AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA)

NIH StrokeNet Clinical Trial

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StrokeNet NCC PI: Joe Broderick
ARCADIA Data Core PI: Caitlyn Ellerbe

Study Cores:
Blood Laboratory: Eldad Hod
Echocardiography: Marco Di Tullio
ECG: Elsayed Soliman

Drug supply: BMS-Pfizer Partnership
Laboratory assay support: Roche
Left Atrium = Unrecognized Source of Cardiac Embolism?

• Dysrhythmia that defines atrial fibrillation (AF) associated with other atrial derangements
  – Termed “atrial cardiopathy”
• Atrial cardiopathy may cause embolism in absence of dysrhythmia
Efficacy of Anticoagulation Likely To Differ Based on Stroke Mechanism

• Likely of benefit in atrial cardiopathy:
  – Parallels with AF
  – Evidence of treatment modification by NT-proBNP

• Unlikely of benefit in artery-artery embolism:
  – WASID
  – SAMMPRIS/VISSIT
  – ARCH
  – CADISS
ARCADIA: Anticoagulation for Cryptogenic Stroke + Atrial Cardiopathy

• Primary hypothesis:
  – Apixaban superior to aspirin for preventing recurrent stroke in patients with cryptogenic stroke and atrial cardiopathy

• Atrial cardiopathy defined as ≥1 of following:
  – PTFV$_1$ >5000 $\mu$V*ms on 12-lead ECG
  – Left atrial size index ≥3 cm/mL$^2$ on echocardiogram (severe enlargement)
  – Serum NT-proBNP >250 pg/mL
Screening Procedures to Identify Atrial Cardiopathy

- Site investigators will ascertain severe left atrial enlargement on standard-of-care echocardiogram
- Standard-of-care ECG uploaded for measurement of PTFV₁ by ECG core
- Blood sample shipped to lab core for NT-proBNP assay (paid by study, not standard-of-care)
IDENTIFY POTENTIAL ESUS CASES

REVIEW:
1. MRI/CT
2. Vessel imaging
3. ECG
4. Telemetry
5. TTE/TEE

EXCLUDE:
1. Lacunes
2. >50% large-artery atheroembolism
3. Other known causes

FOLLOW UP
- 30-day phone call
- 3-month visit
- 6-month visit
- 9-month visit
- 12-month visit
- 18-month visit (MINIMUM)
- q6-month visits
- 48-month visit (MAXIMUM)

CHECK EXCLUSION CRITERIA

EXCLUDE:
1. Bleeding diathesis
2. Recent GI bleed
3. Renal failure
4. Need for clopidogrel or anticoagulation

SCREEN FOR ATRIAL CARDIOPATHY

STEPS:
1. Obtain written consent
2. Review echo report
3. Upload ECG
4. Send blood sample

RANDOMIZE SUBJECTS WITH ATRIAL CARDIOPATHY
Informed Consent Process

• Requesting waiver of informed consent and HIPAA authorization to screen medical records
• Written, informed consent will be obtained prior to any study-specific procedures including blood collection for NT-proBNP assay
• Surrogate consent allowed with stringent safeguards in place
• Optional short additional consent for biorepository at end of main consent
Enrollment Options

• Option 1: Screening and randomization both occur during initial hospitalization/clinic visit
• Option 2: Screening during initial hospitalization/clinic visit and randomization at subsequent clinic visit
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How Post-Enrollment AF Detection Will Be Handled

- ≥24 hours continuous heart-rhythm monitoring required before enrollment
- Other pre- or post-enrollment AF monitoring per each site’s standard practice
- AF detected after enrollment -> cross-over to open-label anticoagulation at MD discretion
- Primary analysis: intention to treat
Sample Size Estimation

- 1,100 patients (150 recurrent stroke events) needed for 80% power
- Allows one interim look for efficacy and futility (O’Brien-Fleming type Lan-DeMets error spending function with nonbinding futility boundaries)
Estimated Number of Eligible Patients

• Proportion with ESUS = 30-40%
• Proportion who will meet our criteria = 25%
• 5-10% of all ischemic strokes will be eligible
Recruitment Plans

