites will be supplied with 4 kits containing:
 - apixaban (5 mg) + aspirin placebo
 - apixaban (2.5 mg) + aspirin placebo
 - aspirin + apixaban (5 mg) placebo
 - aspirin + apixaban (2.5 mg) placebo
- Number of study drug kits sent in subsequent shipments will depend upon expected refills and the enrollment rate at your site.

Prohibited and Discouraged Medications

Prohibited Medications

Participants should not take any open-label **anticoagulant or antiplatelet agent** while on the study drug.

- Concurrent use of apixaban with these agents is expected to increase the risk of bleeding in comparison to use of apixaban alone.

Discouraged Medications

Participants should be discouraged from taking **NSAIDs and SSRIs/SNRIs** while on study drug as these medications have antiplatelet activity.

Use of medications that are **strong P-gp or CYP3A4 inhibitors and inducers** should also be discouraged:

- P-gp inhibitors/P-gp inducers can increase/reduce absorption of apixaban
- CYP3A4 inhibitors/ CYP3A4 inducers can decrease/increase metabolism of apixaban

Prohibited Medications: Anticoagulants

Generic Name	Brand Name
Oral anticoagulants	
Dabigatran	Pradaxa
Edoxaban	Savaysa, Lixiana
Rivaroxaban	Xarelto
Warfarin	Coumadin
Parenteral antithrombotics	
Dalteparin	Fragmin
Enoxaparin	Lovenox
Fondaparinux	Arixtra
Heparin	multiple

Prohibited Medications: Antiplatelets

Generic Name	Brand Name
aspirin (ASA)	Ecotrin, others
clopidogrel	Plavix
ticlopidine	Ticlid
ticagrelor	Brilinta
prasugrel	Effient

If an open-label antiplatelet agent is indicated (e.g., clopidogrel after implantation of a coronary artery stent), then study drug must be stopped until the open-label antiplatelet agent is stopped.

Discouraged Medications: NSAIDs

Generic Name	Brand Name
celecoxib	Celebrex
ibuprofen	Advil, Motrin, Nuprin
indomethacin	Indocin
ketorolac	Toradol
naproxen	Naprosyn
salsalate	Anaflex, Disalcid
others	

Discouraged Medications: SSRIs and SNRIs

Generic Name	Brand Name
citalopram	Celexa
duloxetine	Cymbalta
escitalopram	Lexapro
fluoxetine	Prozac
paroxetine	Paxil
sertraline	Zoloft
venlafaxine	Effexor
others	

Discouraged Medications

- Refer to (and provide participants with) *ASPIRE Prohibited and Discouraged Medications*
 - lists medications by generic and brand names
- Use judgment/experience as clinician
- Call/email aspire@yale.edu if you have questions about concurrent medications

Initiation of Study Drug

- Subjects receiving antiplatelet, anticoagulant, or no antithrombotic therapy at the time of the index ICH should be considered eligible for the study and for randomization to either aspirin or apixaban monotherapy.
- All baseline antiplatelet and anticoagulant therapies will be stopped at randomization.

Study Drug Instructions for Participants

- Study drug should be started on day of randomization but *must* be initiated within 48 hours of randomization.
- Study drug cannot be given until at least 12 hours after last dose of an anticoagulant (even at a prophylactic dose).
- Subject should take a single tablet **once a day from Bottle 1** (active or placebo ASA) and a single tablet **twice a day from Bottle 2** (active or placebo apixaban).
- Study drug can be taken with or without food.
- If patient is unable to swallow whole tablets, they may be crushed and suspended in 60 mL water, D5W, or apple juice or mixed with applesauce.
- For delivery through a nasogastric tube, crushed tablets may be suspended in 60 mL water or D5W followed by immediate delivery.
- A missed dose may be taken if it is more than 6 hours until next scheduled dose – otherwise, dose should be skipped.

