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

NIH StrokeNet Clinical Trial

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ARCADIA Data Core PI: Caitlyn Ellerbe

Study Cores:
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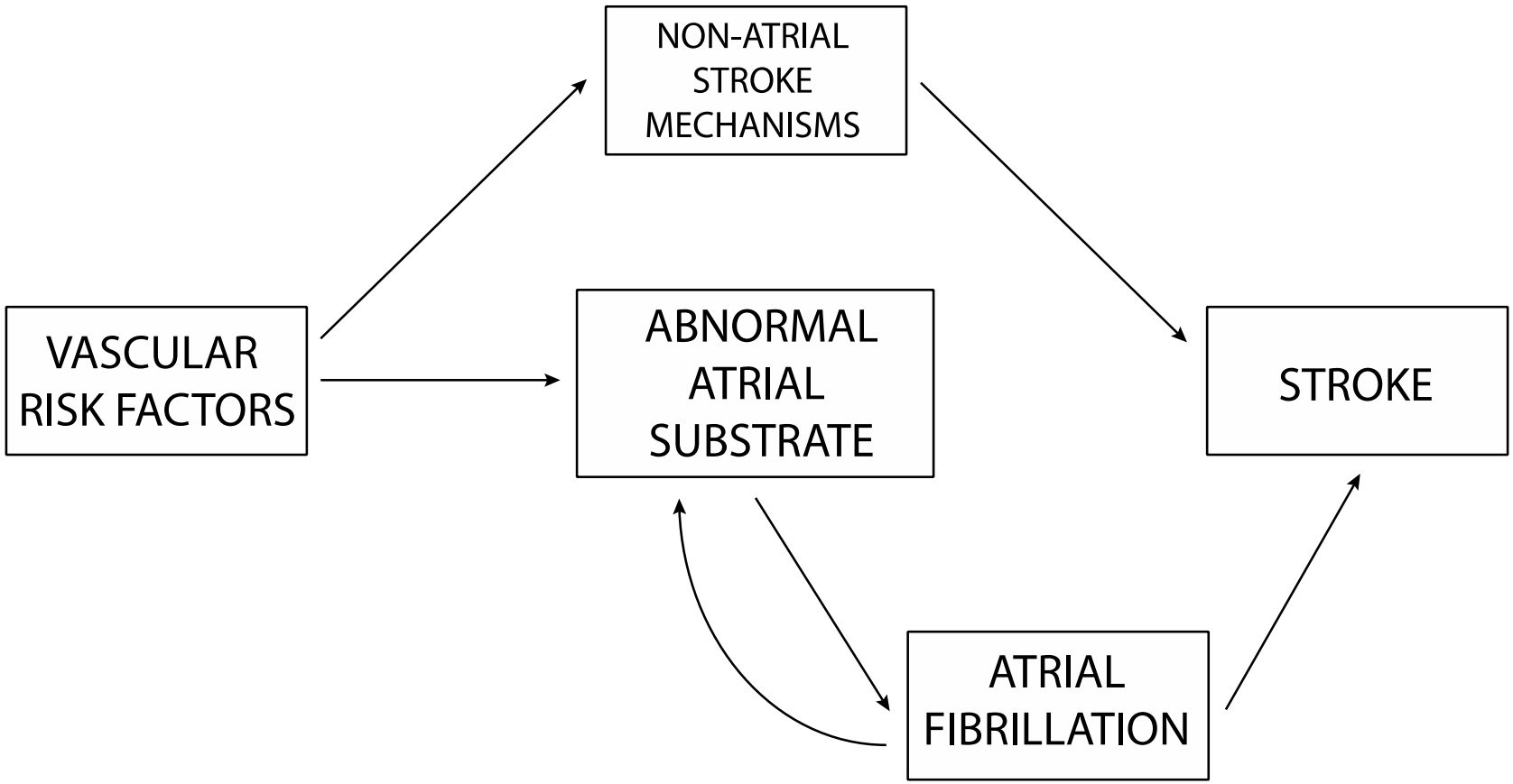
Echocardiography: Marco Di Tullio
ECG: Elsayed Soliman

