ARCADIA

Investigator Meeting Slides

ARCADIA

AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke

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

First Investigator Meeting
November 17, 2017
Atlanta Marriott

Principal Investigators

Mitch Elkind, MD
Columbia University

Hooman Kamel, MD
Weill Cornell

Will Longstreth, MD
University of Washington

David Tirschwell, MD
University of Washington

Welcome!

Ancient site of Orchomenus in Arcadia Greece

- Study Statistician
  - Dick Kronmal, PhD, University of Washington
- StrokeNet National Clinical Coordinating Center (U 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

Welcome!

- NIH/NINDS Team
  - Scott Janis, PhD
  - Claudia Moy, PhD
  - Joanna Vivalda
- DSMB
  - Chair: Karen Furie, MD
- Independent Medical Safety Monitor
  - David Gladstone, MD

The Villagers of Arcadia

By Nicolas Poussin

Funding and Support

- NIH
- BMS-Pfizer Alliance
  - George Sands (Pfizer)
  - Charlotte Jones-Burton (BMS)
  - Donna Mills (BMS)
- Roche Diagnostics

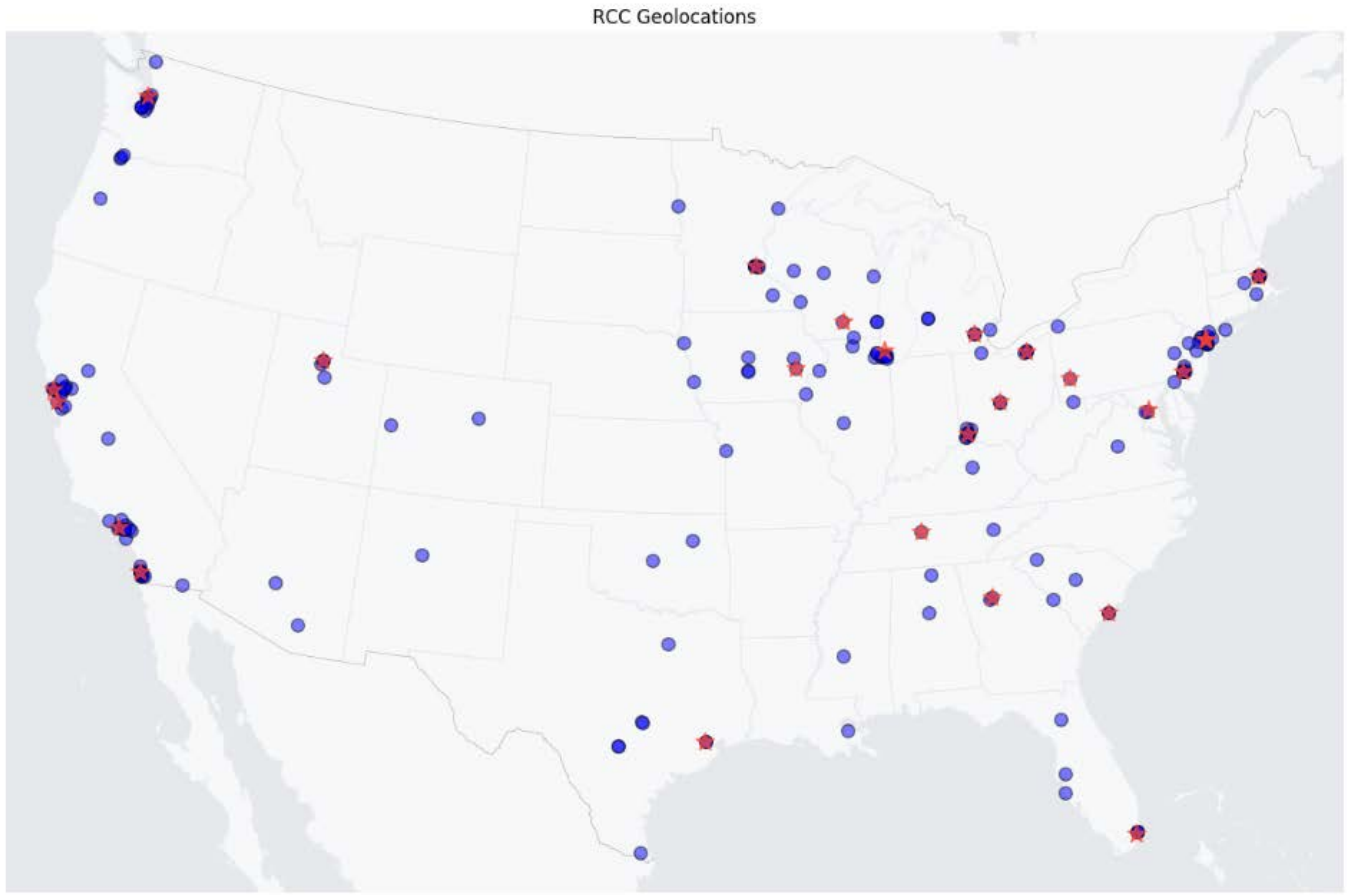
Thank you!

Megalopoli, Arcadia

Study organization

- NIH/NINDS
- Executive Committee
- Trial Operations Committee
- Clinical Coordinating Center (Director, Joe Broderick, Univ Cincinnati)
  - Project Management- Irene Ewing
  - 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)

120 Sites



- 25 Regional coordinating centers
- 4400 patients to be screened
- 1100 patients with ESUS/atrial cardiopathy to be randomized

Arcadia

A beautiful, idyllic, secluded, rustic area in Greece

Its inhabitants led simple, pastoral, happy lives

A utopia or paradise

ARCADIA

By Danno1 - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=4127058

Mount Lykaion
Arcadia

Αρκαδίας (Arcadia)

NIH StrokeNet

PREVENTION | TREATMENT | RECOVERY

Coming together is a beginning.
Keeping together is progress.
Working together is success.

~Henry Ford

www.NIHStrokeNet.org

Background

- NINDS created StrokeNet in 2013 to better support our clinical stroke program
- National Network that includes stroke prevention, acute treatment, and recovery.
- Multi-site Exploratory to Confirmatory Phase III Trials, biomarker validation
- Centralized infrastructure for contracts, cIRBs (inclinding VA hospitals), managing and sharing data, and running trials.
- Big – 25 regional centers with over 375 satellite hospitals thus far.

Vision

- To be the leading platform for stroke trials in the U.S. and globally

How we are trying to achieve our vision:

- Increase trial efficiency

  Decreases time to finish studies

- Balanced, prioritized set of trials in prevention, treatment and recovery.

- Improved research man/woman power in stroke research.

  Provides stable funding for research effort, fellowship training

- Improved data sharing.

  Single data center with uniform governance for data access

- Stable infrastructure

  Enables improved team research among different subspecialties.

- Improved ability to work in public-private partnerships with non-profits, industry and international partners.

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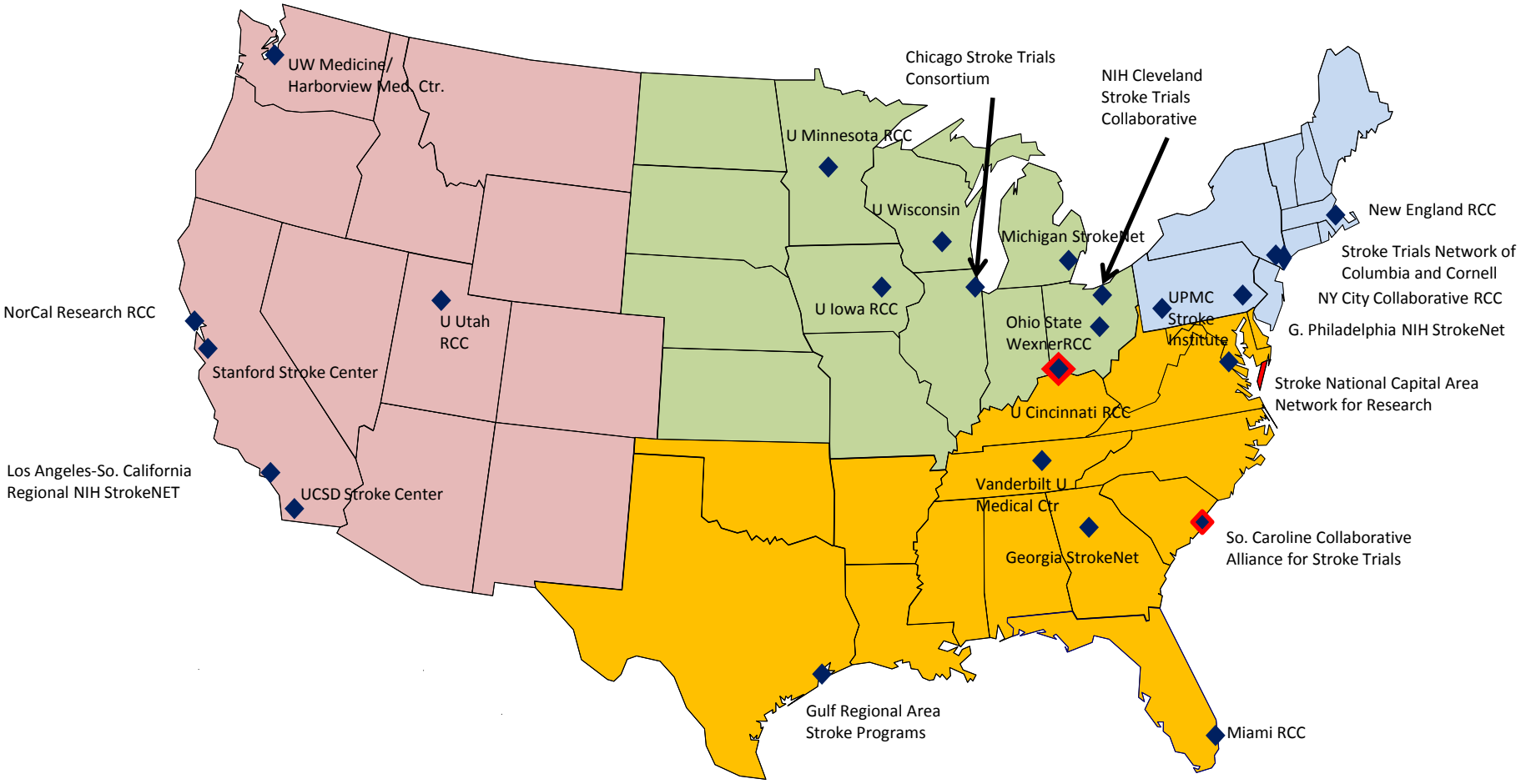
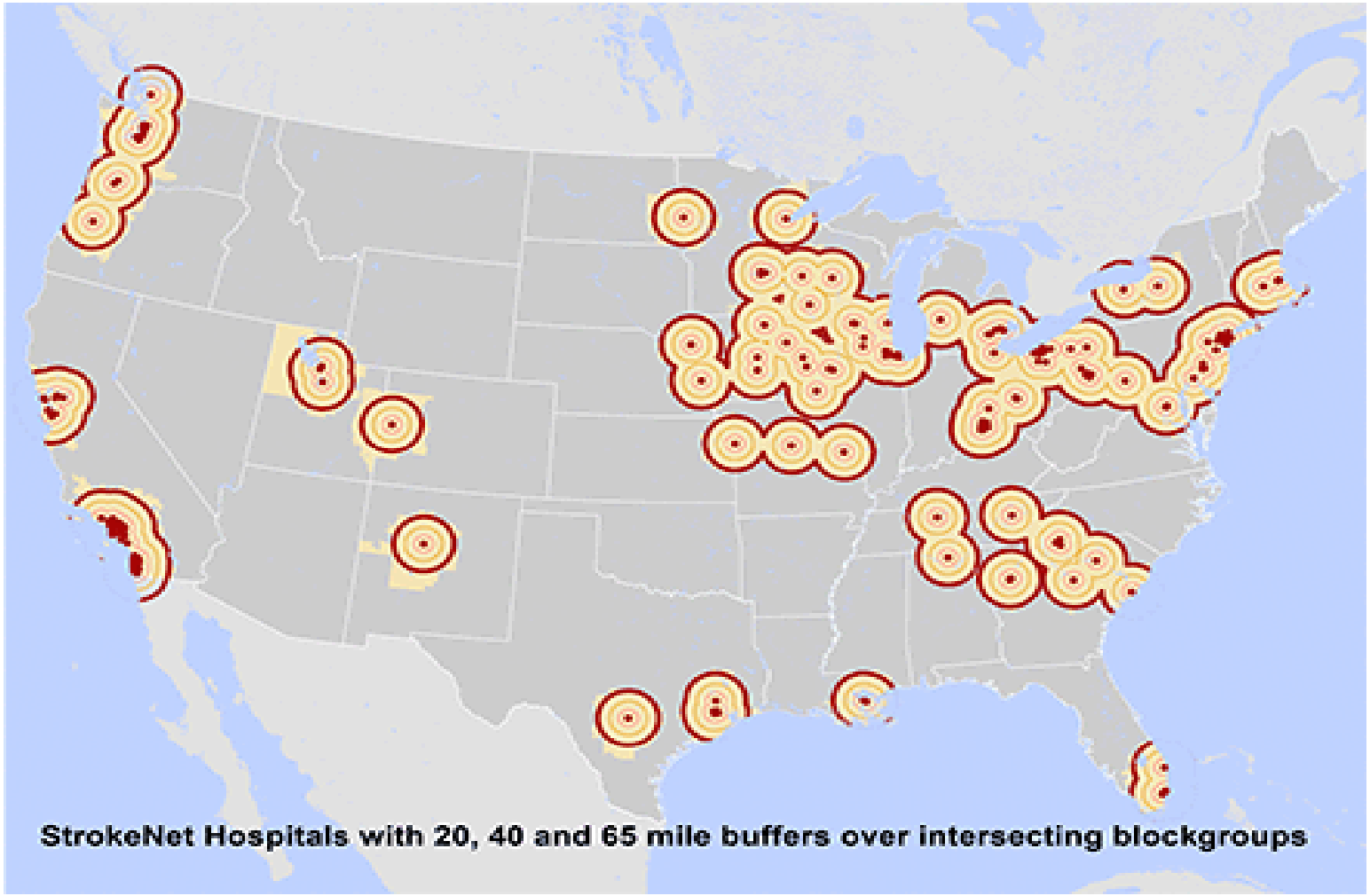


National Institute of Neurological Disorders and Stroke

StrokeNet hospitals have access to 50% of the US population



Ongoing NIH StrokeNet Trials

Current Trials	Domain	PI	Actively enrolling
CREST 2	Prevention	Tom Brott	Yes
MISTIE III	**Acute**	**Daniel Hanley**	**Recruitment Completed**
iDEF	**Acute**	**Magdy Selim**	**Recruitment Completed**
TeleRehab	Recovery & Rehabilitation	Steve Cramer	Yes (121 of 124)
DEFUSE III	**Acute**	**Greg Albers**	**Completed Early**
ARCADIA	Prevention	Mitch Elkind, Hooman Kamel, Dave Tirschwell, Will Longstreth	Not yet

Recently Approved Trials 9/2017 Council

Current Trials	Domain	PI
SLEEP-SMART	Prevention/Recovery	Devon Brown (Contact PI) Ronald Chervin
MOST	Acute	Ope Adeoye (Contact PI) Andrew Barreto Jim Grotta Joe Broderick

Ancillary Studies

Study	Domain	PI
CREST H (CREST2 trial)	Prevention (Ancillary)	R. Marshall, MD

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defuse·3

Prime Award Site
Stanford University

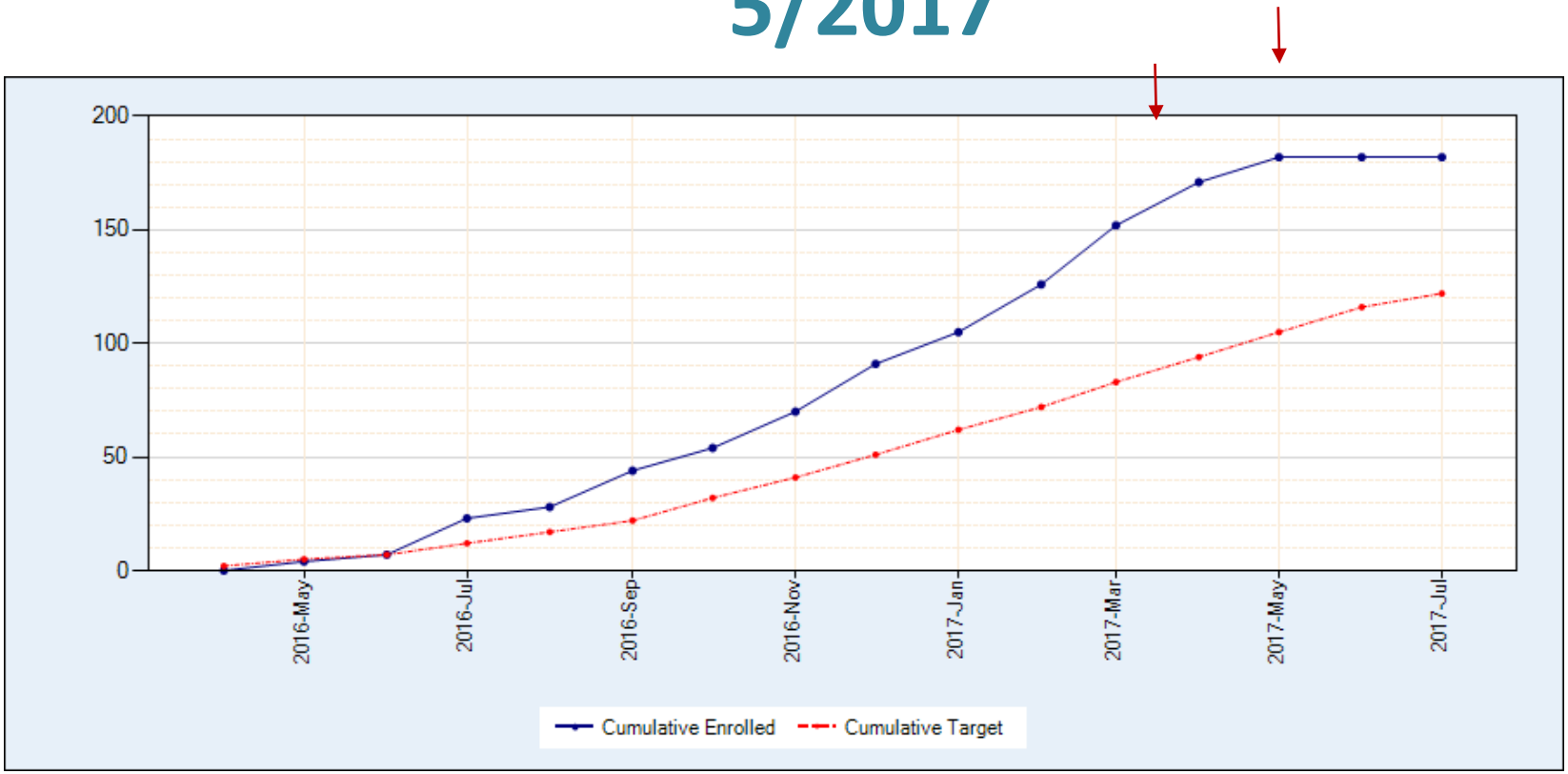
Protocol PI
Gregory Albers, MD

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

NIH
Funded by a grant from the National Institutes of Health

UNIVERSITY OF Cincinnati

DEFUSE III – Stopped at 182 Subjects in 5/2017



As of 2/28/17

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iDEF
Intracerebral Hemorrhage Deferoxamine Trial

