AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke

NINDS U01 NS095869
Supported by BMS-Pfizer Alliance and Roche Diagnostics
clinicaltrials.gov: NCT03192215
Principal Investigators

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Study Organization

- Study Statistician
  - Dick Kronmal, PhD, University of Washington

- StrokeNet National Clinical Coordinating Center (UC Cincinnati)
  - Joe Broderick, MD, PI
  - Irene Ewing, Program Manager

- StrokeNet Data Management Center (MUSC)
  - Yuko Palesch, PhD, PI
  - Caitlyn Ellerbe, PhD, Statistician
  - Catherine Dillon, Data Operations Manager

- VA
  - Seemant Chaturvedi, University of Miami

Ancient site of Orchomenus in Arcadia Greece
Study organization

- NIH/NINDS
- Executive Committee
- Trial Operations Committee
- Clinical Coordinating Center (Director, Joe Broderick, Univ Cincinnati)
  - Pam Plummer PM
  - Research Pharmacy
  - Central IRB
  - Contracts Management
- Data Management Center (MUSC)
- DSMB/Med safety monitor
- Cores:
  - Eligibility and Recruitment (Director, David Tirschwell)
  - Outcomes Adjudication (Director, Will Longstreth)
  - Echocardiography Core Lab (Director, Marco Di Tullio, Study Cardiologist)
  - Blood Laboratory Core/Biobank (Directors, Mitch Elkind/Eldad Hod, Clinical Pathologist)
  - ECG Core Laboratory (Director, El-Sayed Soliman)
Up to 200 Sites

- 25 Regional coordinating centers in the U.S.
- Up to 30 sites in Canada
- 4400 patients to be screened
- 1100 patients with ESUS/atrial cardiopathy to be randomized
Rationale and Protocol
Etiologic subtypes ("Causes") of ischemic stroke:
The Northern Manhattan Stroke Study
Embolic stroke of undetermined source (ESUS)

Requires full evaluation to establish the following:

• Non-lacunar stroke detected by CT or MRI
• Absence of extracranial or intracranial atherosclerosis causing >50% luminal stenosis in arteries supplying territory
• No major-risk cardioembolic source of embolism based on TTE and >24 hr monitoring (AF/flutter, prosthetic valve, LVEF<30%, etc.)
• No other specific cause identified (dissection, vasculitis, spasm, etc.)

Embolic Stroke of Undetermined Source (ESUS)

Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.

Most Unexplained Strokes Seem Embolic
Occult Atrial Fibrillation?

Sanna et al, NEJM, 2014
Occult Atrial Fibrillation?

Sanna et al, *NEJM*, 2014
Occult AF Does Not Explain ESUS

- 70% of ESUS patients had no AF during 3 years of continuous heart-rhythm monitoring
- Subclinical AF does not explain most cryptogenic strokes

Kamel, *NEJM*, 2014
Hypothesis: Atrial Cardiopathy

• Arrhythmia that defines AF \(\leftrightarrow\) other atrial derangements
• Atrial cardiopathy may cause embolism in absence of arrhythmia
Atrial Cardiopathy $\leftarrow$ Stroke

Markers of atrial cardiopathy $\leftarrow$ stroke, independent of AF

- P-wave terminal force in ECG lead $V_1$ (PTFV$_1$)
- NT-proBNP
- Left atrial size/function on echocardiogram

P wave Terminal Force in EKG lead V1 reflects left atrial electrical and structural properties

## PTV1 in NOMAS: Case-cohort analysis

**Associations between P-Wave Terminal Force in Electrocardiogram Lead V\textsubscript{1} and Incident Ischemic Stroke Subtypes (n=1107)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadj</th>
<th>Adj</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ischemic stroke</td>
<td>1.24 (1.07-1.42)</td>
<td>1.20 (1.03-1.39)</td>
</tr>
<tr>
<td>Ischemic stroke subtypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic or cardioembolic</td>
<td>1.31 (1.10-1.55)</td>
<td>1.31 (1.08-1.58)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>1.29 (0.99-1.68)</td>
<td>1.29 (0.96-1.72)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>1.32 (1.07-1.62)</td>
<td>1.23 (0.97-1.56)</td>
</tr>
<tr>
<td>Non-cardioembolic</td>
<td>1.14 (0.94-1.40)</td>
<td>1.14 (0.92-1.40)</td>
</tr>
</tbody>
</table>

Results are reported as the hazard ratio (95% CI) for each 1-standard deviation increase in PWV\textsubscript{1}.

