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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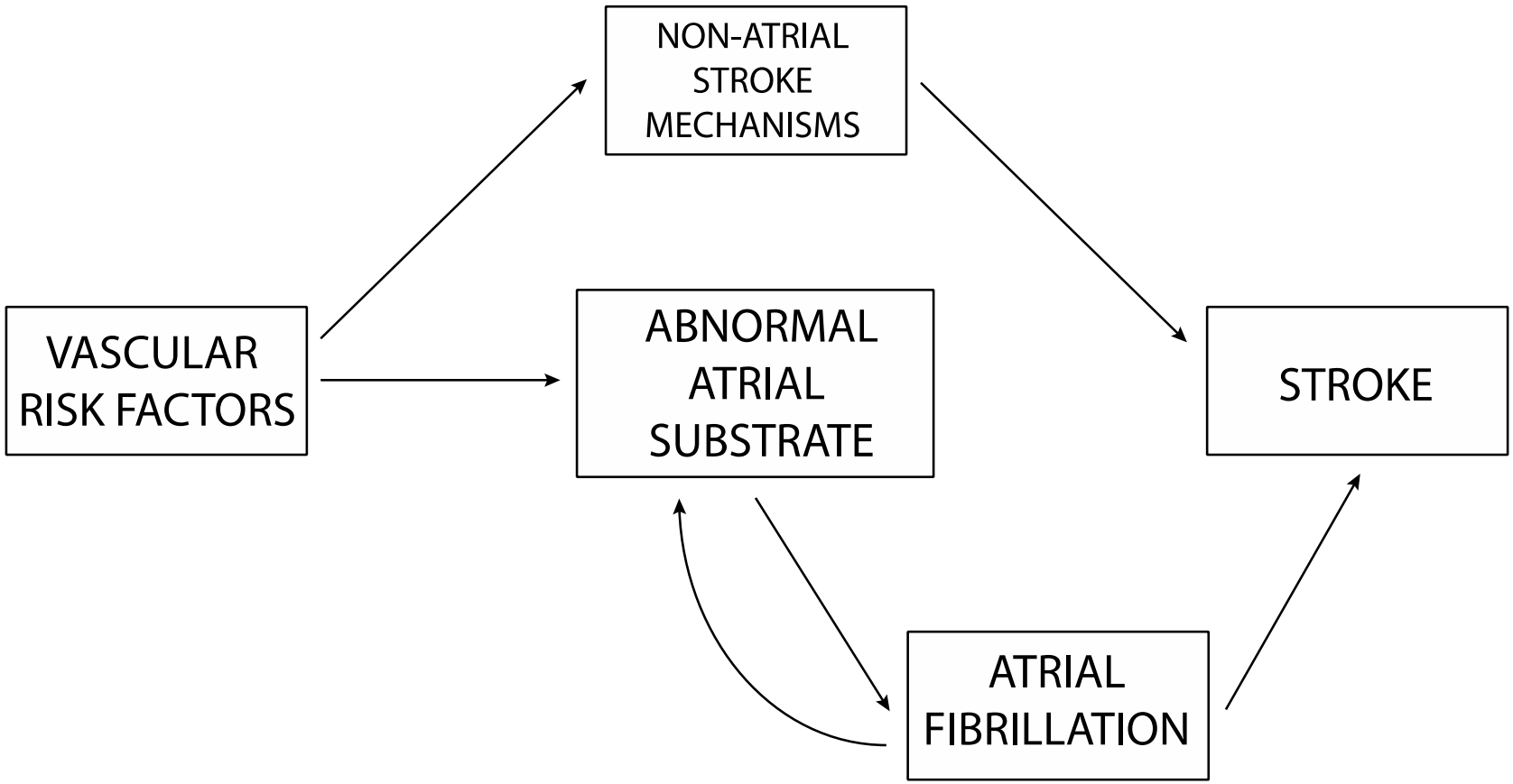
Echocardiography: Marco Di Tullio
ECG: Elsayed Soliman