Prime Award Site
Harvard Medical School

Protocol PI
Magdy Selim, MD

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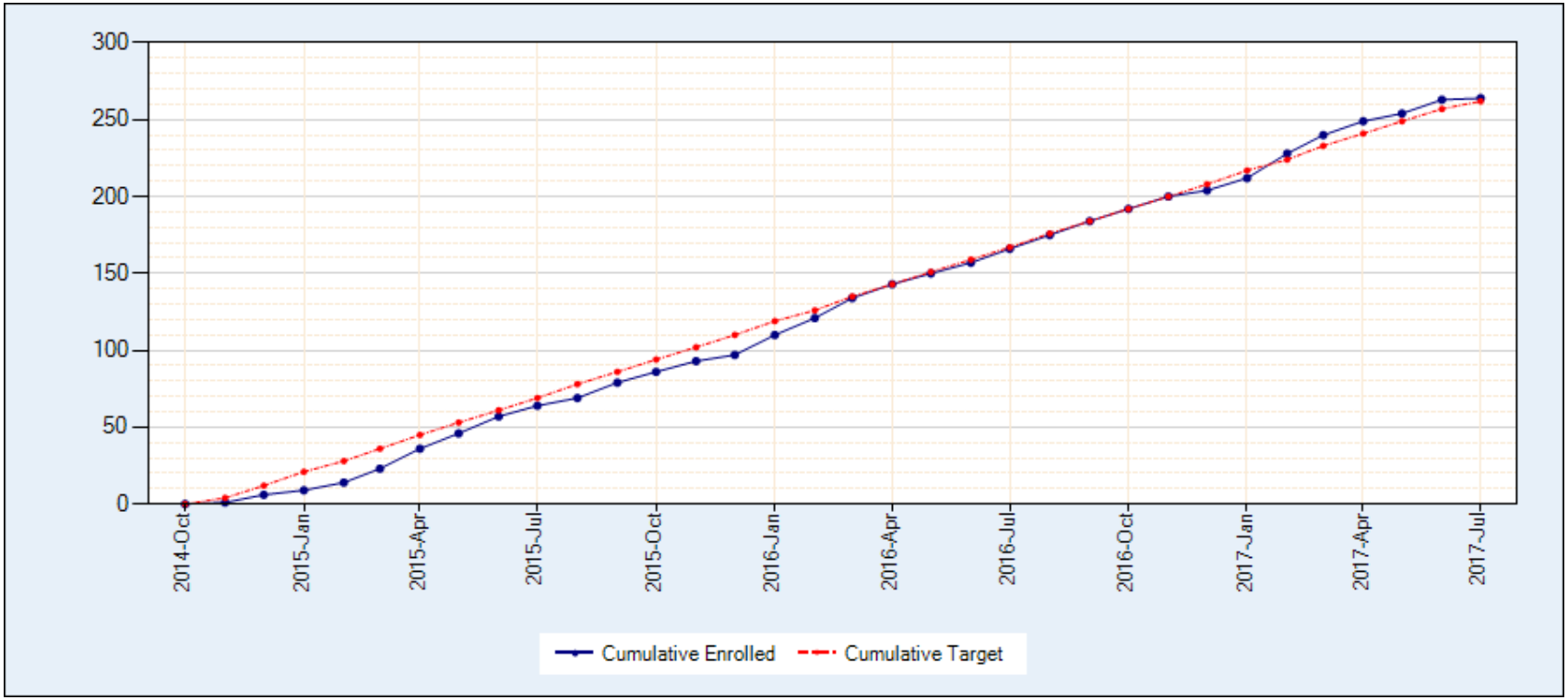
iDEF Trial (N = 294 of 294)



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CREST-2

The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study

Health and Hope for Patients at Risk for Stroke

Prime Award Site
Mayo Clinic Florida
University of Alabama at Birmingham

Protocol PI
Thomas Brott, MD
George Howard, PhD

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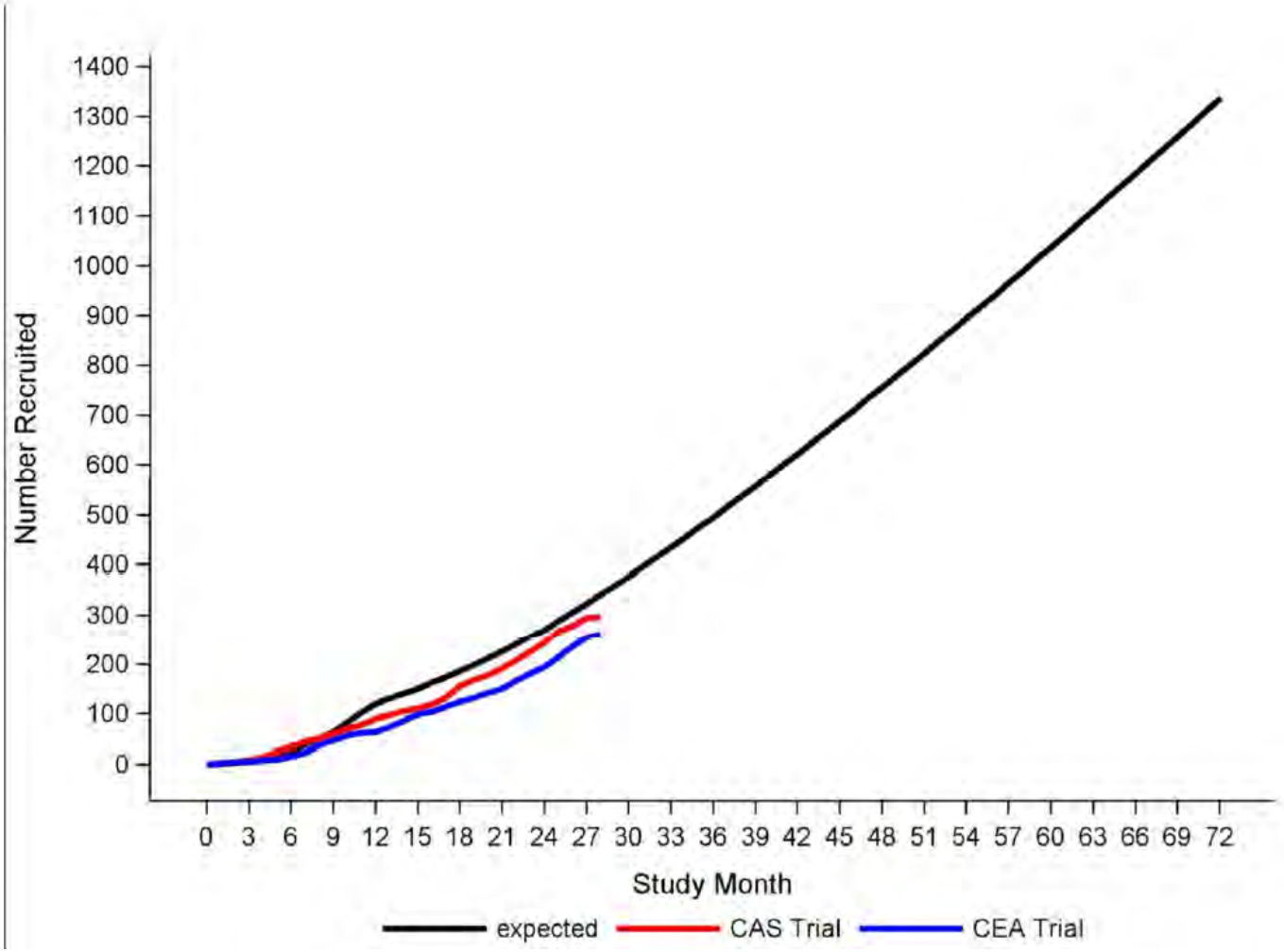
Crest 2 Trial (N = 833 of 2480)



Thank You!

Scott Janis, Ph.D.

Stroke Program Director

National Institute of Neurological Disorders and Stroke

Email: janiss@ninds.nih.gov

Website: http://www.ninds.nih.gov/

Rationale and Protocol

Hooman Kamel

ARCADIA

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Many Strokes Are Unexplained

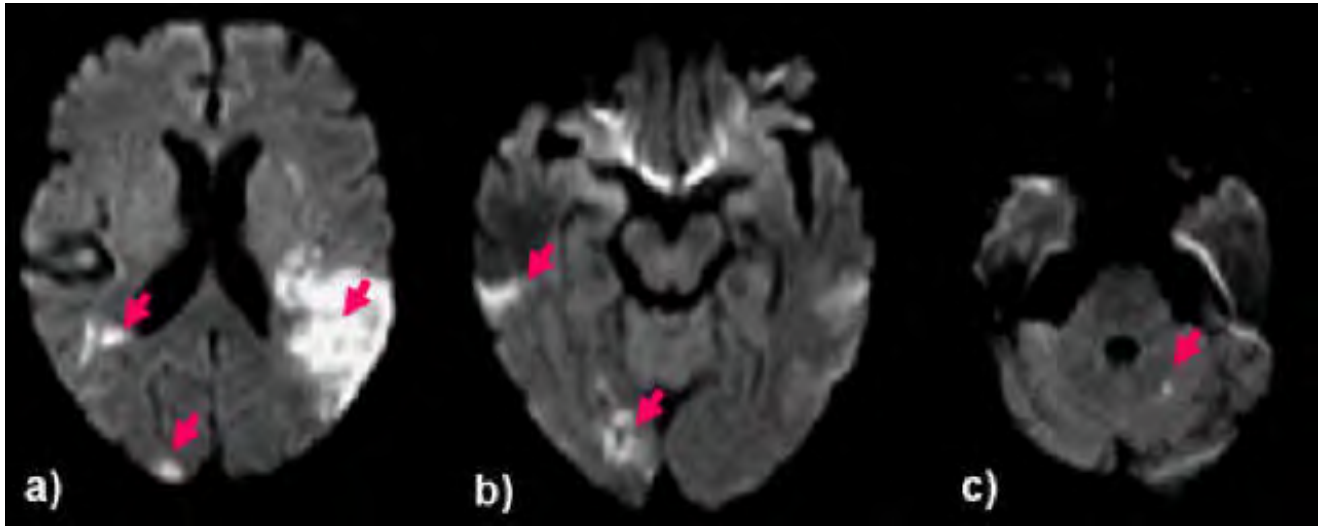
About 1 in 6 ischemic strokes have no identifiable direct cause

Table 1. Criteria for Diagnosis of Embolic Stroke of Undetermined Source (ESUS)*

1. Ischemic stroke detected by CT or MRI that is not lacunar†
2. Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia
3. No major risk cardioembolic source of embolism‡
4. No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, and drug abuse)

Hart et al, *Stroke*, 2017

Most Unexplained Strokes Seem Embolic



Sources of Cryptogenic Stroke?

- Large-artery atherosclerosis
- Cardiac embolism

Hart et al, *Lancet Neurol*, 2014

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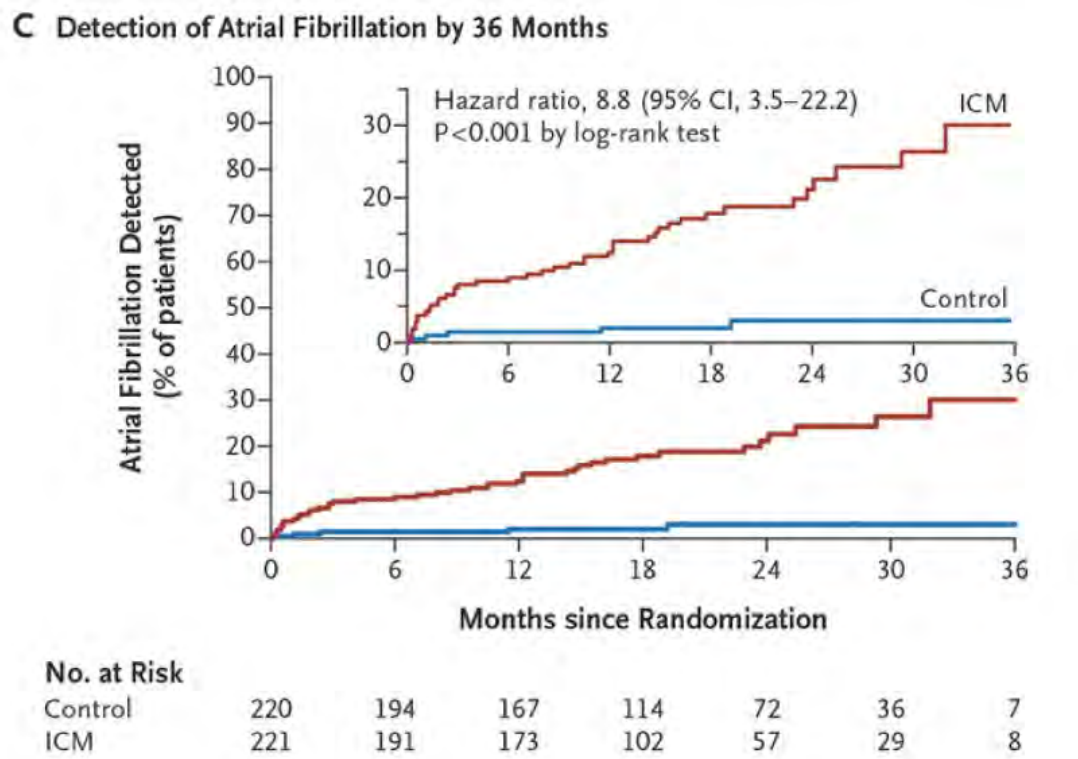
- Large-artery atherosclerosis
- Cardiac embolism