Adjusted model includes age, sex, race, education, smoking status, diabetes, hypertension, lipid levels, atrial fibrillation, and heart failure.

Atrial Fibrillation and Mechanisms of Stroke
Time for a New Model

Hooman Kamel, MD; Peter M. Okin, MD; Mitchell S.V. Elkind, MD, MS; Constantino Iadecola, MD

- Mechanisms of atrial dysfunction and thromboembolism
  - Stasis
  - Endothelial dysfunction
  - Myocardial fibrosis
  - Impaired myocyte function
  - Chamber dilatation
  - Inflammation
  - Thrombophilia
  - Left atrial appendage dysfunction

Amino Terminal Pro–B-Type Natriuretic Peptide, Secondary Stroke Prevention, and Choice of Antithrombotic Therapy


Stroke. 2013;44:714-719; originally published online January 22, 2013;
doi: 10.1161/STROKEAHA.112.675942

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WARSS/APASS: Effect of warfarin vs aspirin on recurrent stroke/death among those with elevated NT-proBNP

NT-proBNP ≤ 750 pg/ml

NT-proBNP > 750 pg/ml

ARCADIA: Only ESUS + Atrial Cardiopathy

- ATrial Cardiopathy and ANTithrombotic Drugs In prevention After cryptogenic stroke

- Hypothesis: apixaban is superior to aspirin for prevention of recurrent stroke in patients with ESUS and atrial cardiopathy
ARCADIA: Only ESUS + Atrial Cardiopathy

Secondary hypothesis: benefit of apixaban increases with severity of atrial cardiopathy
- Personalized prediction of risk/benefit
- May help set stage for primary prevention trial
Inclusion Criteria

• Age ≥45 years
• Clinical diagnosis of ischemic stroke
• mRS score ≤4
• Randomization possible within 3-180 days post stroke
• ESUS
What Is ESUS?

• Not a lacunar stroke
• No extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis of an artery supplying area of brain infarct
• No major source of cardiac embolism
• No other specific cause of stroke
What is Atrial Cardiopathy?

Atrial cardiopathy defined as ≥1 marker

- PTFV$_1$ >5000 $\mu$V*ms on 12-lead ECG
- Left atrial size index ≥3 cm/m$^2$ on echocardiogram (severe LAE)
- Serum NT-proBNP >250 pg/mL
Exclusion Criteria

- Any AF
- Clear indication for anticoagulation
- Need for antiplatelet, including aspirin
- History of intracranial hemorrhage
- CKD with creatinine ≥2.5 mg/dL
- Chronic anemia/thrombocytopenia
- Others: bleeding diathesis, recent major bleeding, pregnancy risk, known allergy, participation in another trial of drug/intervention
Stepwise Enrollment Process

1. Apply inclusion/exclusion criteria
2. Obtain consent
3. Test for atrial cardiopathy
4. Randomize if atrial cardiopathy
Enrollment: Key Points

• Must complete all SOC tests before consenting
• Consenting/randomization can be at same visit or different visits
  • Consenting & Randomization can be done remotely
• Consenting time window: Post-stroke days 1-180
• Randomization time window:
  • Post-stroke days 14-180 if NIHSS ≥11, hemorrhagic conversion on initial imaging, or uncontrolled hypertension
  • Otherwise, post-stroke days 3-180
• Post-stroke day 0 = calendar day (12:00 a.m. through 11:59 p.m.) of stroke onset (or first presentation, if time of onset unknown)
Enrollment: Key Points

• Must rescreen immediately before randomization

• Cannot randomize if these occur after consenting:
  • Any exclusion criteria are met, including any AF
  • Recurrent stroke

• No need to repeat SOC tests if interval between consent/randomization, but check if anything has been done for clinical purposes (e.g., heart-rhythm monitoring, creatinine)
Study Medications

Apixaban (5mg) BID (experimental therapy)
VERSUS
Aspirin 81 mg daily (standard of care)

• Standard of care: “...based on the results of studies performed in multiple vascular indications, the best balance of the efficacy and safety of aspirin appears to be ≈75 to 100 mg/d.”

What is apixaban?