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


NON-ATRIAL
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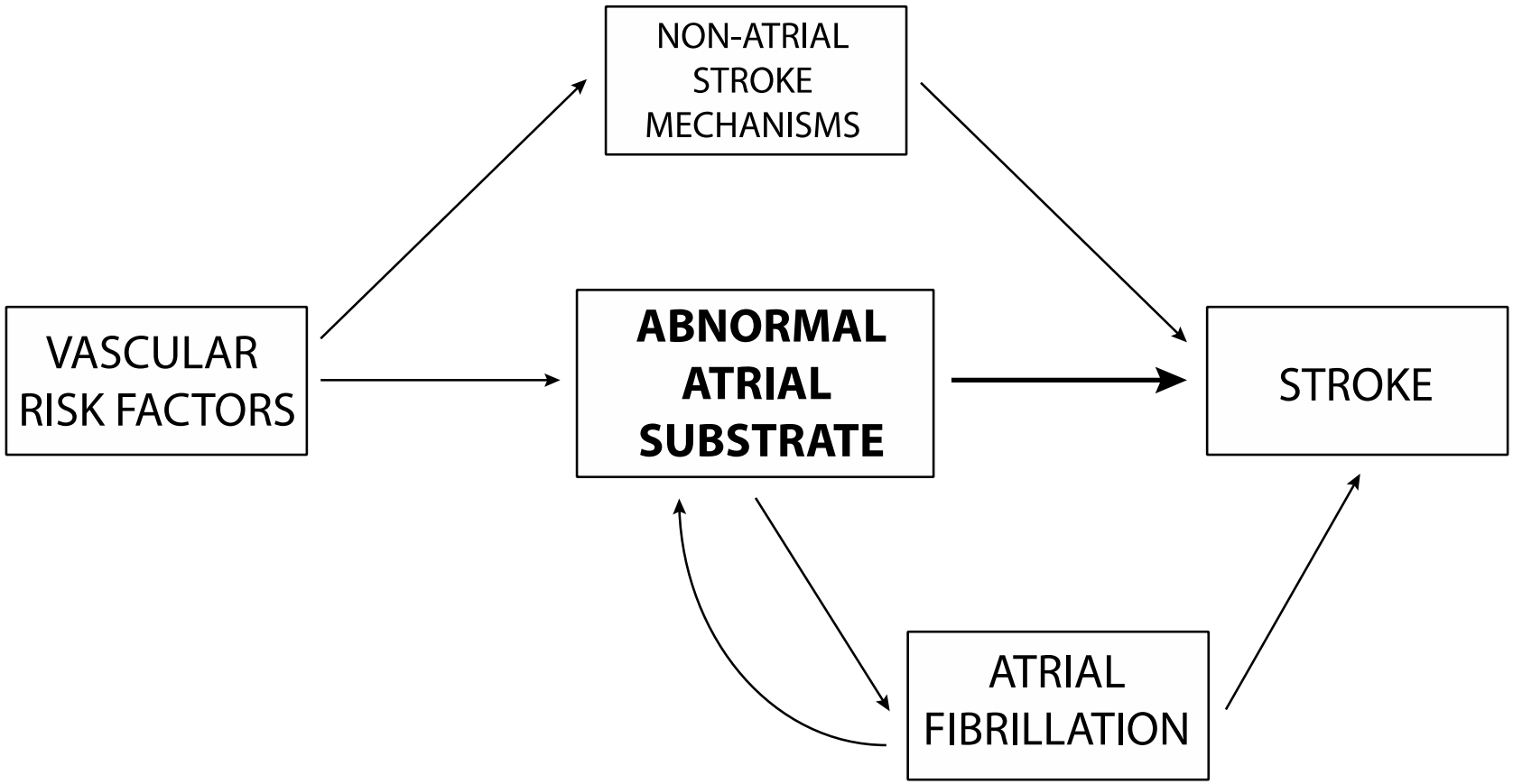
MECHANISMS
VASCULAR
RISK FACTORS
ABNORMAL
ATRIAL
SUBSTRATE
STROKE
ATRIAL
FIBRILLATION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Efficacy of Anticoagulation Likely To Differ Based on Stroke Mechanism