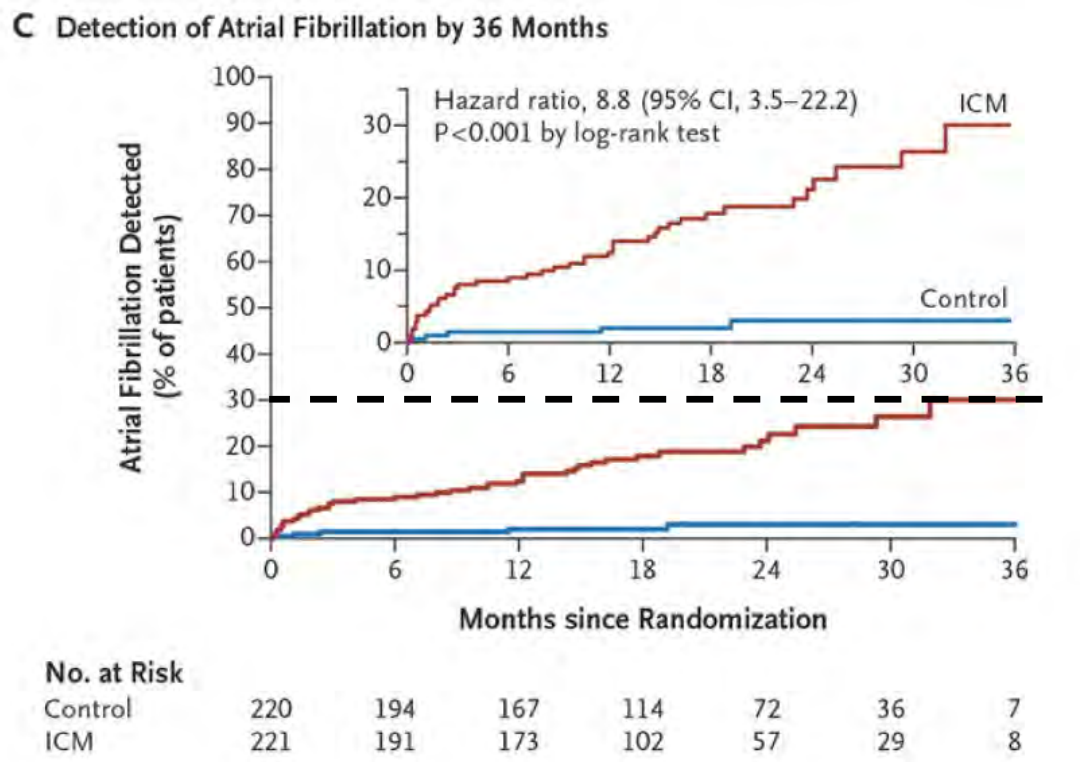
Hart et al, *Lancet Neurol*, 2014

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

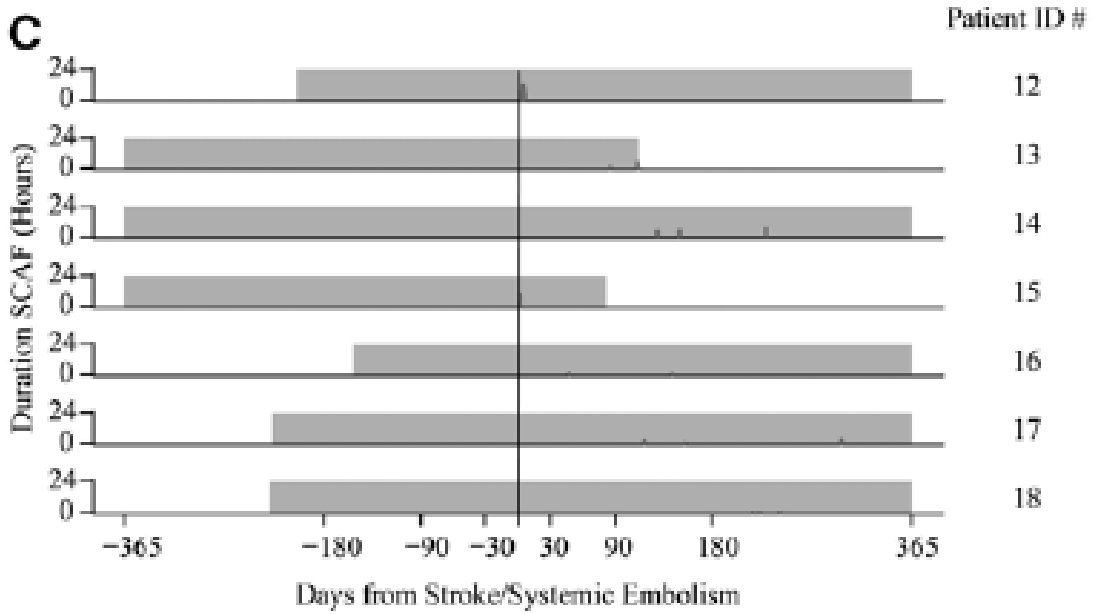
Kamel, *NEJM*, 2014

Hypothesis: Atrial Cardiopathy

- Arrhythmia that defines AF <—> other atrial derangements
- Atrial cardiopathy may cause embolism in absence of arrhythmia

Atrial Cardiopathy <—> Stroke

Poor temporal relationship between arrhythmia (AF) and stroke



Brambatti et al, *Circulation*, 2014

Atrial Cardiopathy <—> Stroke

Markers of atrial cardiopathy <—> stroke, independent of AF

- P-wave terminal force in ECG lead V_1 ($PTFV_1$)
- NT-proBNP
- Left atrial size/function on echocardiogram

Longstreth et al, *Stroke*, 2013; Kamel et al, *Stroke*, 2014; Kamel et al, *Stroke*, 2015; Kamel et al, *Ann Neurol*, 2015; Yaghi et al, *Stroke*, 2015

Atrial Fibrillation and Mechanisms of Stroke

Time for a New Model

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

Received October 28, 2015; accepted December 4, 2015.
From the Feil Family Brain and Mind Research Institute (H.K., C.I.) and Division of Cardiology (P.M.O.), Weill Cornell Medicine, New York, NY; and Department of Neurology, College of Physicians and Surgeons, and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY (M.S.V.E.).
The opinions expressed in the article are not necessarily those of the editors or of the American Heart Association.
Guest Editor for this article was Seemant Chaturvedi, MD.
Correspondence to Hooman Kamel, MD, 407 E 61st St, New York, NY 10065. E-mail hok9010@med.cornell.edu
(*Stroke*. 2016;47:895-900. DOI: 10.1161/STROKEAHA.115.012004.)
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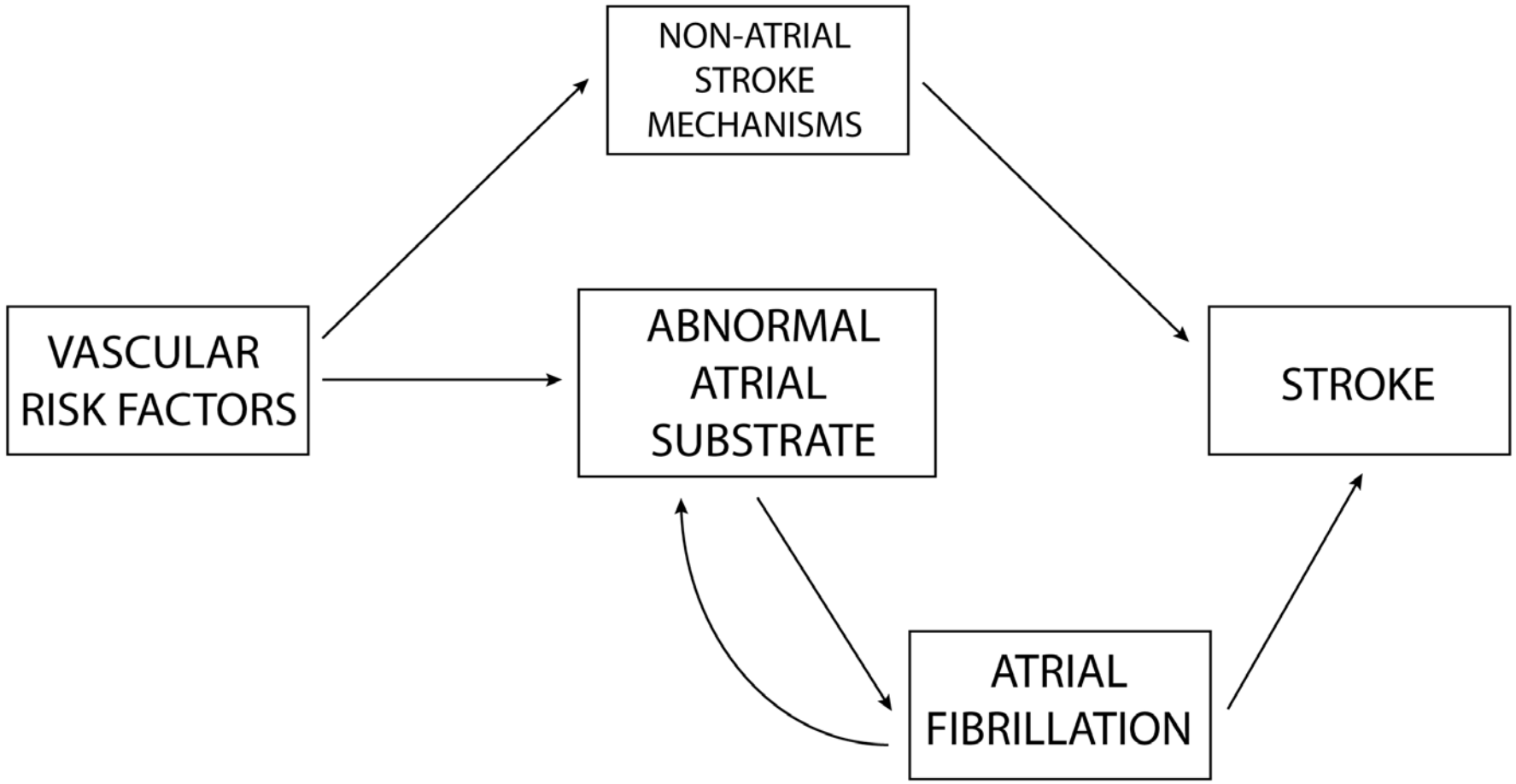
Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.115.012004


NON-ATRIAL
STROKE
MECHANISMS
VASCULAR
RISK FACTORS
ABNORMAL
ATRIAL
SUBSTRATE
STROKE
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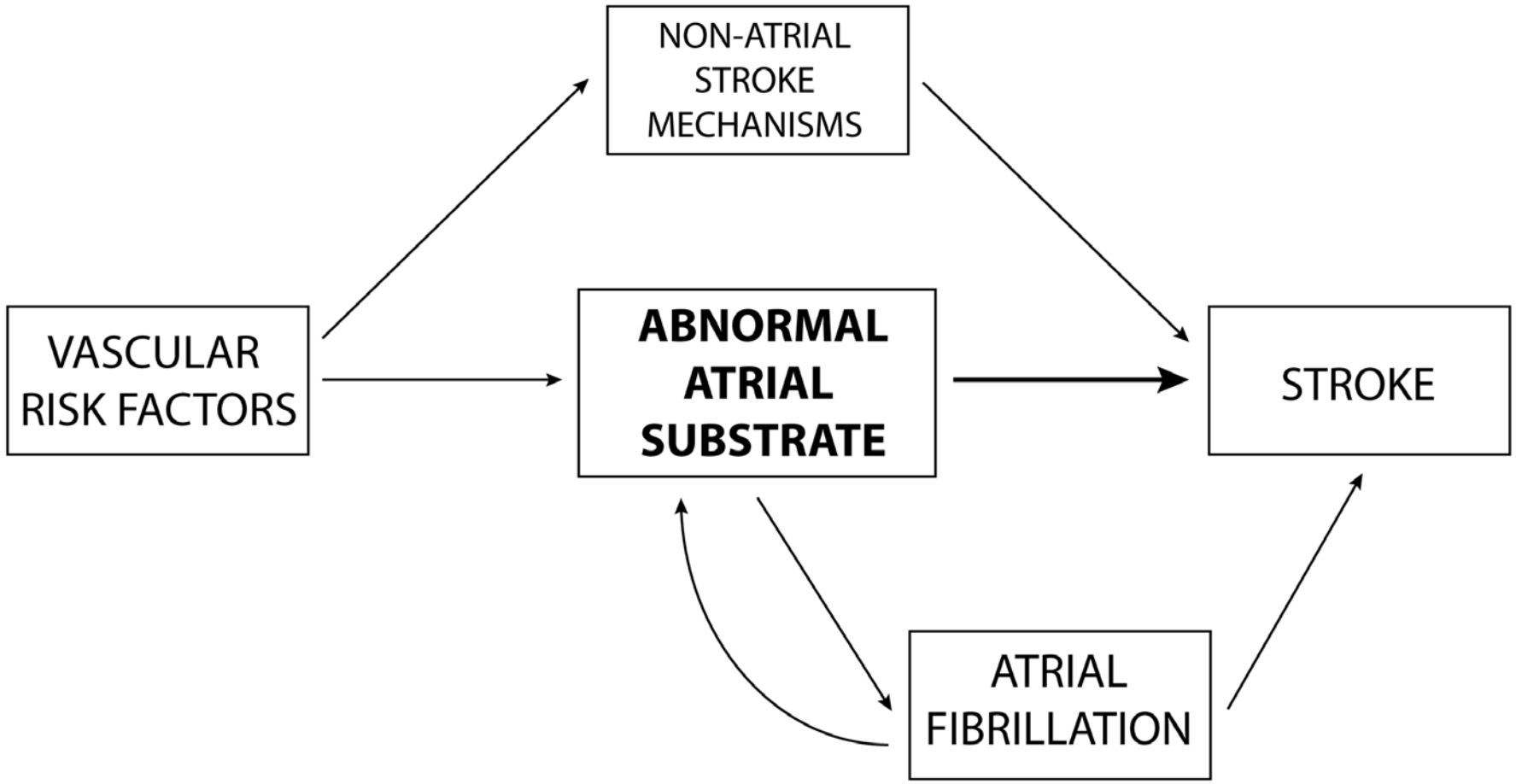
FIBRILLATION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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Atrial Cardiomyopathy

A Useful Notion in Cardiac Disease Management or a Passing Fad?

Jean-Baptiste Guichard, MD,[a,b] Stanley Nattel, MD[a,c,d]

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Thus, a variety of lines of evidence suggest that atrial cardiomyopathy may be an independent determinant of stroke risk. The most extreme possibility (which seems unlikely, but should at least be considered) is that it is not AF per se that causes stroke, but rather AF-associated atrial cardiomyopathy.

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If atrial cardiomyopathy is a significant stroke risk factor, independent of AF, can individuals without an AF history who are at increased risk of atrial thromboembolic events be identified and protected by OAC?

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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

W.T. Longstreth, Jr, Richard A. Kronmal, John L.P. Thompson, Robert H. Christenson, Steven R. Levine, Rebecca Gross, Robin L. Brey, Richard Buchsbaum, Mitchell S.V. Elkind, David L. Tirschwell, Stephen L. Seliger, J.P. Mohr and Christopher R. deFilippi

Stroke. 2013;44:714-719; originally published online January 22, 2013;
doi: 10.1161/STROKEAHA.112.675942
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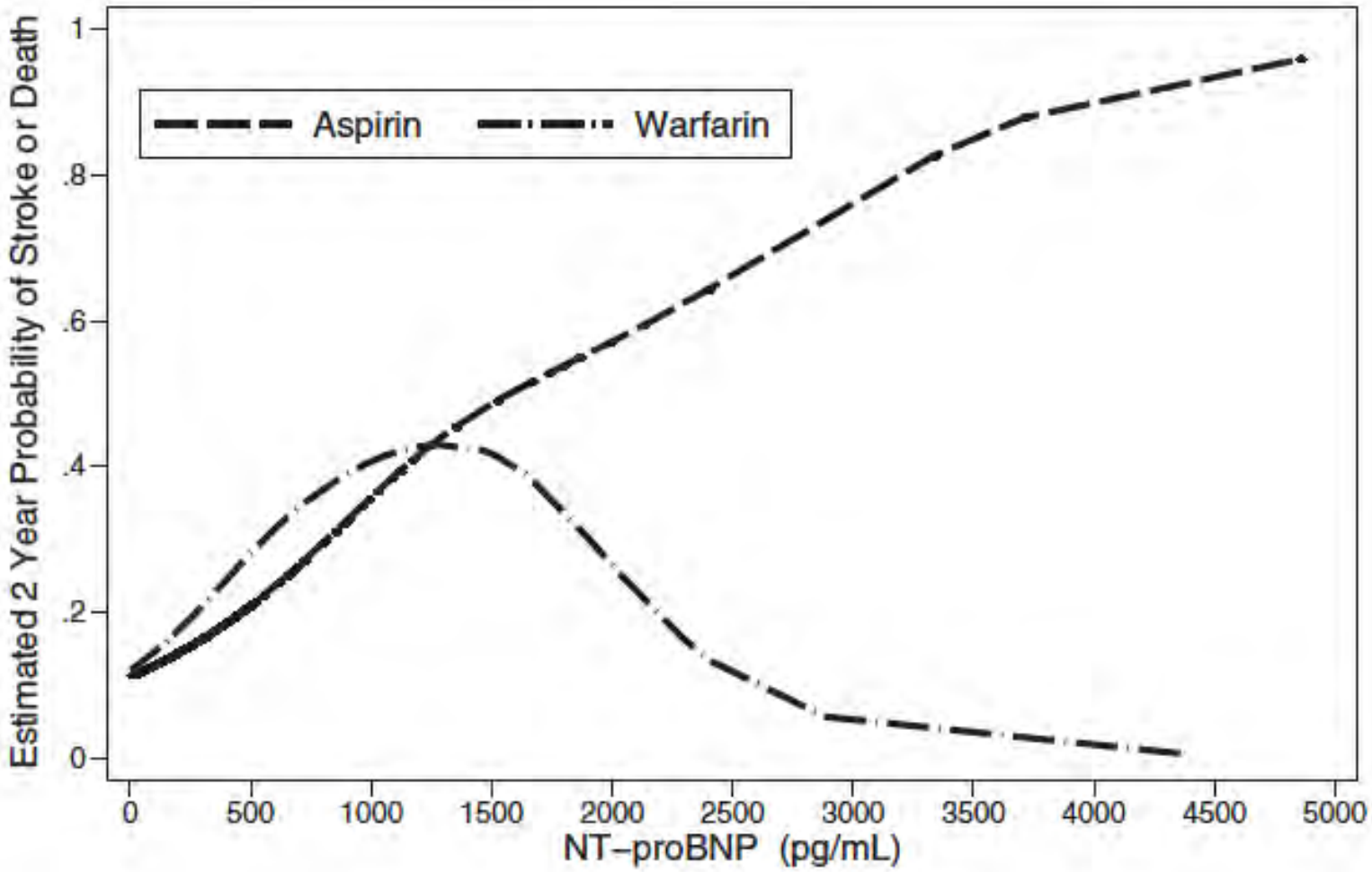
Aspirin
Warfarin
Estimated 2 Year Probability of Stroke or Death
0
.2
.4
.6
.8
1
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
NT–proBNP (pg/mL)

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The possibility that atrial cardiomyopathic risk factors can be used to identify patients with sinus rhythm who might have strokes that could be prevented by OAC would need to be tested in a prospective randomized trial.

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

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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

What is Atrial Cardiopathy?