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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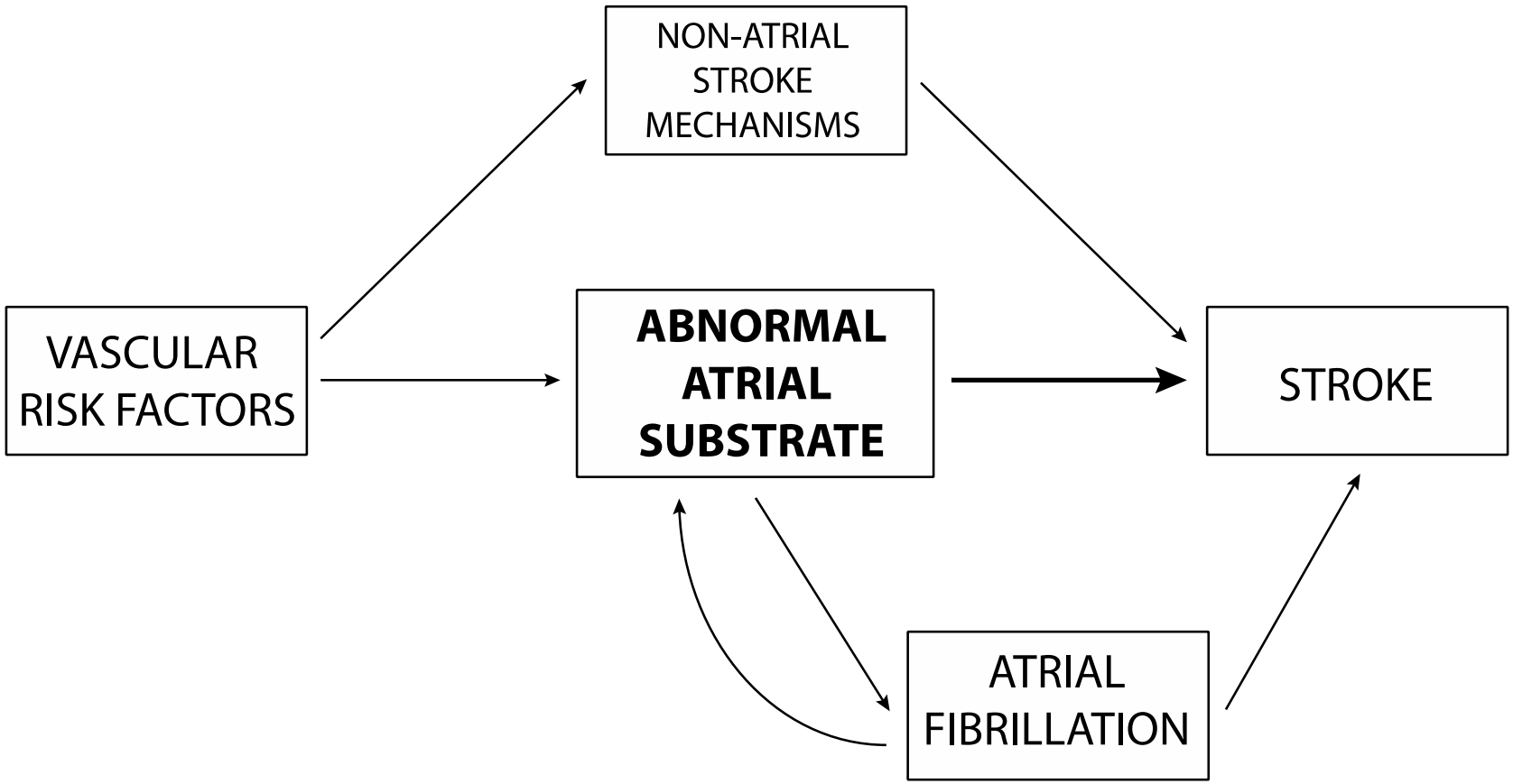
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# Efficacy of Anticoagulation Likely To Differ Based on Stroke Mechanism