• Selective Factor Xa inhibitor
  • Decreases thrombin generation
  • No direct antiplatelet effects
Why apixaban?

ARISTOTLE

Randomized, double-blind trial designed to test for non-inferiority

Apixaban 5 mg twice daily vs warfarin (target INR 2.0 to 3.0)

N=18,201 patients with AF and at least one additional risk factor for stroke

Primary outcome ischemic or hemorrhagic stroke or systemic embolism

Key secondary objectives of testing for superiority and rates of major bleeding and death from any cause.

**Why apixaban?**

<table>
<thead>
<tr>
<th>Table 2. Efficacy Outcomes.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Primary outcome: stroke or systemic embolism</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Ischemic or uncertain type of stroke</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
</tr>
<tr>
<td>Systemic embolism</td>
</tr>
<tr>
<td>Key secondary efficacy outcome: death from any cause</td>
</tr>
<tr>
<td>Other secondary outcomes</td>
</tr>
<tr>
<td>Stroke, systemic embolism, or death from any cause</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Stroke, systemic embolism, myocardial infarction, or death from any cause</td>
</tr>
<tr>
<td>Pulmonary embolism or deep-vein thrombosis</td>
</tr>
</tbody>
</table>

* Analyses were performed on data from the intention-to-treat population and included all events through the cutoff date for efficacy outcomes of January 30, 2011; comparisons of the primary outcome and of death from any cause were analyzed as part of hierarchical sequence testing (starting with testing the primary outcome for noninferiority, then the primary outcome for superiority, then major bleeding, and finally death from any cause), to control the type I error.

ARISTOTLE
Why apixaban?

AVERROES TRIAL

N=5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable

apixaban 5 mg twice daily or aspirin (81 to 324 mg daily)

Mean follow up period 1.1 yrs

Primary outcome stroke or systemic embolism
Why apixaban?

- Vitamin K Antagonist (warfarin) therapy *(Class I; Level of Evidence A)*
- Apixaban *(Class I; Level of Evidence A)*
- Rivaroxaban and dabigatran *(Class I; Level of Evidence B)*
- all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent.


*Stroke* 2014;45(7):2160-236.
Study Drug Administration

- Experimental therapy: Apixaban (5mg) BID PLUS Aspirin placebo
  VERSUS

  Standard of care: Apixaban placebo BID PLUS Aspirin 81 mg daily
Study Drug Administration: Double-blind, double-dummy

- Experimental therapy: Apixaban (5mg) BID PLUS Aspirin placebo

  VERSUS

Standard of care: Apixaban placebo BID PLUS Aspirin 81 mg daily

Apixaban
OR
apixaban placebo

**TWICE** a day from one bottle

Aspirin
OR
aspirin placebo

**ONCE** a day from second bottle
Study Drug Administration

Adjusted dose apixaban: 2.5 mg BID

Only for those patients who meet TWO of the following criteria:

1. Age > 80 years of age
2. Weight < 60 kg
3. Creatinine > 1.5 mg/dl
   a. For Canadian sites only, estimated creatinine clearance (eCrCl) < 15 mL/min is also an exclusion criterion.
Study Drug Kits

There will be 4 different dosing groups:

• Apixaban (5mg) + aspirin placebo
• Apixaban (2.5mg) + aspirin placebo
• Aspirin + Apixaban (5mg) placebo
• Aspirin + Apixaban (2.5mg) placebo

Experimentals

Standard
Study Drug Administration

The criteria for adjusted dose apixaban (2.5 mg) could change for a given patient during the course of follow up:

Only for those patients who meet **TWO** of the following criteria:

1. Age > 80 years of age
2. Weight ≤60 kg
3. Creatinine ≥1.5 mg/dl

For Canadian sites only, an adjusted dose of apixaban 2.5 mg will be used for subjects with eCrCl 15-24 mL/min regardless of other factors, as per national regulatory requirements.

We will not **require** study-sponsored patient weights or laboratory monitoring but if this information becomes available, then the dosage can change and we will provide the new medication dosage at the time of the medication resupply (90 day intervals).
Initiation of study medication

• For subjects who were receiving antiplatelet therapy prior to their qualifying stroke, there is no high-quality evidence to support switching to another antiplatelet agent empirically or based on the results of platelet resistance assays.