Atrial cardiopathy defined as ≥1 marker

- $PTFV_1$ >5000 μV*ms on 12-lead ECG
- Left atrial size index ≥3 cm/m^2 on echocardiogram (mod-to-severe LAE)
- Serum NT-proBNP >250 pg/mL

Inclusion Criteria

- Age ≥45 years
- Clinical diagnosis of ischemic stroke
- mRS score ≤4
- Ability to be randomized no later than 120 days after stroke onset
- 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

Exclusion Criteria

- Any AF
- Clear indication for anticoagulation or antiplatelet therapy
- History of intracranial hemorrhage
- CKD with creatinine ≥2.5 mg/dL
- Chronic anemia/thrombocytopenia

Exclusion Criteria

- Any AF
- Clear indication for anticoagulation or antiplatelet therapy
- 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

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ARCADIA Biobank

- Samples may be used for ancillary studies of stroke and cardiac disease
- ARCADIA participants may decline participation in Biobank
- No genetic testing will be performed without amendment of protocol and informed consent form
- Biobank repository will be kept at Columbia University Medical Center
- Access to samples will require approval by ARCADIA Executive Committee
- Specimens will be destroyed 10 years after publication of primary manuscript describing results of ARCADIA trial

ARCADIA

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

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Safety Endpoints

- Primary endpoints
  - Symptomatic intracranial hemorrhage
  - Major hemorrhage other than intracranial hemorrhage
- Secondary endpoint: all-cause mortality

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

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

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Why Another ESUS Trial?

- RESPECT-ESUS
- NAVIGATE-ESUS

Why Another ESUS Trial?

- RESPECT-ESUS
- NAVIGATE-ESUS

ARCADIA IS NOT JUST AN ESUS TRIAL!

ARCADIA = Different Question Than ESUS Trials

- ESUS trials involve heterogeneous group of patients
  - Likely a mix of occult cardiac and large-artery sources
- Anticoagulation less likely to be effective for large-vessel disease
- NAVIGATE-ESUS stopped early due to futility

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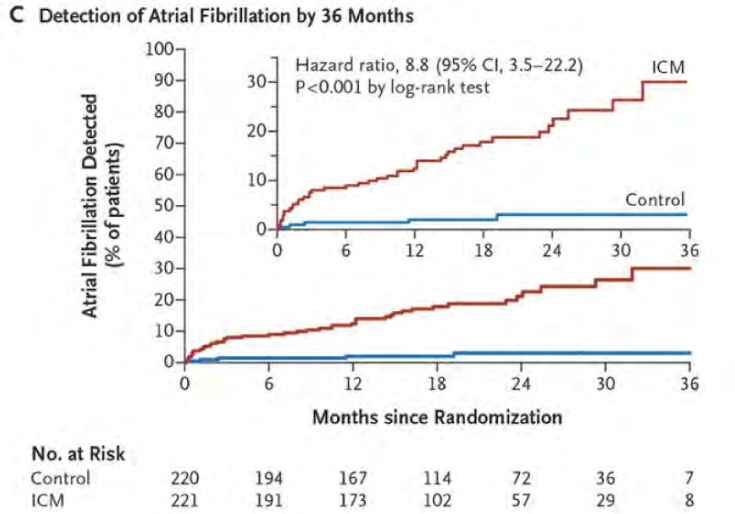
ARCADIA = Different Question Than ESUS Trials

- 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

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

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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

twitter
@ARCADIA_trial

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Eligibility and Randomization

Presented by: David Tirschwell

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Agenda

- Review approach to establishing eligibility
- Consent
- Hotline
- Overview of WebDCU processes for eligibility and randomization

Approach to establishing eligibility

- An appropriately credentialed research coordinator, the site PI or site co-Is all able to review medical records to assess for eligibility
- To screen for eligibility, full access to the medical record is required
  - review of a medical record from the ARCADIA site hospital
  - obtaining outside medical records, including imaging studies
- Often, investigators and coordinators will use a paper copy of the CRF for screening chart review.
- Timing of Study Screening - The study team may begin screening procedures as soon as the patient is admitted to the hospital for stroke (Day 0).

Inclusion Criteria

- Age ≥ 45 years.
- Clinical diagnosis of ischemic stroke + brain imaging to rule out hemorrhagic stroke.
- Modified Rankin Scale (MRS) score ≤ 4.
- Ability to be randomized no later than 120 days after stroke onset.
- ESUS, i.e. NOT
  - Lacunar
  - Large vessel atherosclerotic
  - Cardioembolic
  - Other specific cause of stroke identified

NOT Lacunar

- Lacunar is defined as a subcortical (this includes pons and midbrain) infarct in the distribution of the small, penetrating cerebral arteries whose largest dimension is **≤1.5 cm on CT**, **≤2.0 cm on MRI diffusion**, or **≤1.5 cm on MRI T2-weighted images**.
- The following are not considered lacunes
  - multiple simultaneous small deep infarcts
  - lateral medullary infarcts
  - cerebellar infarcts
- Patients with a clinical lacunar stroke syndrome and no infarct on imaging are excluded.

NOT Large vessel atherosclerotic

- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis of the artery supplying the area of ischemia.
- Patients must undergo vascular imaging of the extracranial and intracranial vessels using either catheter angiography, CT angiogram (CTA), MR angiogram (MRA), or ultrasound
- We encourage the use of CTA and MRA over ultrasound for the evaluation of patients to minimize operator-dependent variation.

NOT Cardioembolic, 1

- No major-risk cardioembolic source
  - Atrial Fibrillation
  - intracardiac thrombus
  - mechanical valve
  - atrial myxoma or other cardiac tumors
  - mitral stenosis
  - MI within the last 4 weeks
  - left ventricular ejection fraction <30%
  - valvular vegetations or infective endocarditis.
- Patent foramen ovale is NOT an exclusion.

NOT Cardioembolic, 2

- All patients must undergo electrocardiogram, transthoracic or transesophageal echocardiography (TTE or TEE)
- All patients must undergo at least 24 hours of cardiac rhythm monitoring (Holter monitor or telemetry or equivalent).
- Additional cardiac rhythm monitoring, at the discretion of the treating physician and local principal investigator.
  - And can be ongoing during enrollment/randomization

NOT Other Specific Cause of Stroke

- No other specific cause of stroke identified, such as arteritis, dissection, migraine, vasospasm, drug abuse, or hypercoagulability.
- Special testing, such as toxicological screens, serological testing for syphilis, and tests for hypercoagulability, at the discretion of the treating physician and local principal investigator.
- Consider obtaining hypercoagulability tests among appropriate patients with patent foramen ovale.

Exclusion Criteria, 1

- Any atrial fibrillation
- Any non-stroke indication for anticoagulation or antiplatelet therapy (including aspirin)
- History of spontaneous intracranial hemorrhage
  - *Includes non-traumatic SAH/ICH/SDH/EDH*
  - *Traumatic intracranial hemorrhages of any variety are NOT exclusionary*
- Chronic kidney disease with serum creatinine ≥2.5 mg/dL

Exclusion Criteria, 2

- Clinically significant bleeding diathesis.
  - *any recent bleeding leading to transfusion or hospitalization where the cause remains unclear or untreated (leaving the patient at continued risk) or any laboratory value that the investigator feels may place the patient at higher risk of a bleeding complication; clinical judgement applies*
- Anemia (hemoglobin <9 g/dL) or thrombocytopenia (<100 x 109/L) that is chronic in the judgment of the investigator.
- GI bleeding within the past year considered clinically significant by the investigator.

Exclusion Criteria, 3

Pregnancy risk:

- Female patient who is known to be pregnant.
- Female patient who is sexually active and premenopausal without a negative pregnancy test performed after stroke onset.
- Female patient who is sexually active and premenopausal, and who does not commit to adequate birth control.
- Male patient who is sexually active with a premenopausal female partner, and who does not commit to adequate birth control.

Exclusion Criteria, 4

- Active hepatitis or hepatic insufficiency with Child-Pugh score B or C.

Hepatic Encephalopathy Grades

- Grade 1: Changes in behavior, mild confusion, slurred speech, disordered sleep
- Grade 2: Lethargy, moderate confusion
- Grade 3: Marked confusion (stupor), incoherent speech, sleeping but arousable
- Grade 4: Coma, unresponsive to pain

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Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time			
Seconds over control	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease); 7 to 9 is class B (significant functional compromise); and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85 percent; class B: 80 and 60 percent; and class C: 45 and 35 percent.

INR: international normalized ratio.

Graphic 78401 Version 11.0

Exclusion Criteria, 5

- Known allergy or intolerance to aspirin or apixaban.
- Concomitant participation in another clinical trial involving a drug or acute stroke intervention.
- Considered by the investigator to have a condition that precludes follow-up or safe participation in the trial.
- Inability to obtain written, informed consent from patient or surrogate for trial participation.

Introducing study, consent

Once it is determined that a patient is eligible by above criteria:

- The site team, with appropriate permissions, will approach the patient to introduce the study and that they may be eligible to participate.
- During the initial conversation, ask the patient if it is OK to contact their primary care physician and other providers to make sure they approve of the patient enrolling in ARCADIA
  - Regardless, patient will retain the independent right to participate in ARCADIA
- If the PCP agrees enrollment is reasonable, and the patient is interested, an **Informed Consent Process** is the next step

Consent highlights

- A CIRB-approved informed consent is required from all patients prior to participating in this study
  - the trial will allow inclusion of subjects via the use of surrogate consent
- Capacity to consent will be determined by local investigator
  - If lacking, LAR/proxy – if not then : (a) the spouse (if not legally separated from the subject) or the domestic partner; (b) a son or daughter eighteen (18) years of age or older; (c) a parent; (d) a brother or sister eighteen (18) years of age or older; (e) a close friend (meaning a person eighteen [18] years of age or older who has maintained such regular contact with the subject as to be familiar with the subject's activities, health and beliefs)

Consent, continued

- Study personnel will provide the patient and/or surrogate with consent forms describing in detail the study agent, study procedures, and risks.
- Informed consent will be performed in a language in which the patient or surrogate is fluent.
  - Translation of foreign-language ICF documents (i.e, short-form and full-version translations) is managed by the NCC Policy for Translations. The NCC will cover the costs of all consent translations.
  - language ≥10% of the patient population, full-version provided.
  - language <10%, initially only a short-form, once a short-form use , NCC will send a full-version, need to re-consent the subject/LAR in their native language within 30 days.

Consent, continued

- At that same visit with the patient and/or surrogate, or at a future scheduled "Baseline visit", the investigative team will
  - provide a comprehensive explanation of the purpose, procedures, possible risks/benefits of the study in language that is understandable to a non-medically trained person;
  - describe participant responsibilities and the fact that his/her participation is voluntary, that he or she may withdraw from the study at any time, and that the decision not to participate or to withdraw will not affect the patient's care in any way.
  - give ample opportunity to ask questions and to consider their decision.
  - Ask for explanation back of the study to confirm understanding.
- If sustained interest, a signed and dated written informed consent will be obtained.
- A copy of the consent form will be given to the patient and/or surrogate, and another copy placed in his or her medical record, if allowable per institutional policy.

Consent, continued

Each subject should have documentation of the informed consent process in the subject's permanent medical record/study file which addresses:

- Verification that the ICF is the most recently approved version.
- Process that was followed prior to signing the ICF.
- That consent was obtained PRIOR to any study assessments or procedures being performed.

- Patients who provide consent at this stage will be considered consented but not randomized.
- Patients will be randomized only if they meet ≥1 of the atrial cardiopathy criteria below.

  - PTFV1 >5,000 µV*ms on 12-lead ECG (ECG criterion).
  - Serum NT-proBNP >250 pg/mL (NT-proBNP criterion).
  - Left atrial diameter index ≥3 cm/m^2 on echocardiogram (i.e., severe left atrial enlargement) (ECHO criterion)

Baseline visit, additional items

- Performance of a physical exam (vitals, NIHSS, mRS)
- Collection of blood samples for NT-proBNP assay and potential future use and shipment to the Laboratory Core
- Uploading of copy of 12-lead ECG to WebDCU™
- Determination of left atrial diameter index from the local echocardiogram report
- Sending a copy of echocardiogram images to the Echocardiography Core
- Scheduling a Randomization Visit. This visit can occur later during the index hospitalization or at a subsequent clinic visit (randomization can occur as early as day 3 and before Day 120 after index stroke).
  - Could be next minutes if also meets ECHO criteria for atrial cardiopathy…

To determine whether a patient meets the ECHO criterion

- the site investigator will determine from the report of the clinically performed echocardiogram whether the patient has severe left atrial enlargement, defined as left atrial size index ≥3 cm/m^2
- This ECHO criterion is the only atrial cardiopathy marker determined at the site, and if present, may allow the patient to be randomized in ARCADIA on the same day as their baseline visit.
- ECHO results will be entered in the WebDCU CRF #xx

To determine whether a patient meets the ECG criterion

- the first ECG done as part of the standard stroke evaluation will be used
- A copy of this ECG will be sent via procedures outlined in the MOP to the ECG Core at Wake Forest for standardized measurement of $PTFV_1$.
- The ECG Core will enter the $PTFV_1$ measurement into WebDCU™ within 2 business days of receipt of the ECG so that the Eligibility Core can determine eligibility.

To determine whether a patient meets the BNP criterion

- A blood sample will be sent, via procedures outlined in the MOP, to the study Laboratory Core at Columbia for NT-proBNP measurement.
- The Laboratory Core will enter the NT-proBNP measurement into WebDCU™ within 2 business days of receipt of the blood sample so that the Eligibility and Recruitment Core can determine eligibility.

WebDCU™ will tabulate the results of the Echo, ECG, and BNP criteria. An automated email will be triggered to the enrolling site notifying them of the patient's eligibility for randomization.

Randomization visit

- Timing - as early as post-stroke day 3 (but no later than day 120)
  - Must be delayed until at least post-stroke **day 14** for patients with
    - severe strokes (NIHSS ≥11)
    - hemorrhagic transformation of index stroke
    - uncontrolled hypertension
- Rescreen participants immediately prior to randomization
  - Review medical hx, medications, QVSFS, and physical examination including vital signs
  - Must continue to meet all inclusion and exclusion criteria
  - None of the other tests need to be repeated; but also screen for interval events that would make the patient ineligible (e.g., development of spontaneous intracranial hemorrhage, AF, recurrent stroke). If any tests have been repeated as part of standard clinical care, those results should be reviewed to ensure continued eligibility

Hotline 1-833-427-2234 = 1-833-4ARCADI(a)

- Available 24/7/365
- Will sequentially forward and ring to cell phones of the 4 PIs
  - Order to vary, first is “who is on call”
  - So let it ring!
- PLEASE DO NOT CALL YOUR FAVORITE PI DIRECTLY, USE THE HOTLINE.
- Appropriate for any emergent/urgent question about study procedures. Such urgent topics might include, but not be limited to…
  - eligibility criteria
  - study procedures
  - Safety concerns
  - emergency medical issues

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But PLEASE also remember…

Non-urgent questions can be addressed to other ARCADIA team members as follows:

- WebDCU issues: Cassidy Conner, connerc@musc.edu, 843-876-1105
- Study drug issues: Elizabeth Costea, MS, PharmD, strokenetcpharmacy@ucmail.uc.edu
- Monitoring issues: Erin Klintworth, klintwor@musc.edu, 843-876-2616
- Site personnel issues: Irene Ewing, RN, ewingi@ucmail.uc.edu
- Other: Irene Ewing, RN, ewingi@ucmail.uc.edu

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Recruitment Challenges and Strategies

Scott Kasner, MD

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Frequency of cryptogenic stroke in recent studies

Study	Population	N / mean age	% cryptogenic
ASTRAL (2010)	Registry	1633 / 73 yrs	16%
WARSS (2001)	RCT	2206 / 63 yrs	26%
PRoFESS (2008)	RCT	20,332 / 66 yrs	16%
South Korea (2003)	Registry	204 / 67 yrs	18%
PERFORM (2011)	RCT	19,100 / 67 yrs	22%
German Stroke Databank (2001)	Registry	5017 / 66 yrs	23%
Bern Registry (2008)	Registry	1288 / NR	39%
Buenos Aires (2010)	Retro case series	155 / 67 yrs	27%
Besancon (2000)	Registry	1776 / 71 yrs	18%
Athens Registry (2000)	Registry	885 / 70 yrs	21%
Mannheim Registry (2012)	Registry	103 / 69 yrs	30%

Wide variation mainly due to nonstandard criteria.

Embolic Stroke of Uncertain Source Key Elements

- Stroke detected by CT or MRI that is not lacunar
  - Subcortical infarct ≤1.5 cm (≤2.0 cm on DWI) in largest dimension, and in the distribution of the small, penetrating cerebral arteries.
- Absence of extracranial or intracranial atherosclerosis
  - Causing a ≥50% luminal stenosis in arteries supplying the area of ischemia
- No major-risk cardioembolic source of embolism
  - AF, intracardiac thrombus, prosthetic valve, myxoma/tumors, mitral stenosis, recent MI, EF<30%, vegetations
- No other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, drug misuse)

ESUS Global Registry

City, Country	Ischemic strokes		ESUS* n (%)
	N	Mean age (years)	
Buenos Aires, Argentina	73	68	26 (36%)
Perth, Australia	114	67	25 (22%)
Brussels, Belgium	119	74	23 (19%)
Sao Paulo, Brazil	86	60	22 (26%)
Hamilton, Canada	172	73	46 (27%)
Beijing, China	69	59	11 (16%)
Paris, France	69	69	25 (36%)
Heidelberg, Germany	91	73	18 (20%)
Galway, Ireland	140	71	30 (21%)
Rome, Italy	91	67	19 (21%)
Tokyo, Japan	75	68	18 (24%)
Mexico City, Mexico	225	56	25 (11%)
Amsterdam, Netherlands	99	68	2 (2%)
Manila, Philippines	175	62	24 (14%)
Coimbra, Portugal	123	74	24 (20%)
Moscow, Russia	106	66	24 (23%)
Seoul, South Korea	124	69	26 (21%)
Glasgow, United Kingdom	73	67	5 (7%)
Philadelphia, United States	120	67	19 (16%)
Total	2144	67	412 (19%)

ESUS and ARCADIA

- 15-20% of all ischemic strokes are ESUS
- Enrollment in industry ESUS trials
  - Goal = 1 subject / site / month (12/year)
  - Actual = 0.7 / site / month (9/year)
  - U.S. = 0.35 /site / month (4/year)
- ARCADIA-eligible ~25% of ESUS population

- If the typical U.S. site sees 600 strokes per year, and 100 are ESUS, why are only 4 enrolled???