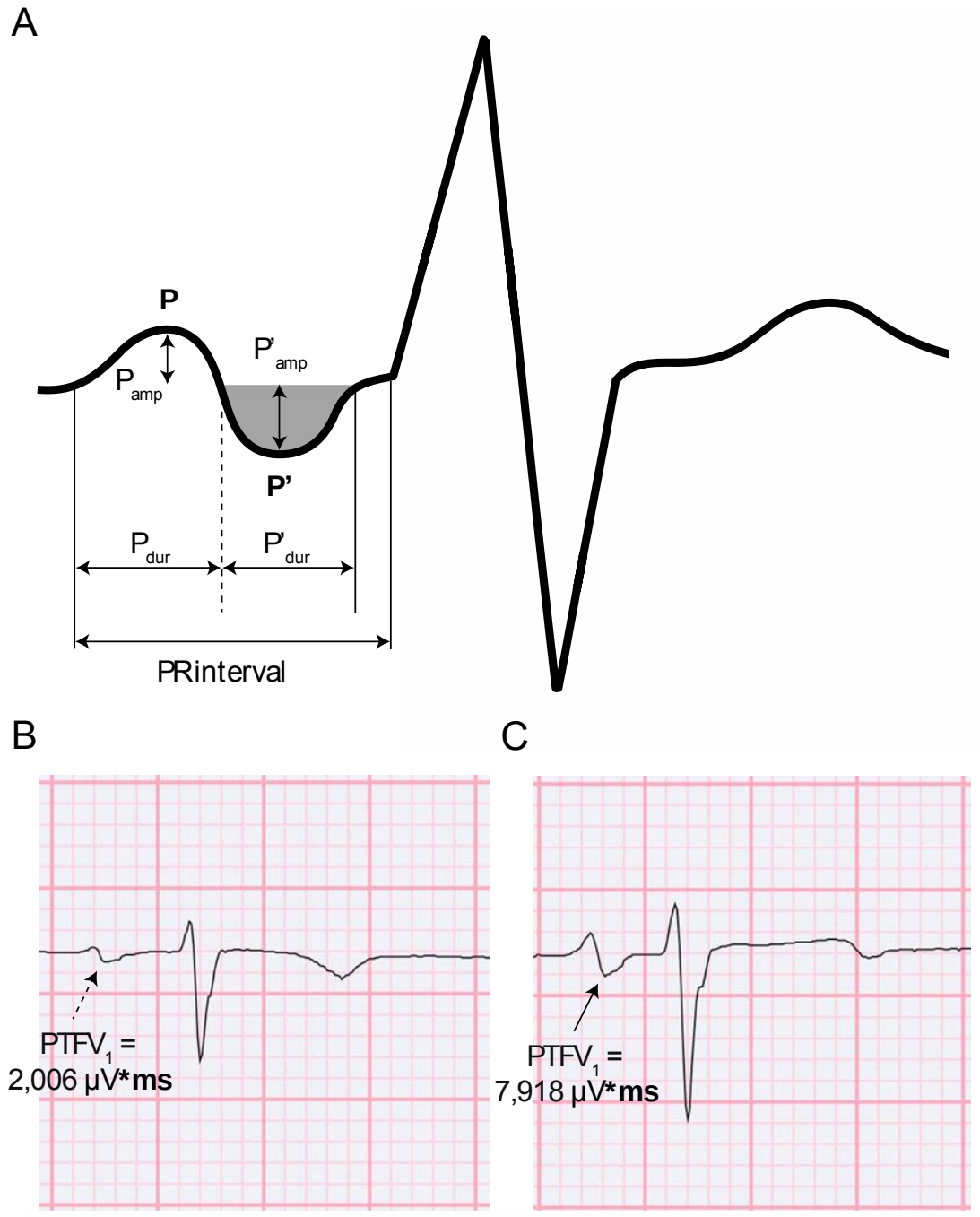
- Likely of benefit in atrial cardiopathy:
  - Parallels with AF
  - Evidence of treatment modification by NT-proBNP
- Unlikely of benefit in artery-artery embolism:
  - WASID
  - SAMMPRIS/VISSIT
  - ARCH
  - CADISS

# 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 μV*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 measure $PTFV_1$ 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
P
P'amp
Pamp
P'
Pdur
P'dur
PRinterval
B
PTFV1 =
2,006 µV*ms
C
PTFV1 =
7,918 µV*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

**SCHEDULE OF ASSESSMENTS**

| Procedure | S* | R* | 3 (±1) mos | 6 (± 2) mos | 12 (±2) mos | 18 (±2) mos | 24 (±2) mos | 30 (±2) mos | 36 (±2) mos | 42 (±2) mos | 48 (±2) mos |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eligibility form | x | x | | | | | | | | | |
| Consent | x | x | | | | | | | | | |
| Randomization form | | x | | | | | | | | | |
| Medical history | x | x | | x | x | x | x | x | x | x | x |
| Modified Rankin Scale | x | x | | x | x | x | x | x | x | x | x |
| Vital signs | x | x | | | | | | | | | |
| Physical examination | x | x | | | | | | | | | |
| NIH Stroke Scale | | x | | x | x | x | x | x | x | x | x |
| Brain imaging (CT or MRI) | o | | | | | | | | | | |
| Vascular imaging (head and neck) | o | | | | | | | | | | |
| 12-lead ECG | o | | | | | | | | | | |
| ≥24 hrs cardiac monitoring | o | | | | | | | | | | |
| Echocardiogram (TTE or TEE) | o | | | | | | | | | | |
| Serum chemistry | o | | | | | | | | | | |
| Complete blood count | o | | | | | | | | | | |
| Coagulation studies (PT, PTT, INR) | o | | | | | | | | | | |
| Serum liver function tests | o | | | | | | | | | | |
| Pregnancy test, if applicable | o | | | | | | | | | | |
| Blood sample send-out to core lab | x | | | | | | | | | | |
| ECG transmission to core lab | x | | | | | | | | | | |
| Echo transmission to core lab | x | | | | | | | | | | |
| AE/SAE assessment | | x | x | x | x | x | x | x | x | x | x |
| Medication adherence assessment | | x | x | x | x | x | x | x | x | x | x |
| Concomitant med. assessment | | x | x | x | x | x | x | x | x | x | x |

# 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

EM2

## Slide 13

**EM2** 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
- $PTFV_1$ 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