• Subjects receiving aspirin, clopidogrel, aspirin/dipyridamole, warfarin or a DOAC should be considered eligible for this trial and randomization to either aspirin or apixaban monotherapy.

• All baseline antiplatelet therapy will be stopped after randomization.

• In the rare instance that the site investigator feels that a short course of dual antiplatelet therapy is indicated, randomization cannot occur until after this course is completed.

• Open label antiplatelets will NOT be permitted during the trial.
Initiation of study medication: patients on anticoagulants for prophylaxis of VTE

• The first dose of study drug cannot be given until at least 12 hours after the last dose of an anticoagulant (heparin, enoxaparin, etc), even if at a prophylactic dose.

• Guidelines from the AHA/ASA recommend prophylactic-dose anticoagulation for “treatment of immobilized subjects to prevent DVT.”

• For immobilized subjects receiving prophylactic-dose anticoagulation per these guidelines, randomization should be performed at a time such that study drug is not started until after discontinuation of prophylactic-dose anticoagulation.
For PI/coordinator/patient to know:

- The first doses of study medication can begin on the day of randomization but *must* be initiated within 48 hours of randomization.
- May be taken with or without food
- If patient unable to swallow whole tablets, may crush 5 mg or 2.5 mg tablets and suspend in 60 mL of water, D5W, or apple juice or mix with applesauce; administer immediately.
- For delivery through a nasogastric tube, crushed tablets may be suspended in 60 mL of water or D5W followed by immediate delivery.
- Crushed tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.
For PI/coordinator/patient to know:

• If a dose of study drug is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and the usual schedule of administration should then be resumed.

• The dose should not be doubled to make up for a missed dose.

• The package insert for apixaban does not recommend regular monitoring of laboratory parameters such as creatinine or liver function tests. Thus, such tests are not required as part of this study.

• Patient information sheet will be provided/available on study website and WebDCU.
### Prohibited Medications: Anticoagulants & Antiplatelet Agents

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab</td>
<td>Reopro</td>
<td>Dabigatran</td>
<td>Pradaxa</td>
<td>Prasugrel</td>
<td>Effient</td>
</tr>
<tr>
<td>“Non Study” Apixaban</td>
<td>“Non-Study” Eliquis</td>
<td>Dalteparin</td>
<td>Fragmin</td>
<td>Rivaroxaban</td>
<td>Xarelto</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Acova</td>
<td>Edoxaban</td>
<td>Lixiana, Savaysa</td>
<td>Tacagrelor</td>
<td>Brilinta</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Angiomax</td>
<td>Enoxaparin</td>
<td>Lovenox</td>
<td>Ticlopidine</td>
<td>Ticlid</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Pletal</td>
<td>Fondaparinux</td>
<td>Arixtra</td>
<td>Tinzaparin</td>
<td>Innohep</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Plavix</td>
<td>Heparin</td>
<td>Hep-Lock, Hep Pak CVC, Heparin Leo, Heparin Lock Flush</td>
<td>Warfarin</td>
<td>Coulmidin, Jantoven</td>
</tr>
<tr>
<td>“Non Study” Aspirin</td>
<td>Durlaza, various store brand names, Combination products: Adalat, Aggrenox, Alka Seltzer, Anacin, Endodan, Fiorinal, Percodan, Rivacodan, various less common combination names</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Prohibited Medications:

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

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Celebrex, Consensi (combo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac Sodium / Diclofenac</td>
<td>Cambia, Cataflam, Dyloject, Flector,</td>
<td>Ketoralac</td>
<td>Toradol, Toronova, Acular, Acuvail, Sprix, Acunistat (combo), Omidria</td>
</tr>
<tr>
<td>Potassium</td>
<td>Pennsaid, Solaraze, Vofenal, Voltaren, Voltaren XR, Zipsor, Zorvolex, Arthrotec (combo)</td>
<td></td>
<td>(combo)</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Dolobid</td>
<td>Nabumetone</td>
<td>Relafen</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Lodine, Lodine XL</td>
<td>Naproxen</td>
<td>Aleve, Anaprox, Naprelan, Naprosyn, Naxen, Treximet (combo), Vimovo (combo)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Advil, Caldolor Motrin, NeoProfen, Nuprin, Combunox (combo), Duexis (combo), Reprexain (combo), Vicoprofen (combo)</td>
<td>Oxaprozin</td>
<td>Daypro</td>
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<tr>
<td>Indomethacin</td>
<td>Indocin, Indocin SR, Tivorbex</td>
<td>Piroxicam</td>
<td>Feldene</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Anafen, Ketophene, Orudis, Orudis KT, Oruvail</td>
<td>Salsalate</td>
<td>Disalcid, Marhritic, Mono-Gesic, Salflex, Salsitab</td>
</tr>
</tbody>
</table>