ARCADIA

Challenges

- Gotta have rhythm
- Size matters

- Plavixism
- Cardiologists

- As seen on TV
- What I don’t see can’t hurt me

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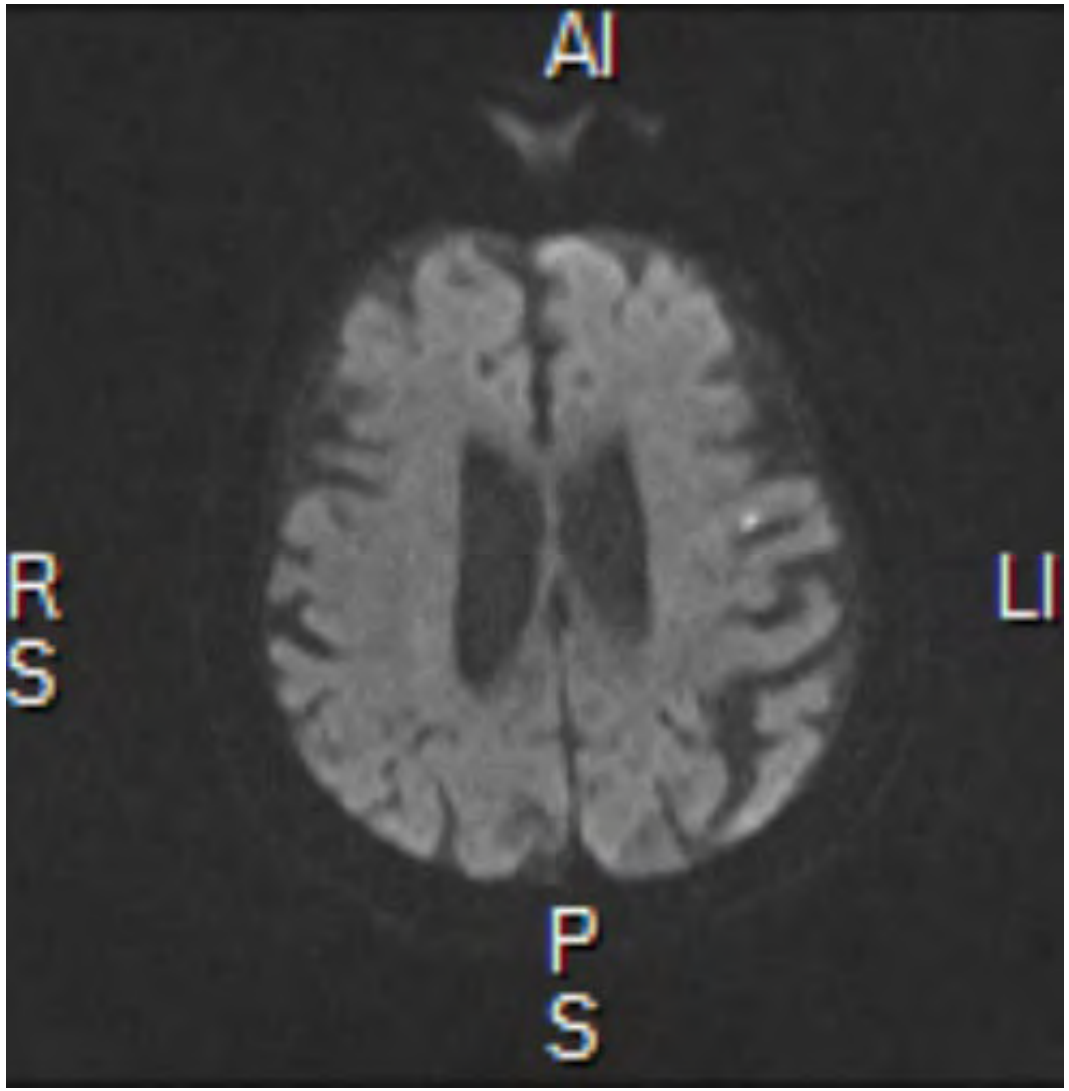
Gotta Have Rhythm

- Required: ≥ 24 hours heart rhythm monitoring
- Common:
  - Mobile cardiac outpatient telemetry, 28 days
  - Insertable loop recorder, up to 3 years
  - Major challenge for industry ESUS trials
  - Both are OK in ARCADIA
- Do not wait for longer term monitor results

Size Matters

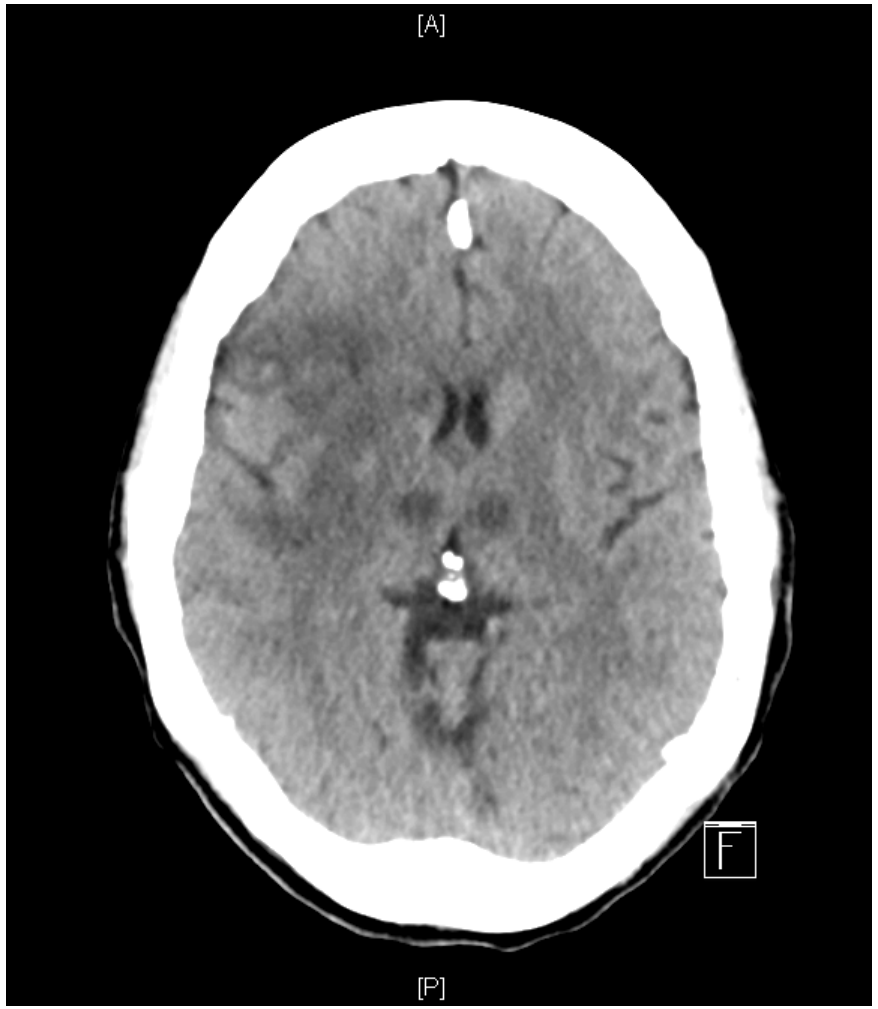
- Stroke detected by CT or MRI that is not lacunar.
- Lacunar is defined as a subcortical (this includes pons and midbrain) infarct in the distribution of the small, penetrating cerebral arteries whose largest dimension:
  - ≤1.5 cm on CT or T2
  - ≤2.0 cm on MRI diffusion images
- Not lacunes: multiple simultaneous small deep infarcts, lateral medullary infarcts, and cerebellar infarcts

Clinical event: Aphasia for a few hours



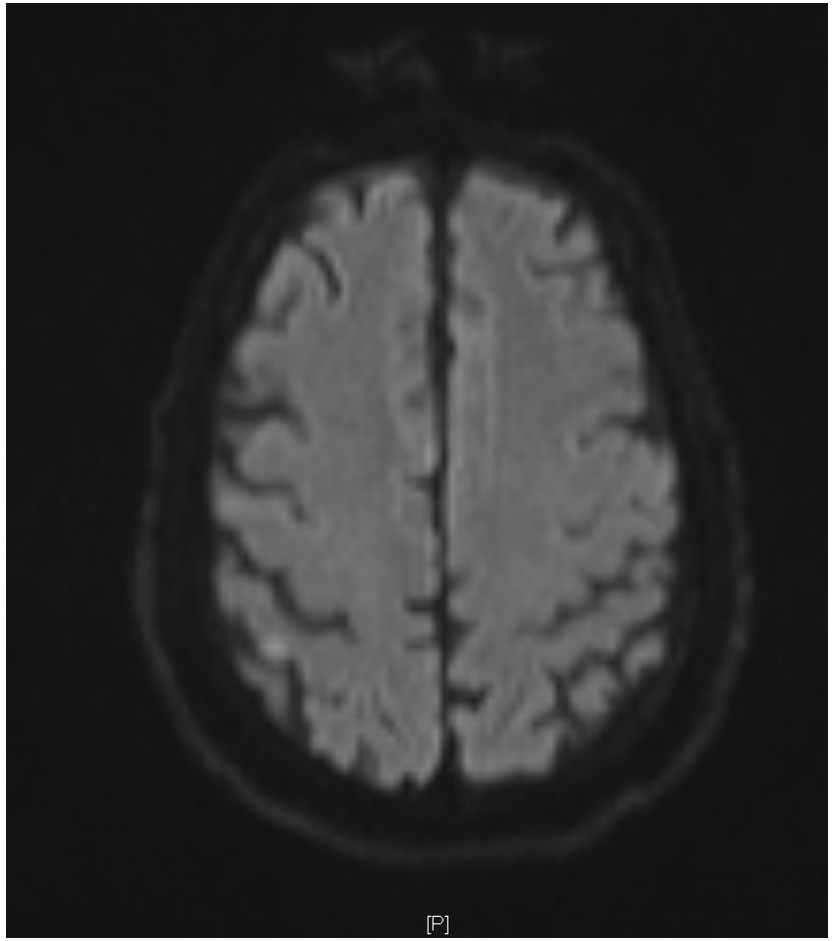
Radiologist Impression: Tiny acute lacunar infarct along the left frontoparietal cortex

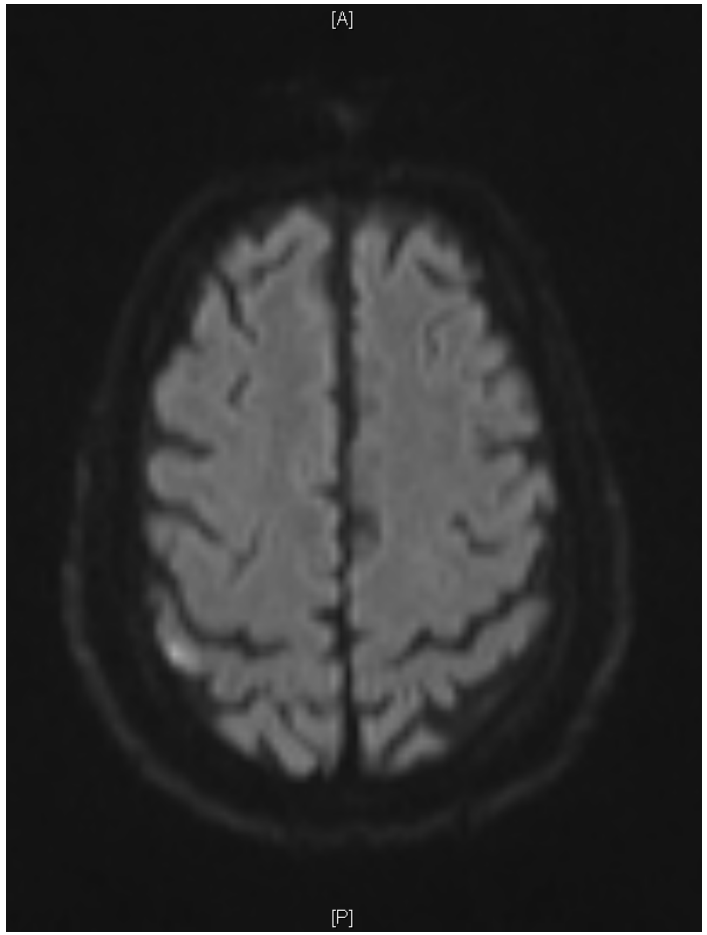
Clinical event: Nearly recovered from recent R MCA infarct. Sudden confusion.



Radiologist Impression: Recent R MCA infarction with typical evolution over 1 month. New acute lacunar infarcts in the thalami bilaterally.

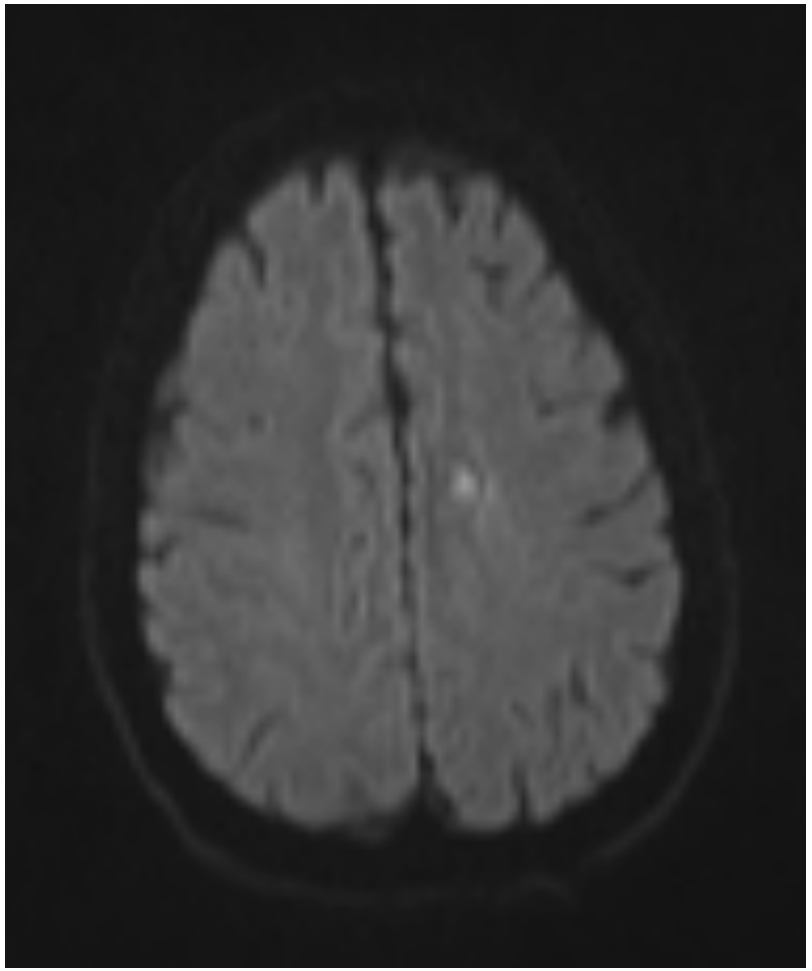
Clinical event: Left sided visual distortions, vague difficulty identifying and manipulating objects in left hand.





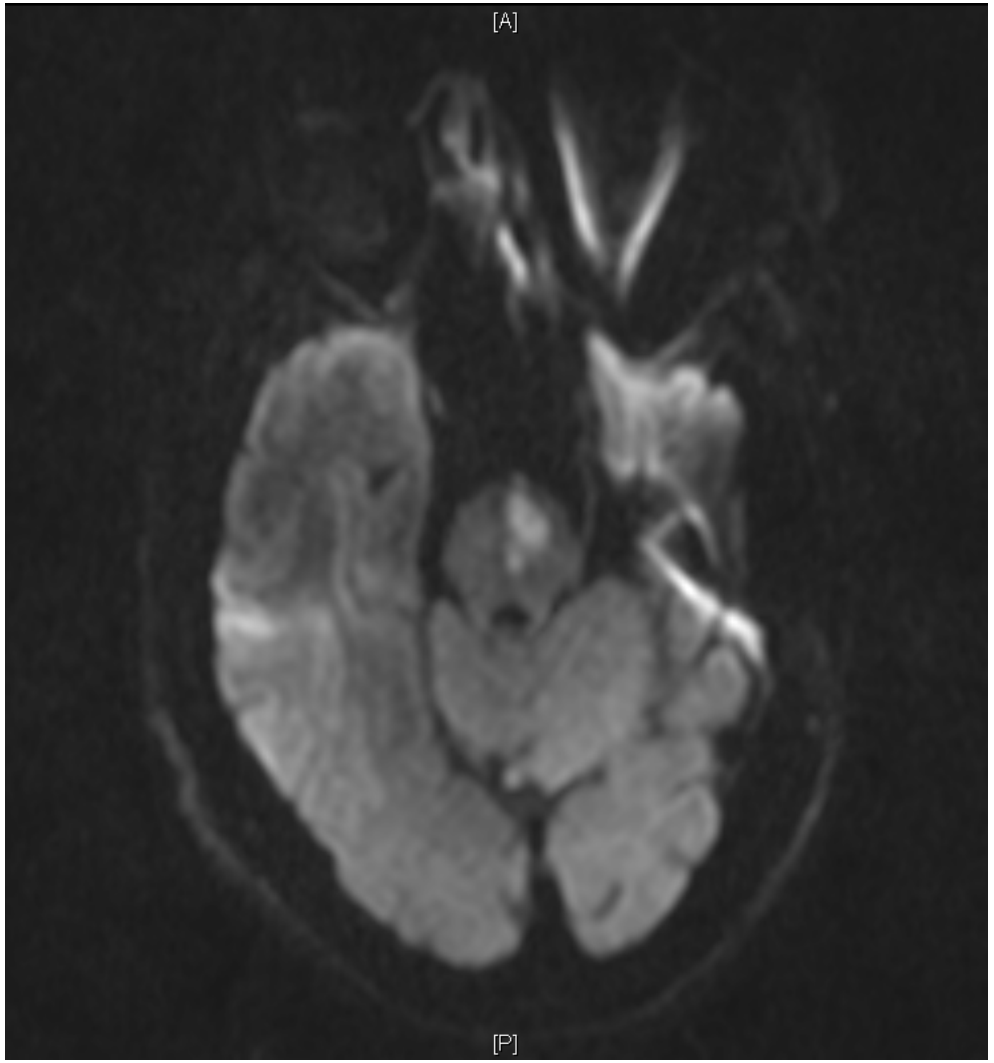
Radiologist impression: Subcentimeter focus of diffusion/signal abnormality in the right parietal lobe including post central gyrus, possible infarct vs. artifact.