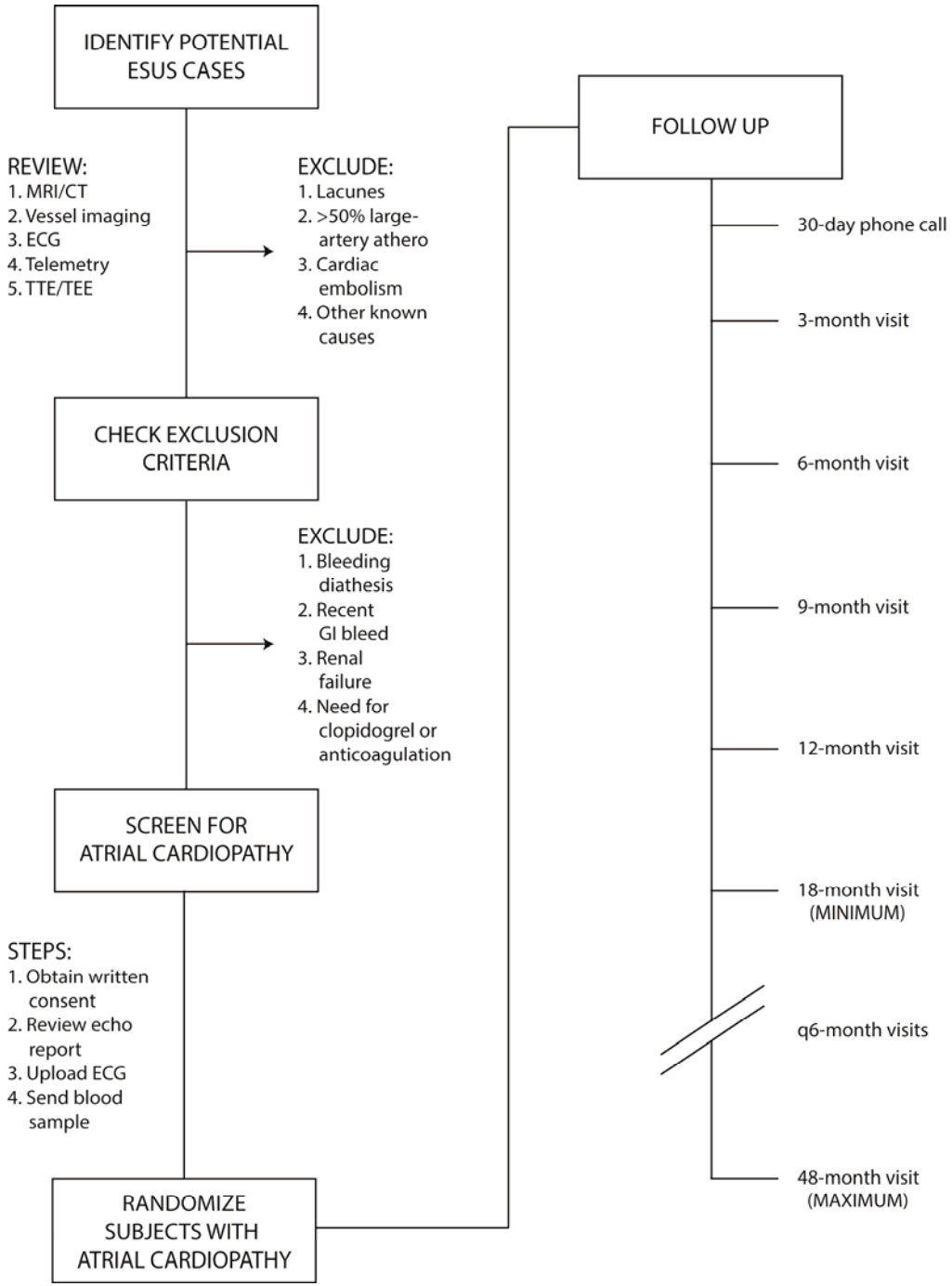
- Likely of benefit in atrial cardiopathy:
  - Parallels with AF
  - Evidence of treatment modification by NT-proBNP
- Unlikely of benefit in artery-artery embolism:
  - WASID
  - SAMMPRIS/VISSIT
  - ARCH
  - CADISS

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 ascertain severe left atrial enlargement on standard-of-care echocardiogram
- Standard-of-care ECG uploaded for measurement of $PTFV_1$ 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 athero
3. Cardiac embolism
4. Other known causes
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
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)

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

Procedure	E	R	30 ±7 days*	3 mos ±7 days	6 mos ±7 days	9 mos ±7 days	12 mos ±7 days	q6 mos ±7 days[#]	Close out[$]
Eligibility form	x	x							
Consent	x								
Randomization form		x							
Medical history[||]	x	x		x	x		x	x	
QVSFS^		x	x	x	x	x	x	x	
Modified Rankin Scale	x			x	x		x	x	
Vital signs	x	x							
Physical examination	x	x							
NIHSS	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								
PROMIS Global Health Form							x		
PROMIS Phys. Func. Short Form							x		
AE assessment			x	x	x	x	x	x	x
Medication adherence assessment			x	x	x	x	x	x	
Concomitant med. assessment	x	x	x	x	x	x	x	x	

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

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

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