*NIH StrokeNet*
Discouraged Medications: SSRIs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>Fluvoxamine</td>
<td>Luvox, Luvox CR</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Cipralex, Lexapro</td>
<td>Paroxetine</td>
<td>Brisdelle, Paxil, Paxil CR, Pexeva</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac, Sarafem, Symbyax (combo)</td>
<td>Sertraline</td>
<td>Zoloft</td>
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</table>
### Other Discouraged Medications: CYP3A4 Inducers

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apalutamide</td>
<td>Erleada</td>
<td>Enzalutamide</td>
<td>Xtandi</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Carbatrol, Epitol, Equetro, TEGretol, TEGretol XR</td>
<td>Phenobarbital</td>
<td>Luminal Sodium, Bellergal (combo), Diclophen (combo), Donnatal (combo), Phenaphen (combo), Tedral (combo)</td>
</tr>
<tr>
<td>Primidone</td>
<td>Mysoline, Sertan</td>
<td>Mitotane</td>
<td>Lysodren, Opeprim</td>
</tr>
<tr>
<td>Lumacaftor &amp; Ivacaftor</td>
<td>Orkambi</td>
<td>Phenytoin</td>
<td>Dilantin, Phenytek, Tremytoine</td>
</tr>
<tr>
<td>Rifampin / Rifampicin</td>
<td>Rifadin, Rimactane, Rofact, IsonaRif (combo), Rifamate (combo), Rifater (combo)</td>
<td>Fosphenytoin</td>
<td>Cerebyx</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>OTC natural product</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Other Discouraged Medications: CYP3A4 Inducers

<table>
<thead>
<tr>
<th>Generic Name</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cobicistat</td>
<td>Evotaz (combo), Genvoya (combo), Prezobix (combo), Stribild (combo), Symtuza (combo), Tyboost</td>
<td>Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir</td>
<td>Viekira Pak, Viekira Pak XR</td>
</tr>
<tr>
<td>Darunavir</td>
<td>reszista, Prezobix (combo), Symtuza (combo)</td>
<td>Itraconazole</td>
<td>Onmel, Sporanox, Sporanox PulsePak, Tolsura</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir, Kelatra (combo), Technie (combo), Holkira Pak (combo), Viekira Pak (combo), Viekira Pak XR (combo)</td>
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<td></td>
</tr>
</tbody>
</table>
# Other Discouraged Medications: CYP3A4 Inducers

<table>
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<tr>
<th>Generic Name</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Nefazodone</td>
<td>Serzone</td>
<td>Nelfinavir</td>
<td>Viracept</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>Korlym, Mifeprex, Mifegymiso (combo)</td>
<td>Ombitasvir, Paritaprevir, and Ritonavir</td>
<td>Technivie</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Noxafil, Posanol</td>
<td>Indinavir</td>
<td>Crixivan</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Zydelig</td>
<td>Grapefruit Juice</td>
<td>Dietary Interaction</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Biaxin, Biaxin XL</td>
<td>Ketoconazole (oral)</td>
<td>No Oral Brand Name</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Evotaz (combo), Reyataz</td>
<td>Lopinavir &amp; Ritonavir</td>
<td>Kaletra, Aluviran</td>
</tr>
<tr>
<td>Ketoconazole (oral)</td>
<td>No Oral Brand Name</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Efficacy Endpoint = Recurrent Stroke

• Primary endpoint: recurrent stroke of any type
  • Ischemic
  • Hemorrhagic (i.e., symptomatic, nontraumatic intracerebral hemorrhage)
  • Other (e.g., venous)
  • Undetermined type

• Secondary composite endpoints
  • Recurrent ischemic stroke or systemic embolism
  • Recurrent stroke of any type or death
Safety Endpoints

• Primary endpoints
  • Symptomatic intracranial hemorrhage
  • Major hemorrhage other than intracranial hemorrhage