Clinical event: Acute right leg weakness



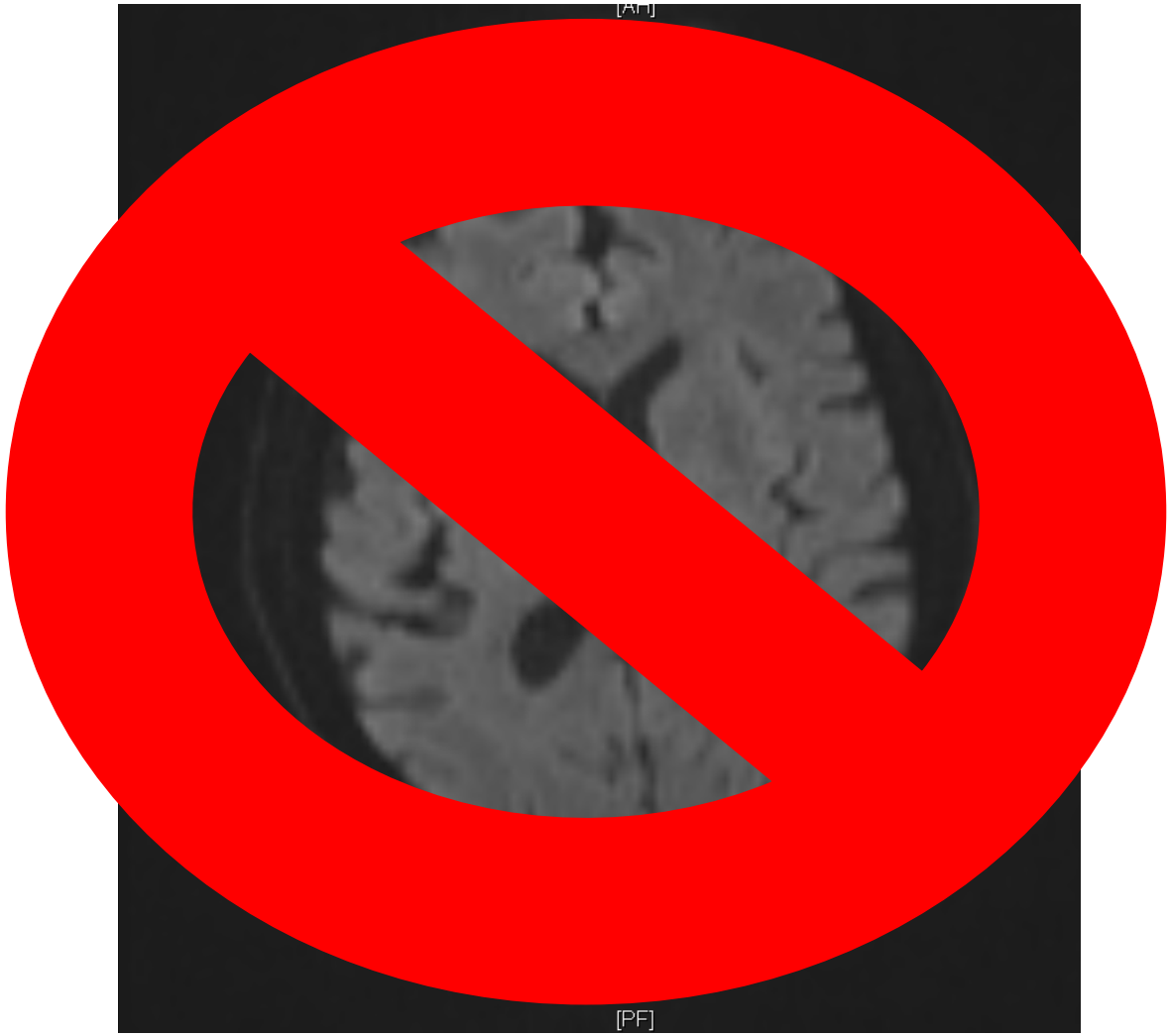
Radiologist impression: Acute tiny (4 mm) infarction in the left corona radiata.

Clinical event: acute right weakness and abnormal speech



Radiologist interpretation: Acute pontine infarct in territory of basilar artery perforator. (No measurement provided.)

Clinical event: R weakness and speech disturbance for a few hours



Radiologist impression: subcentimeter focus of increased diffusion signal in the left lateral thalamus , likely embolic in this patient with known cardiopathy

Plavixism

- "How can I randomize this patient in a trial where one of the treatments is just aspirin, when he/she was already on aspirin when this stroke occurred? I need to prescribe Plavix!"
  - Corollary: Platelet function testing…
- Possible responses:
  - No compelling evidence that clopidogrel>aspirin for stroke in general or after event on aspirin
  - No data for ESUS or atrial cardiopathy

Stroke									
Clopidogrel (nyrs=6054*)	298	17	33	11	74	433	7·15%	7·3% (−5·7 to 18·7)	0·26
Aspirin (nyrs=5979)	322	16	37	14	72	461	7·71%		

Cardiologists

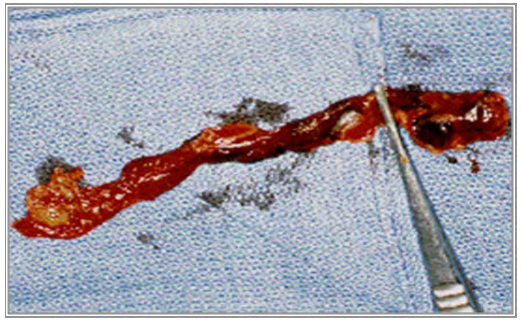
- “I don’t see why you need it, you don’t have AF”
- “Let’s put in an insertable loop recorder and see what happens”
- “I like (other anticoagulant) better”
- “Maybe you should carry the pills in your pocket and just take one if you feel palpitations”

- Possible responses:
  - If your cardiologist knew how to prevent strokes, you wouldn’t need me
  - Unfortunately many cardiologists are not sufficiently aware of the advances in stroke diagnosis and treatment
  - I would be happy to talk to your cardiologist

As Seen on TV (and the Web)

- Possible responses:
  - Many thousands of patients in trials, millions in practice
  - Major bleeding risks similar to aspirin in AVERROES
    - 1.4 vs. 1.2%
  - Your own comfort in using apixaban for AF and VTE

What I Don't See Can't Hurt Me



- "If all my tests are normal, why can't I just take aspirin?"
- Possible responses:
  - The role of aspirin for ESUS is not clear.
  - We need to do better than aspirin, as people do have recurrent strokes.
  - In recent years as we have started to actually pull clots out and look at them under the microscope, we see that ESUS is a lot like AF, which benefits from anticoagulation.
- "I've been fine for 3 months, why should I change treatment now?"

Enroll Early (and Often)!

- You have everything you need prior to discharge
- Patient has greatest sense of urgency and uncertainty (and so do you)
- Fewer outsiders to offer opinions
- This is your best opportunity to enroll
  - Approach used in top enrolling countries in ESUS trials
- Make sure you address these issues proactively or it could interfere with compliance and retention.

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Study Medications

Mitch Elkind

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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."

Kernan WN et al. AHA/ASA Secondary Stroke Prevention Guidelines.

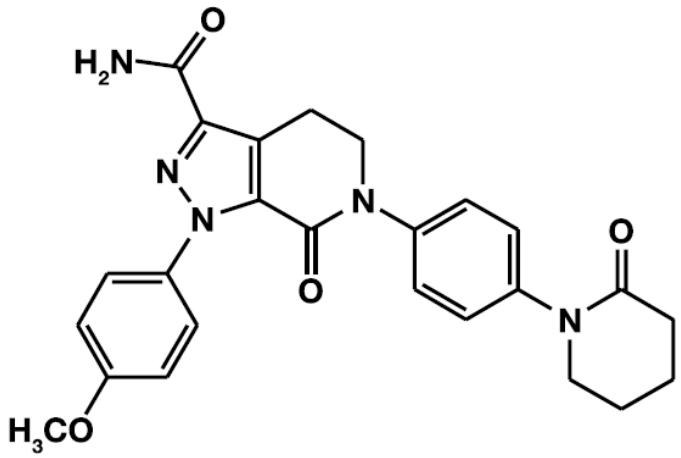
Stroke 2014;45(7):2160-236.

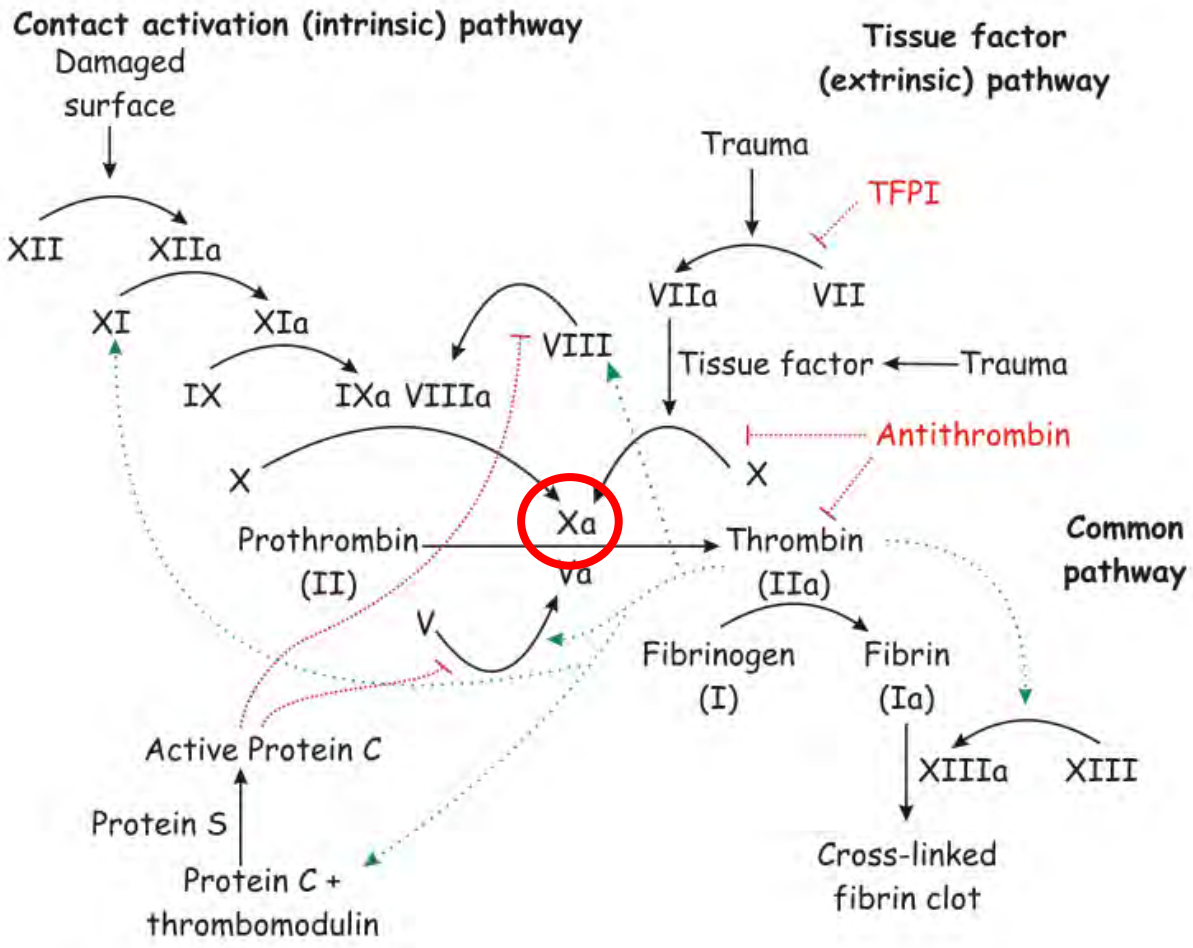
Study Medications

- Apixaban, aspirin and matching placebo for each is being provided by Bristol Meyers Squibb
- The Central Pharmacy at the University of Cincinnati (NCC) will be repackaging and shipping study drug to all sites.

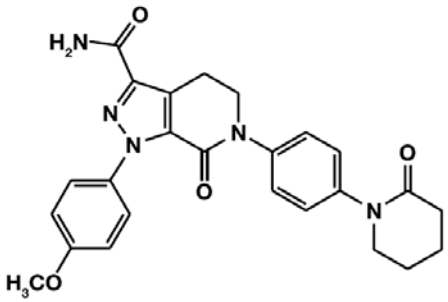
What is apixaban?

- Selective Factor Xa inhibitor
  - Decreases thrombin generation
  - No direct antiplatelet effects





What is apixaban?



- T ½ = 12 hours (twice daily dosing)
- Excretion: primarily metabolized by CYP3A4; no active metabolites; ~ 25% renal
- Doses available 2.5 mg, 5 mg
- Not affected by food
- Prolongs clotting tests such as PT, INR, and aPTT, though changes observed in these clotting tests at the expected therapeutic dose are small, variable, and not useful in monitoring anticoagulation effect of apixaban.
- Indications:
  - reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
  - prophylaxis of DVT/PE in patients who undergo hip or knee replacement
  - treatment of DVT/PE, and to reduce risk of recurrent DVT/PE

Why apixaban?

ARISTOTLE

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

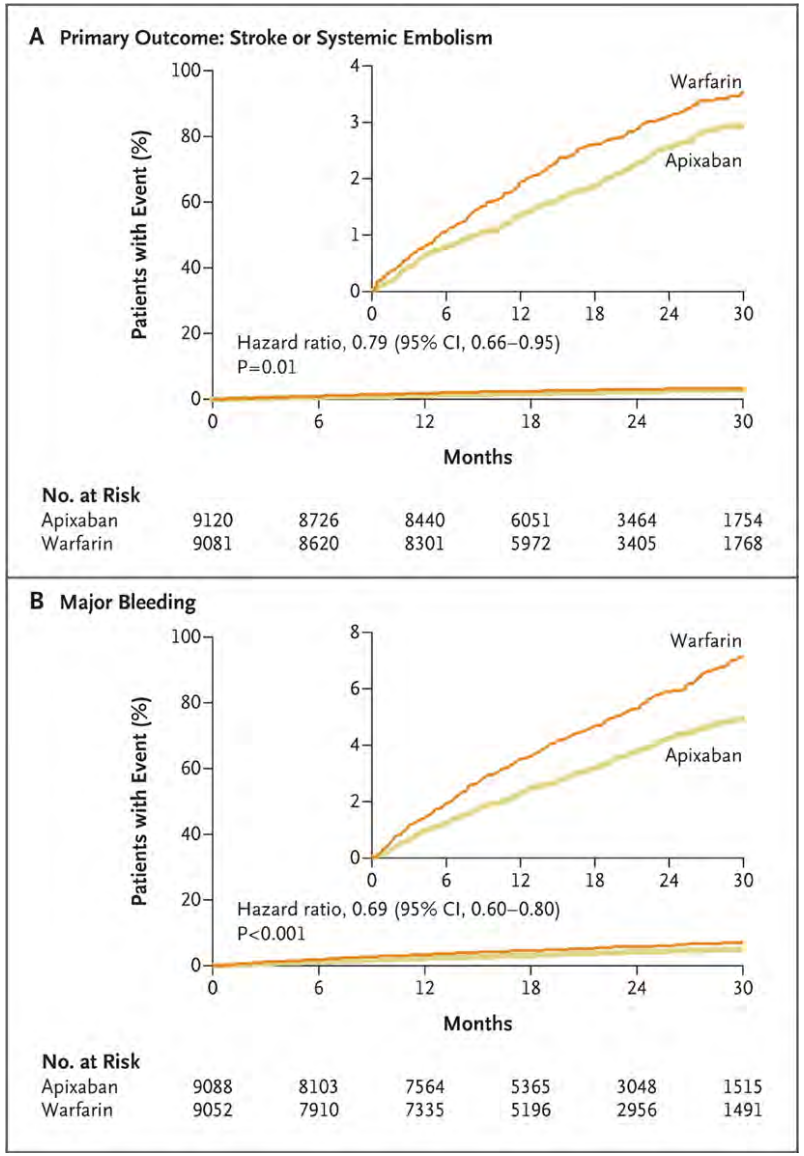
Apixaban 5 mg twice daily vs warfarin (target INR 2.0 to 3.0)

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.

Granger CB et al. N Engl J Med 2011;365:981-992.



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Why apixaban?