- 25 StrokeNet RCCs comprising 120 sites
- 4400 subjects consented -> 1100 randomized
- Only randomized subjects will be followed
  - Pending ancillary studies
- 4 year study period
  - 2.5 year recruitment period
  - Minimum 1.5 years of follow-up
  - Maximum 4 years of follow-up
Site Selection Criteria

• Participating in NAVIGATE or RESPECT?
• How many cryptogenic strokes per year?
• Willing to randomize prior to completion of outpatient heart-rhythm monitoring?
• Digital echocardiographic capability?
• Level of enthusiasm?
Training Requirements

• Evaluation of cryptogenic stroke/ESUS
• NIH Stroke Scale
• Modified Rankin Scale
• Minority recruitment and retention
• Informed consent/surrogate consent
• ECG processing
• Laboratory collection and shipping
• Evidence-based secondary stroke prevention
• Adverse event reporting
• Apixaban dosing
  – Dose adjustment
  – Interruption for elective invasive procedures
  – Emergency unblinding
## Progress To Date

<table>
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<td>FDA IND exemption letter obtained</td>
<td>April 2015</td>
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<tr>
<td>Grant submitted</td>
<td>June 2015</td>
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<td>Grant resubmitted</td>
<td>March 2016</td>
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<td>Notification letter to anticipate funding received</td>
<td>September 2016</td>
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<td>Planning calls initiated</td>
<td>October 2016</td>
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<td>Site selection surveys completed</td>
<td>November 2016</td>
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<td>Site start-up plan developed</td>
<td>December 2016</td>
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<td>Initial protocol drafted</td>
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<td>Site protocol trial agreements drafted</td>
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<tr>
<td>Final protocol submitted to cIRB</td>
<td>February 2017</td>
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<td>Initial DSMB meeting</td>
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Challenges

• ESUS definitions/testing
• Shifting practices in AF monitoring
• NAVIGATE, RESPECT, and COMPASS
• Biobanking
• Mortality as competing risk
• Vascular risk factor management guidelines
• Emergency unblinding/elective procedures
• Safety reporting process with BMS
Start-up Timeline

cIRB review: March 8
Award funding anticipated: March 22
NCC to initiate site protocol trial agreements: June 1
Database and study cores ready: June 1
Study drug distribution starts: July 1
MOP finalized: July 1
Investigator start-up meeting 1 (60 sites): July 15
Initial sites released for enrollment: August 15
First enrollment: September 1
Investigator start-up meeting 2 (60 sites): September 30
Potential Ancillary Studies

- Proteomics
- Metabolomics
- RNA expression
- Cardiac MRI
- Atherosclerotic plaque imaging
- Trajectories of functional recovery
- Serial neuroimaging
- Continuous heart-rhythm monitoring
Why Another Trial of Anticoagulation for Cryptogenic Stroke?

• Apixaban = only NOAC with Class I recommendation from AHA/ASA
• Apixaban = only NOAC shown more effective than and as safe as aspirin (AVERROES)
• Key advantage of proposed trial = a priori specification of a biologically distinct group
• May lead to primary prevention trials in high-risk atrial cardiopathy patients
Why Another Trial of Anticoagulation for Cryptogenic Stroke?

• Without specification of subgroups, broader trials may:
  – Fail to show overall benefit despite clear benefit in atrial cardiopathy
  – Show overall benefit driven mostly by known AF
What If RESPECT or NAVIGATE is Positive?

• Feature a very heterogeneous population
  – Patients with up to 6 minutes of AF eligible
  – Include many patients with undiagnosed AF
  – Include many patients artery-to-artery embolism
  – Difficult to assess risk/benefit without prespecified delineation of biologically distinct subgroups
Likely Benefits of ARCADIA

• Maximize chance of success by targeting the most biologically plausible group (i.e., those most similar to AF)
• Allow personalized treatment for preventing recurrent stroke
• Advance understanding of stroke pathogenesis
• Potentially set the stage for a primary prevention trial in patients with atrial cardiopathy