• Secondary endpoint: all-cause mortality
Follow-up: Assessments

• Did the subject have a stroke?
• Has the subject had any heart-rhythm monitoring done or been told they have atrial fibrillation?
• Any contraindications to study drugs?
  • Known change in renal function?
  • New indication/contraindication to anticoagulation?
  • New concomitant med that is prohibited?
• How is adherence?
• Subject’s functional status?
Follow-up: Key Points

Visits can be in-person or remote

• Year 1: standard visit every 3 months

• Years 2-4:
  • Standard visit: Months 18, 24, 30, 36, 42, 48
  • Study drug resupply visit: Months 21, 27, 33, 39, 45

• Study drug will be provided to subjects in a 3-month supply

• For study drug resupply visits starting in Year 2:
  • Can ship drug to subject, deliver drug in person, or arrange in-person pick-up
  • Either way, must make contact to assess SAEs
Post-Randomization AF Is Expected

• Expectation: ~16% of subjects diagnosed with AF post randomization
• Switch to open-label therapy
• Accounted for in statistical analysis plan and power calculation
• AF detection rate will be monitored during trial
Other Issues Occurring during Follow-up

• Treatment interruption for surgery
• Indication for open-label anticoagulant/antiplatelet therapy
• Unblinding
  • Major bleeding
  • Indication for tPA
Other Issues Occurring during Follow-up

• Treatment interruption for surgery
• Indication for open-label anticoagulant/antiplatelet therapy
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  • Major bleeding
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Statistical Analysis Plan

• Intention-to-treat approach
• Survival analysis with log-rank test to compare treatment groups
• Interim analysis after ½ of primary outcome events (75)
• Secondary analysis: test interaction between atrial cardiopathy marker levels and relative benefit of apixaban vs. aspirin
Why Another ESUS Trial?

- RESPECT-ESUS
- NAVIGATE-ESUS
ARCADIA = Different Question Than ESUS Trials

- ESUS trials include patients with known AF or easily discoverable AF
  - Up to 6 minutes per day of AF allowed
  - No heart-rhythm monitoring after randomization
ARCADIA = Different Question Than ESUS Trials

• ESUS trials include patients with known AF or easily discoverable AF
  • Up to 6 minutes per day of AF allowed
  • No heart-rhythm monitoring after randomization
• Will be difficult to sort out effects of this crucial subgroup
• Cannot determine benefits in atrial cardiopathy strictly defined
ARCADIA = Different Question Than ESUS Trials

ARCADIA = NO AF

• Patients with any known AF excluded
• Heart-rhythm monitoring encouraged before/after randomization
ARCADIA Protocol Key Points

1. Identify ESUS
2. Apply inclusion/exclusion criteria
3. Consent and test for atrial cardiopathy
4. Randomize if atrial cardiopathy
5. Follow-up visits q3 months to resupply meds/identify outcomes
6. If AF, switch to open-label therapy and continue to follow
Likely Benefits of ARCADIA

• Target biologically plausible group but novel subset of ESUS
• Allow personalized treatment for preventing recurrent stroke
• Advance understanding of stroke pathogenesis
• Set stage for primary prevention trial in patients with atrial cardiopathy
ARCADIA Biobank

- Samples collected from participants at time of screening will be used to assay NT-proBNP to determine eligibility for the study.
- Samples may also be used for other ancillary studies of stroke and cardiac disease as part of a Biobank.
- Participants may decline participation in the ARCADIA Biobank.
- No genetic testing will be performed without further amendment of this protocol and informed consent form.
- The biobank repository will be kept at the Laboratory Core for the study, in the Center for Advanced Laboratory Medicine (CALM) at Columbia University Medical Center (CUMC).
- Access to the repository for future research studies will be limited to those approved by the ARCADIA Executive and Ancillary Studies Committees.
- Specimens will be destroyed 10 years after the publication of the primary manuscript describing the results of the ARCADIA study.
ARCADIA Biobank

• Specimens that will be kept in Biobank:
  • Serum Separator Tube (SST): NT-proBNP (required for ARCADIA)
    ?other markers?
  • K$_2$-EDTA tube: ?proteomics
  • 2 PAXgene Blood RNA tubes: RNA expression profile (pending ancillary study)
Arcadia

A beautiful, idyllic, secluded, rustic area in Greece

Its inhabitants led simple, pastoral, happy lives

A utopia or paradise