ARISTOTLE

Granger CB et al. N Engl J Med 2011;365:981-992.

Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

* 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.

Why apixaban?

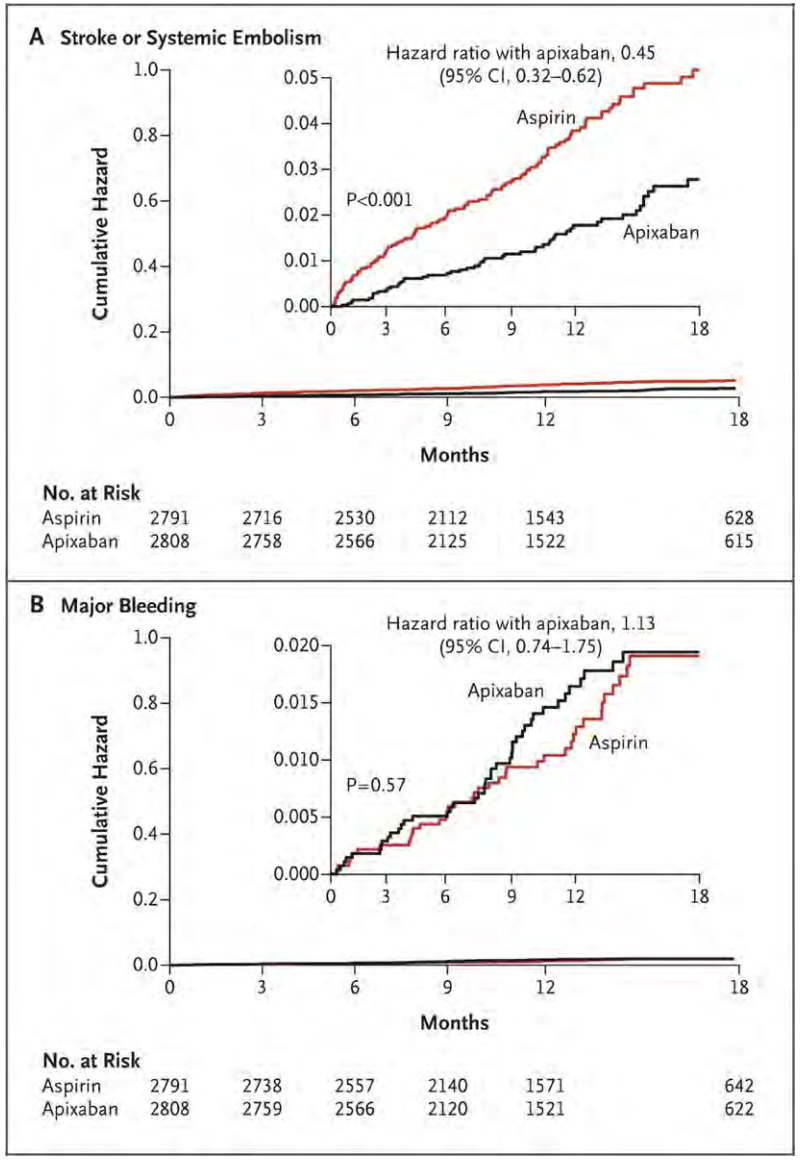
AVERROES TRIAL
Connolly SJ et al. N Engl J Med 2011;364:806-817

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.

Kernan WN et al. AHA/ASA Secondary Stroke Prevention Guidelines.

Stroke 2014;45(7):2160-236.

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."

Kernan WN et al. AHA/ASA Secondary Stroke Prevention Guidelines.

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

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

Experimental

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

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 24 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.

Study drug interactions

- **Pharmacodynamic Interactions**
- The concurrent use of apixaban with **other anticoagulants**, **antiplatelet agents**, and **nonsteroidal anti-inflammatory** agents is expected to increase the risk of bleeding in comparison to use of apixaban alone.

Prohibited Medications: Other anticoagulants

Generic Name	Brand Name
Oral anticoagulants Dabigatran	Pradaxa
Edoxaban	Savaysa, Lixiana
Rivaroxaban	Xarelto
Warfarin	Coumadin
Parenteral antithrombotics Dalteparin Enoxaparin Fondaparinux	Fragmin Lovenox Arixtra
Heparin	multiple

Prohibited Medications: Other antiplatelet agents

Generic Name	Brand Name
Antiplatelets	
aspirin (ASA)	Ecotrin, others
clopidogrel	Plavix
ticlopidine	Ticlid
ticagrelor	Brilinta
prasugrel	Effient

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, SSRIs

Generic Name	Brand Name
NSAIDs	
celecoxib	Celebrex
ibuprofen	Advil, Motrin, Nuprin
indomethacin	Indocin
ketorolac	Toradol
naproxen	Naprosyn
salsalate	Anaflex, Disalcid
others	

Discouraged Medications: NSAIDs, SSRIs

Generic Name	Brand Name
SSRIs	
citalopram	Celexa
escitalopram	Lexapro
paroxetine	Paxil
paroxetine	Paxil
fluoxetine	Prozac
sertraline	Zoloft
others	

Study drug interactions

- *Pharmacokinetic Interactions*
- 1. The absorption of apixaban is mediated by P-glycoprotein (P-gp).
  - P-gp inhibitors can increase the absorption of apixaban, increasing both AUC and Cmax.
  - P-gp inducers can reduce the absorption of apixaban, decreasing AUC and Cmax.
- 2. The metabolism of apixaban is mediated by CYP3A4.
  - CYP3A4 inhibitors can decrease the metabolism of apixaban, increasing both AUC and Cmax.
  - CYP3A4 inducers can increase the metablism of apixaban, decreasing AUC and Cmax
- 3. Agents that interfere with both P-gp and CYP3A4 are likely to cause more significant interactions with apixaban than agents that interfere with P-gp or CYP3A4 alone.

Study drug interactions

Drug Class	Examples	Known or Probable Effect	US PI Recommendations	Suggested Management Guidelines
Combined P-gp inhibitor and *strong* inhibitor of CYP3A4 (increase uptake and decrease metabolism)	cobicistat, conivaptan, indinavir, itraconazole, ketoconazole, nefazadone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	***Significant increase*** in apixaban concentration	Avoid use or reduce apixaban dose to 2.5mg twice daily. In patients already taking 2.5mg twice daily, avoid coadministration	AVOID USE

https://depts.washington.edu/anticoag/home/content/apixaban-drug-interaction-potential

Study drug interactions

Drug Class	Examples	Known or Probable Effect	US PI Recommendations	Suggested Management Guidelines
Combined P-gp inhibitor and/or *moderate* CYP3A4 inhibitor (increase uptake and decrease metabolism)	amiodarone, azithromycin, cimetidine, clarithromycin, diltiazem, dronedarone, erythromycin, felodipine, nicardipine, verapamil chloramphenicol, cyclosporine, fluconazole, grapefruit, lapatinib, mifepristone, quinidine, ranolazine, tamoxifen, ticagrelor	***Moderate increase*** in apixaban concentrations in patients with normal renal function. Potentially significant increase in apixaban concentrations in patients with severe renal insufficiency	No dose adjustment recommended	USE WITH CAUTION in patients with normal renal function. AVOID USE in patients with severe renal insufficiency (CrCl < 30ml/min), age > 80 yrs, or low body weight (< 60 kg)

https://depts.washington.edu/anticoag/home/content/apixaban-drug-interaction-potential

Study drug interactions

Drug Class	Examples	Known or Probable Effect	US PI Recommendations	Suggested Management Guidelines
Combined P-gp inducer and strong CYP3A4 inducer	carbamazepine, dexamethasone, St Johns wort rifampin	***Significant reduction*** in apixaban concentration	Avoid use	AVOID USE
Strong inducers of CYP3A4	Fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone bosentan, efavirenz, etravirine, nafcillin, nevirapine, rifabutin, rifapentine		Not specifically addressed	AVOID USE

https://depts.washington.edu/anticoag/home/content/apixaban-drug-interaction-potential

Real world risks of major bleeding

- Retrospective cohort study using data from the Taiwan National Health Insurance database
- n=91,330 patients with AF who received at least 1 DOAC prescription 2012-2016
- Increased risk of bleeding (adjusted incidence rate per 1000 person years)
  - Amiodarone
  - Fluconazole
  - Rifampin
  - Phenytoin
- Decreased risk of bleeding
  - atorvastatin, digoxin, erythromycin, clarithromycin
- No difference in risk of bleeding
  - verapamil; diltiazem; cyclosporine; ketoconazole, itraconazole, voriconazole, or posaconazole; and dronedarone.

Chang SH et al. JAMA 2017 Oct 3;318(13):1250-1259

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Discouraged medications/Interactions

- Use judgment/experience as clinician
- Not under IND
- The information on prohibited and discouraged medications will be available in the Manual of Procedures (MOP)
- Call/email with questions

Adherence

"Drugs don't work in patients who don't take them."

C. Everett Koop, MD

Surgeon General

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Adherence

- The study site clinical coordinator should discuss in detail with the **patient** instructions for taking the study medications, including:
  - Reinforce the importance of taking all pills, including study pills, regularly;
  - Demonstrate using a pill box or other reminders to remind the patient to take pills;
  - Reinforce taking the pills at the same time each day;
  - Assist subject with setting up a time that is most convenient for the patient: for example, 8 AM (one from Bottle A and one from Bottle B) and 8 PM (one from Bottle A);
  - Reinforce there are NO specific dietary instructions.
  - Reinforce the importance of calling with questions if problems arise.

Adherence: Primary care provider/other providers

- Speak directly with primary care MD and/or cardiologist, neurologist to ensure willingness to have patient's antithrombotic therapy managed by trial
- Emphasize that they are not to give patient any anticoagulant or antiplatelet therapy
- Provide letter to primary MD
- Provide letter to patient to give to primary care MD/other physicians
- Medication alert card for wallet

Enrollment, Follow-up, Retention, and Payments

Hooman Kamel

Irene Ewing

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Enrollment: Process

1. Identify patients with ESUS
2. Check for inclusion/exclusion criteria
3. Approach for consent if all inclusion/exclusion criteria satisfied
4. Assess atrial cardiopathy markers
5. Randomize those who meet at least one atrial cardiopathy criterion

Procedure	B	R	30 ±7 days*	90 ±14 days	180 ±14 days	270 ±14 days	360 ±14 days	q180 ±14 days# afterward	Close out$
Eligibility check^	x	x	x	x	x	x	x	x	
Consent	x								
Randomization form		x							
Medical history[11]	x	x							
QVSFS		x	x	x	x	x	x	x	
Modified Rankin Scale	x				x		x	x	
Vital signs	x	x							
Physical examination	x	x							
NIHSS	x								
Brain imaging	o								
Vascular imaging	o								
12-lead ECG	o								
≥24 hrs cardiac monitoring	o								
Echocardiogram	o								
Serum chemistry	o								
Complete blood count	o								
Coagulation studies	o								
Serum liver function tests	o								
Pregnancy test, if applicable	o								
Blood sample to core lab	x								
ECG to core lab	x								
Echo to core lab	x								
PROMIS Global Health							x		
PROMIS Phys. Func. Short							x		
SAE assessment			x	x	x	x	x	x	x
Study drug safety			x	x	x	x	x	x	
Medication adherence			x	x	x	x	x	x	
Medication resupply				x	x	x	x	x	
Concomitant med.	x	x	x	x	x	x	x	x	

Enrollment: Key Points

- Must complete all SOC tests before consenting
- Consenting/randomization can be at same visit or different visits
- Consenting time window: Post-stroke days 1-120
- Randomization time window:
  - Post-stroke days 14-120 if NIHSS ≥11, hemorrhagic conversion on initial imaging, or uncontrolled hypertension
  - Otherwise, post-stroke days 3-120
- 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)

Follow-up: Process

- Key aims of follow-up:
  - Assess SAEs, including study endpoints
  - Resupply study drug
  - Encourage continued participation and adherence
- Subject contact every 3 months throughout trial
  - Year 1: In-person visits every 3 months
  - Years 2-4: Alternating in-person visits and phone visits

Procedure	B	R	30 ±7 days*	90 ±14 days	180 ±14 days	270 ±14 days	360 ±14 days	q180 ±14 days# afterward	Close out$
Eligibility check^	x	x	x	x	x	x	x	x	
Consent	x								
Randomization form		x							
Medical history[11]	x	x							
QVSFS		x	x	x	x	x	x	x	
Modified Rankin Scale	x				x		x	x	
Vital signs	x	x							
Physical examination	x	x							
NIHSS	x								
Brain imaging	o								
Vascular imaging	o								
12-lead ECG	o								
≥24 hrs cardiac monitoring	o								
Echocardiogram	o								
Serum chemistry	o								
Complete blood count	o								
Coagulation studies	o								
Serum liver function tests	o								
Pregnancy test, if applicable	o								
Blood sample to core lab	x								
ECG to core lab	x								
Echo to core lab	x								
PROMIS Global Health							x		
PROMIS Phys. Func. Short							x		
SAE assessment			x	x	x	x	x	x	x
Study drug safety			x	x	x	x	x	x	
Medication adherence			x	x	x	x	x	x	
Medication resupply				x	x	x	x	x	
Concomitant med.	x	x	x	x	x	x	x	x	

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?
  - New indication/contraindication re: anticoagulation or antiplatelet therapy?
  - New concomitant med that is prohibited?
- How is adherence?
- Subject's functional status?

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TABLE 1. The Questionnaire for Verifying Stroke-Free Status

Item	Question
1	Were you ever told by a physician that you had a stroke?
2	Were you ever told by a physician that you had a TIA, ministroke, or transient ischemic attack?
3	Have you ever had sudden painless weakness on one side of your body?
4	Have you ever had sudden numbness or a dead feeling on one side of your body?
5	Have you ever had sudden painless loss of vision in one or both eyes?
6	Have you ever suddenly lost one half of your vision?
7	Have you ever suddenly lost the ability to understand what people were saying?
8	Have you ever suddenly lost the ability to express yourself verbally or in writing?

Meschia et al, *Stroke*, 2001

Follow-up: Special Assessments

- Special phone visits:
  - 30 days after randomization
  - 30 days after study drug discontinuation at trial end
- PROMIS quality of life assessments at 12-month visit
- Unscheduled visits: If subject experiences SAE or other event which investigator believes requires in-person visit for assessing safety of continued trial participation

Procedure	B	R	30 ±7 days*	90 ±14 days	180 ±14 days	270 ±14 days	360 ±14 days	q180 ±14 days# afterward	Close out$
Eligibility check^	x	x	x	x	x	x	x	x	
Consent	x								
Randomization form		x							
Medical history[11]	x	x							
QVSFS		x	x	x	x	x	x	x	
Modified Rankin Scale	x				x		x	x	
Vital signs	x	x							
Physical examination	x	x							
NIHSS	x								
Brain imaging	o								
Vascular imaging	o								
12-lead ECG	o								
≥24 hrs cardiac monitoring	o								
Echocardiogram	o								
Serum chemistry	o								
Complete blood count	o								
Coagulation studies	o								
Serum liver function tests	o								
Pregnancy test, if applicable	o								
Blood sample to core lab	x								
ECG to core lab	x								
Echo to core lab	x								
PROMIS Global Health							x		
PROMIS Phys. Func. Short							x		
SAE assessment			x	x	x	x	x	x	x
Study drug safety			x	x	x	x	x	x	
Medication adherence			x	x	x	x	x	x	
Medication resupply				x	x	x	x	x	
Concomitant med.	x	x	x	x	x	x	x	x	

Follow-up: Key Points

- Year 1: standard in-person visit every 3 months
- Years 2-4:
  - Standard in-person 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

Follow-up: Key Points

- Subjects who stop study drug must still be followed until end of study
- Stopping study drug is not the same as “withdrawal” from the study
- Withdrawal means only:
  - Subject withdraws consent for further follow-up or investigator withdraws subject from further follow-up due to safety concerns
- Withdrawal should be EXTREMELY RARE and if it occurs the reason should be clearly documented

Retention Is Important

Low rates of subject retention will have a negative impact on a trial

- Low retention reduces statistical power for the study and undermines validity of results
- It can lower staff and participant morale

Retention Starts at the Initial Visit

The key to retention is gathering and sharing information

- Obtain detailed contact information (address, home phone, cell phone, email) for subject and also family and/or close friends
- Ask subjects what is their preferred communication method
- Give reminder 1-2 weeks before a follow-up: phone call, card in mail, email, or text (if permissible)
- Notify subject's PCP of participation and provide information about the study, if given permission by the patient

Good Practices for Subject Retention

- Providing clear written instructions about the study and follow-up requirements to the subject and family
- Give the subject and their family contact information for the study team and instructions on when to call
- Provide calendars to subject for medications and F/U visit reminders
- Provide a prohibited/contraindicated medications list
- Be as flexible as possible when scheduling follow-up visits
- Schedule follow-up visits early in the time window in case they need to be rescheduled.