Study Drug Materials Provided at Randomization

To Subject

- Participant Information Sheet
- Prohibited and Discouraged Medications list
- Alert Card – *identifies subject as ASPIRE participant; contact information for investigator; hotline phone number for unblinding treatment assignment in an appropriate emergency*

To Subject's Regular Physicians

- HCP Baseline Letter – *for primary care provider, neurologist, cardiologist; describe study, and reminds care provider to not prescribe antithrombotic drugs*

Study Drug Materials are posted in the ASPIRE Toolbox in WebDCU

Participant Follow-Up

- Follow-up visits take place every 90 days (± 5) days after randomization.
- Visits should be done in person but may be done via telephone (if in-person visit cannot be arranged and study drug can be shipped or delivered to subject at your site).
- End of study visit will be 3rd annual visit or the last scheduled visit in the study close-out period, whichever comes first.
- In ASPIRE, only the following types of events will be collected during follow-up:
 - Serious adverse events
 - Clinical outcomes events
 - Pregnancies (in female participants or partners of male participants)

Follow-up Visit

- Administer structured screen for SAEs, clinical outcome events and pregnancy
- Complete assessments
 - Functional status (Modified Rankin Scale)
 - Risk factors (blood pressure at every visit, smoking/alcohol use at annual visits)
 - Use of prohibited and preventive medications
 - Repeat cognitive and quality of life measures (at 12-month visit)
- Study drug resupply
 - Assess interim development (or resolution) of contraindication to study drug
 - For pts on study drug: assess adherence using pill counts of returned bottles, confirm criteria (age/weight/creatinine) for apixaban dose, and provide new supply
 - Record reason for any discontinuation or temporary interruption of study drug
 - Subjects who stop study drug must still be followed until end of study

Serious Adverse Events

An SAE is an event that results in any of the following:

- Death
- Risk of death
- In-patient hospitalization or prolongation of hospital stay
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Congenital anomaly or birth defect
- Other important medical event that jeopardizes the subject or requires medical or surgical intervention to prevent one of the preceding outcomes

Clinical Outcome Events

- Ischemic stroke
- Transient ischemic attack (TIA)*
- Intracerebral hemorrhage
- Other intracranial hemorrhage
- Non-intracranial hemorrhage**
- Myocardial infarction
- Deep venous thrombosis
- Pulmonary embolism
- Systemic embolism

*TIA is not a study outcome but will be adjudicated to assess if ischemic stroke criteria are met.

**Non-intracranial hemorrhage should only be reported if (1) it meets criteria for major hemorrhage (*see MOP*), or (2) was not due to trauma and required medical attention to manage.

Event Reporting and Adjudication

- SAEs, clinical outcome events, and pregnancies should be reported on the **Adverse Event** form in WebDCU within 72 hours of first knowledge of event.
- All reported clinical outcome events will be submitted to the Outcomes Adjudication Committee.
- After an adjudicated non-fatal outcome event, participants remain in follow-up until the end of the study.

Statistical Analysis Plan

- Intention-to-treat approach will be used
- Primary outcome: Stroke (ischemic or hemorrhagic) or death due to any cause
 - Survival analysis; log-rank test to compare treatment groups
 - Interim analysis planned after 2/3 of primary outcome events
- Secondary outcome: Change in modified Rankin Scale during follow-up

ASPIRE Protocol Key Points

1. Identify ICH patients with atrial fibrillation
2. Apply inclusion/exclusion criteria
3. Consent patient or surrogate
4. Make plan for randomization (baseline) visit
5. Follow-up visits every 90 days for ascertainment of outcomes

ASPIRE Biobank

- Central repository for neuroimaging and blood samples will be maintained at Yale School of Medicine.
 - Brain Imaging: Scans for baseline ICH event and all neurological events during follow-up.
 - Blood samples: K2-EDTA and PAXgene Blood RNA tubes
 - Providing blood samples for Biobank is not required for participants
- Access to the repository for future research studies will be restricted to those approved by the ASPIRE Executive and Ancillary Studies Committees.

See *ASPIRE Biobank Procedures* in ASPIRE Toolbox in WebDCU for detailed instructions for submissions to the Biobank.

ASPIRE Hotline: 1-800-618-0643

- For any **emergent or urgent questions** regarding:
 - eligibility criteria
 - study procedures
 - safety concerns
 - emergency medical issues
- Available 24/7/365
- Sequentially rings the cell phones of the ASPIRE Principal Investigators

ASPIRE Contact Information

- **WebDCU issues:** Kyle Hatcher, hatcherk@musc.edu, (843) 792-4117
- **Study drug issues:** strokenetcpharmacy@ucmail.uc.edu, (513) 584-3166
- **Monitoring issues:** Aaron Perlmutter, perlmutt@musc.edu, (843) 792-2784
- **Other issues:** aspire@yale.edu
 - Laura Benken, NCC, (513) 558-3935
 - Catherine Viscoli, Yale University, (203) 764-7550

Thank You!

Please complete **Protocol Training Attestation Form** and upload to WebDCU.

Email ASPIRE@YALE.EDU if you have any questions about this material.