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

NIH StrokeNet Clinical Trial

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Study Cores:
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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
VASCULAR RISK FACTORS

ABNORMAL ATRIAL SUBSTRATE

NON-ATRIAL STROKE MECHANISMS

STROKE

ATRIAL FIBRILLATION
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:
  – $\text{PTFV}_1 > 5000 \, \mu V^*\text{ms}$ on 12-lead ECG
  – Left atrial size index $\geq 3 \, \text{cm/mL}^2$ on echocardiogram (severe enlargement)
  – Serum NT-proBNP $> 250 \, \text{pg/mL}$
Screening Procedures to Identify Atrial Cardiopathy

• Site investigators will measure $\text{PTFV}_1$ on standard-of-care ECG (or can use ECG core)
• Site investigators will ascertain severe left atrial enlargement on standard-of-care echocardiogram
• Blood sample shipped to core lab for NT-proBNP assay (paid by study, not standard-of-care)
A

B

C

P_{\text{dur}}

P_{\text{amp}}

P_{\text{amp}}'

P_{\text{dur}}'

PR_{\text{interval}}

PTFV_1 = 2,006 \mu V^{*} \text{ms}

PTFV_1' = 7,918 \mu V^{*} \text{ms}
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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Estimated Number of Eligible Patients

• Ischemic strokes that are cryptogenic = 30%
• Proportion who will meet our criteria = 25%
• 5% of all ischemic strokes will be eligible
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)
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
• Primary analysis: intention to treat
should we add "at discretion of treating physician"
Elkind, Mitchell, 9/22/2016
Site Selection Criteria

• Participating in NAVIGATE or RESPECT?
• How many strokes per year?
• Willing to randomize prior to completion of outpatient heart-rhythm monitoring?
• Digital echocardiographic capability?
• System for phlebotomy/centrifuge/send-out?
• Level of enthusiasm?
Start-up Plan

- Site feasibility survey/selection
- Finalize protocol
- cIRB approval
- Develop training modules
- Program WebDCU
- Training
- BMS-Pfizer -> NCC pharmacy -> site pharmacies supply chain
- All 120 sites are live (August 1)
Training/informational modules

- Screening/eligibility
- PTFV₁ measurement
- Blood sample collection/shipment
- Medication supply/adherence
- Cross over to open-label anticoagulation
- Treatment interruption (e.g., procedures)
- Management of bleeding
- Concomitant antithrombotics/thrombolysis
Potential Ancillary Studies

- Genetics
- Cardiac MRI
- 3D echo
- Trajectories of recovery
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