Additional ideas for Retention

- Home visits are permitted in the trial if allowable at your institution
- If needed, arrange taxi service for patients to get to their follow-up visits
- Reimburse travel expenses for follow-up visits
- Provide meals for subjects while in clinic if permissible at your institution

Any plans for reimbursement to subjects must be detailed in your informed consent and have IRB approval

Lost To Follow-up

- All attempts should be made to avoid any lost to follow-up!
- Before a subject is considered lost to follow-up, the study team should document multiple attempts to reach the subject and his/her contacts
- It may be permissible to reach out to the subject's PCP or other known clinics that the subject visits-dependent on what permissions the subject has previously given.
- If all attempts to contact the subject are unsuccessful, then a certified letter should be sent to the subject's last known residence as a final way of establishing contact and arranging follow-up

Study Payments

- All payments will be made via direct deposit by the NCC to the PTA sub awardee
- Sites must complete the Direct Deposit form and provide Electronic Funds Transfer (EFT) information to the NCC financial team; the request for this information will come with or shortly after your PTA
- Invoices for payment will be generated by the NCC once all CRFs for a visit are complete and verified in WebDCU
- Payment status will be monitored on an ongoing basis and payments made 30-45 days after WebDCU shows that a visit is “Payment ready”
- Sites are able to view payment status in WebDCU

Study Payments

- Start up payments: a one-time non-refundable start-up payment of $2,000 will be made to each StrokeNet Subawardee upon full execution of the FDP Fixed Price Clinical Trial Subaward Agreement (PTA)
- Protocol Trial Agreements are sent out based on your site's cohort

Study Payments

- Minimum subject participation in ARCADIA is 18 months and the maximum is 48 months
- Maximum payment for any single subject would be $7560 plus 42% F&A ($3175.20) = $10,735.20
- Minimum payment for any single subject would be $4260 plus 42% F&A ($1789.20) = $6049.20

The 42% F & A rate is based on the average F & A rate of all StrokeNet sites across the country

Study Payments

- ARCADIA payments will be divided into the following increments
  - Payment 1 will be made after consent, screening, randomization, and 30-day follow-up phone call are complete
  - Payments 2-12 will be made after each follow-up visit is complete
- Payments will only be made after receipt and verification of all required eCRF data and *all* required screening assessments have been received at central core facilities

Payments for Screen Failures

- **CORE LAB ELIGIBILITY SCREEN FAILURE:** A subject who qualifies based on inclusion/exclusion criteria and is consented, but who **fails** to qualify for randomization based on local echo results, central analysis of ECG and BNP
- Payment of **$100.00** will be made for these core lab screen failures: All payments will be made after receipt and verification of the required eCRF data and the screening assessments at central core facilities
- **There will be a limit of 3 screen failures per one randomized subject**; payment for screen failures (up to $300.00) will be made only in tandem with a consented and randomized subject

Screen Failures

- Monthly screen failure logs are to be completed by the 10th of the following month.
- Patients who are identified as having an embolic stroke of unknown source should be included on the screening log.
- If a subject is consented and screening labs obtained, they will be considered enrolled and do not need to be listed on the screen failure log.

➢Screen failures

➢Enrolled, but not randomized

➢Randomized

Enrollment Expectations

- Enrollment is competitive.
- We need to enroll 1100 subjects over 2 ½ years of recruitment.
- If enrollment was spread equally across all 120 sites, each site would randomize approximately 4 subjects/year.
- We anticipate that sites will likely need to **enroll** three patients for every one **randomized** patient.

Enrollment Expectations

- To complete enrollment in the allotted time, we have set enrollment parameters.
- If a site has not randomized a subject within 3 months after going live they will be placed on probation.
- If after 3 additional months that site has not randomized a subject they may be suspended and a new site added in their place.
- Sites may also be put on probation if they have 3 consecutive patients who meet randomization criteria {based on screening biomarkers} but are not randomized.

Management of complications and risk factors: Bleeding, AF, acute stroke, interruptions

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Treatment interruption

- Patients may temporarily interrupt study medication for:
  - Surgical or other procedures that require cessation of study medication
  - Bleeding complications
  - Procedures that require open-label antithrombotic therapies that are not considered compatible with blinded apixaban or aspirin in the context of this study
  - Potential outcome events
- Treatment interruptions will be recorded on a separate CRF.
- Study medication will then be resumed when deemed safe or indicated.

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Elective procedures

- Unblinding will not be performed for elective procedures.
- As a reminder, the FDA label for apixaban states:
  - "ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding.
  - ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled."
- Reminders about these guidelines and updates as needed will be shared with site principal investigators and study coordinators through regular study newsletters.
- Refer to American Academy of Neurology guidelines on periprocedural management of antithrombotic medications in subjects with ischemic cerebrovascular disease. These will be available on WebDCU.

Bleeding

- Minor bleeding:
  - Subjects should be advised to not take further doses of study drugs until the bleeding has stopped and the investigator judges that the potential benefits of resuming study drug outweigh the risk of recurrent bleeding.
- Major bleeding:
  - Further doses of study drug should be held until the bleeding is controlled and the investigator judges that the benefits of resuming study drug outweigh the risk of recurrent bleeding.
  - Standard measures should be taken to control and mitigate the effects of bleeding, such as local control of the bleeding source if possible and administration of intravenous fluids and blood products as necessary.
  - If it is considered likely that bleeding cannot be managed with only the steps above, and that measures specific to reversal of apixaban are required, treating physicians and/or site investigator can perform unblinding by calling the study hotline.

Unblinding in event of acute stroke/?tPA

- If intravenous thrombolysis is being considered for the acute treatment of recurrent ischemic stroke, the treating physicians and/or site investigators can call the study hotline for unblinding.
- Unblinding should only occur for subjects who would be eligible for treatment only if they were on aspirin and not on apixaban.
  - Unblinding is discouraged for subjects who are not eligible regardless of being on aspirin or apixaban, or subjects who meet all of the criteria below and may be able to receive thrombolysis while being on apixaban.
- Subjects assigned to apixaban may be at an increased risk of bleeding if treated with intravenous thrombolysis unless all of the following conditions are met:
  - The subject or surrogate can confirm that no study drug has been taken for the past 48 hours;
  - The subject's renal function is normal (GFR ≥60);
  - The subject's INR and PTT values are normal;
  - Intravenous thrombolysis is otherwise indicated per the site's standard practice.
- After unblinding, subjects assigned to aspirin can be treated with intravenous thrombolysis if indicated per each site's standard practice.

Unblinding

- Once the patient is unblinded, they cannot go back on study medication.
- The site investigator should only request unblinding when it is essential for the subject's safety (e.g.):
  - administration of intravenous thrombolysis for recurrent acute ischemic stroke;
  - managing life-threatening bleeding;
  - undertaking ***emergency*** surgery.

Unblinding

Unblinding can occur if a participant has an emergency clinical need to know if they are taking apixaban vs. aspirin. These clinical emergencies include, but not be limited to:

- An acute ischemic stroke qualifying for use of tPA
- A significant bleeding event
- The need for emergency surgery for any reason

Unblinding may not be necessary for any of these emergencies if **all** of the following conditions are met:

- The subject or surrogate can confirm that no study drug has been taken for the past 48 hours;
- The subject's renal function is normal (GFR ≥60);
- The subject's INR and PTT values are normal.

Unblinding Procedure (1)

For any emergency request for unblinding, the site investigator or emergency care provider should:

- Call the ARCADIA hotline # 833 427-2234 (833-4ARCADI)
- Discuss the case with the PI on call, who will discuss the clinical scenario briefly, including review of conditions whereby unblinding may not be necessary

After discussion, the ARCADIA hotline PI will

- Take down participant ID code
- call the NDMC emergency contact #
- confirm the need for unblinding with NDMC staff, and reason for unblinding
- provide a call back number for the NDMC to reach the site investigator or emergency care provider

Unblinding Procedure (2)

The NDMC will then

- unblind the participant's treatment assignment
- call the site investigator or emergency care provider
- provide the randomized treatment assignment information

The site study team will also need to fill out CRF within 72 hours.

The ARCADIA hotline PI will remain blinded.

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Treatment interruption due to possible outcome event

- If a site identifies an event as a possible primary efficacy outcome, the subject will either continue, pause, or stop study medication at the discretion of the treating physician.
- If the adjudication committee determines the event meets the primary efficacy definition the subject will stop the study; otherwise they may continue or resume treatment at the discretion of the treating physician.

Detection and management of AF

- We will collect data on the development of AF at regular follow up study visits.
- Subjects who manifest AF of any duration as part of standard-of-care follow-up/testing after randomization, as determined by the judgment of the site investigator and other treating physicians, should be switched to open-label anticoagulant therapy per the discretion of the site investigator and treating physicians.
- We recommend but do not mandate switching to open-label apixaban using the same dosing as the study protocol.
- Study drug will **NOT** be provided free of charge to participants after interval diagnosis of AF.
- These patients will continue to be followed for outcome events in the study according to the intention to treat paradigm.

Vascular Risk Factor Management

- AHA/ASA Secondary Stroke Prevention Guidelines will be available on website/WebDCU.
  - Kernan WN et al. AHA/ASA Secondary Stroke Prevention Guidelines. Stroke 2014;45(7):2160-236.
- PIs are expected to follow guidelines for care apart from those related to antithrombotic therapy.
- These include:
  - BP management
  - Use of statin therapy
  - Smoking cessation
  - Diet and exercise

Adherence

- The study site clinical coordinator should discuss in detail with the **patient** instructions for taking the study medications, including:
  - Reinforce the importance of taking all pills, including study pills, regularly;
  - Example of using a pill box or other reminders to remind the patient to take pills;
  - Reinforce taking the pills at the same time each day;
  - Assist subject with setting up a time that is most convenient for the patient: for example, 8 AM (one from Bottle A and one from Bottle B) and 8 PM (one from Bottle A);
  - Reinforce there are NO specific dietary instructions (May take pills with or without food).
  - Reinforce the importance of calling with questions if problems arise.

Adherence: Primary care provider/other providers

- Speak with primary care MD and/or cardiologist, neurologist to ensure willingness to have patient's antithrombotic therapy managed by trial
- Emphasize that they are not to give patient any anticoagulant or antiplatelet therapy
- Provide letter to primary MD
- Provide letter to patient to give to primary care MD/other physicians
- Medication alert card for wallet

Techniques to increase adherence

- Shared decision-making-Engage caregivers and family members to help
- Be aware of cognitive deficits in stroke patients
- Discuss with patient what they consider barriers to adherence to be
  - Visible bruising
  - Fear of bleeding
  - Discussion with their friends
- Have patient explain back what they are to do
- Simplify regimen/Reduce unneeded polypharmacy as able
- Be sensitive to Cultural differences and Language barriers
- Thank them for participating

ARCADIA

Outcomes and Safety Reporting

Erin Klintworth
NDMC Site Monitoring Manager

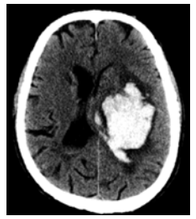
Will Longstreth
co-PI

Efficacy and Safety Endpoints

- Efficacy

  - Primary endpoint
    Stroke of any type
  - Secondary endpoints composite of:
    1) ischemic stroke or systemic embolism
    AND
    2) stroke of any type or death from any cause

- Safety



  - Primary endpoint
    Symptomatic intracranial hemorrhage and other major hemorrhage
  - Secondary endpoint
    All-cause mortality.

Efficacy and Safety Endpoints

- Efficacy

  - Primary endpoint
    Stroke of any type
  - Secondary endpoints composite of:
    1) ischemic stroke or systemic embolism
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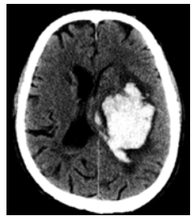
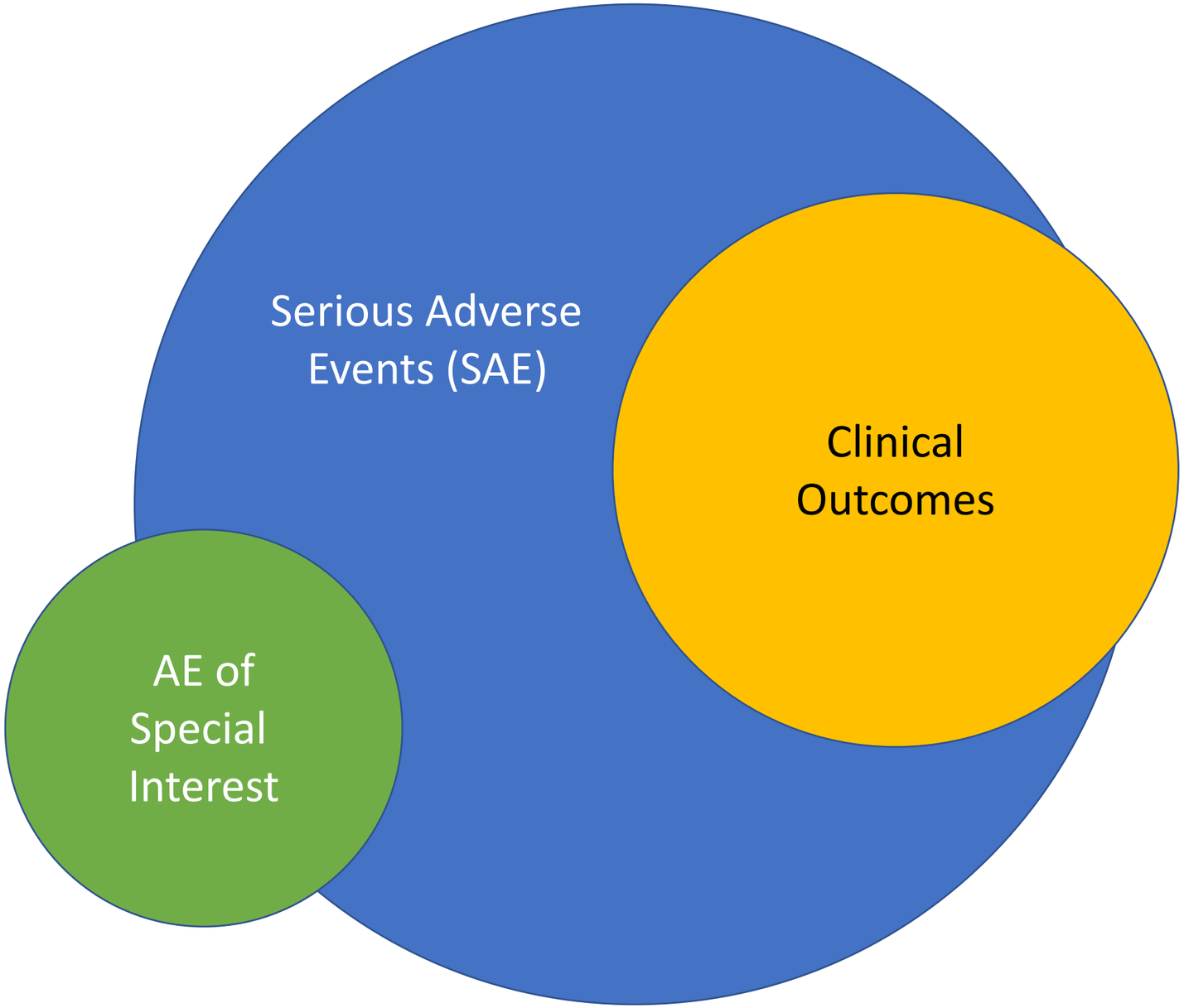


  - Primary endpoint
    Symptomatic intracranial hemorrhage and other major hemorrhage
  - Secondary endpoint
    All-cause mortality.

120 sites recruiting 1,100 patients followed for at least 18 months anticipating 150 recurrent strokes

Adverse Events (AE)



What Is an Adverse Event?

- Any new **untoward** medical occurrence, or worsening of a preexisting condition, in a subject.
- AEs **DO NOT** necessarily have a causal relationship to the study participation
- AEs **DO** have a temporal relationship to the study participation

Reportable Adverse Events

For the purposes of this trial, only the following types of events will be collected:

- Serious adverse events
- Clinical Outcomes
- Four adverse events of special interest, required by the pharmaceutical company

Serious Adverse Events

- Fatal
- Life-Threatening
- Result in hospitalization
  or prolongation of hospitalization,
  excluding optional, pre-planned surgery
- Result in disability or congenital anomaly
- Require intervention to prevent permanent impairment or damage

Adverse Events of Special Interest

Adverse events of special interest should be reported whether or not they are Serious Adverse Events

- Pregnancy of female participant
  or of female partner of male participant
- Overdose, accidental or intentional
- Potential drug-induced liver injury including liver test abnormalities, jaundice, hepatitis, or cholestasis
- Cancer

Clinical Outcomes

- Stroke
- Symptomatic hemorrhagic transformation of ischemic stroke
- Intracranial hemorrhage (subdural or epidural) excluding stroke
- Transient ischemic attack
- Major hemorrhage excluding intracranial hemorrhage
- Minor hemorrhage
- Atrial fibrillation or flutter
- Myocardial infarction
- Systemic embolism
- Symptomatic deep vein thrombosis
- Symptomatic pulmonary embolism

Reporting Adverse Events

Events are reported on the
Adverse Event Case Report Form (CRF)

- Information collected on all AE includes:
  - Event Name
  - Date of onset and resolution
  - Clinician's assessment of severity and relationship to study product
  - Detailed description or narrative of event
  - Relevant tests and laboratory data
  - Relevant history and pre-existing conditions
  - Event packet

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Example Narrative

"A [***age***] year old [***man/woman***] was enrolled in ARCADIA and randomized on [***mm/dd/yy***]. On [***mm/dd/yy***], at [***number***] days post randomization, the patient [***start of event, description of initial symptoms, and course***]. [***description of treatment course in detail and any other relevant information].*** Patient was [***discharged, transferred, or other resolution***] on [***mm/dd/yy***]."

Tips for Reporting Adverse Events

- Report only 1 event per CRF
- Report the diagnosis, not the symptoms:
  Fever, cough, chest pain, crackles = pneumonia
- Avoid abbreviations or colloquialisms
- Death, surgery, intubation, etc. are **NOT** names of adverse events.
  They are outcomes of adverse events
- Do **NOT** identify subject, physician or institution by name in narrative

Reporting Timeframes

- Events should be reported from time of randomization through the end of study participation
- Events must be entered and **submitted** into WebDCU™ within **24 hours** of discovery
  - Reportable events should be updated as additional information becomes available
- Events should be followed until resolution or until 30 days after the subject's participation in the study ends

Processing of Reports

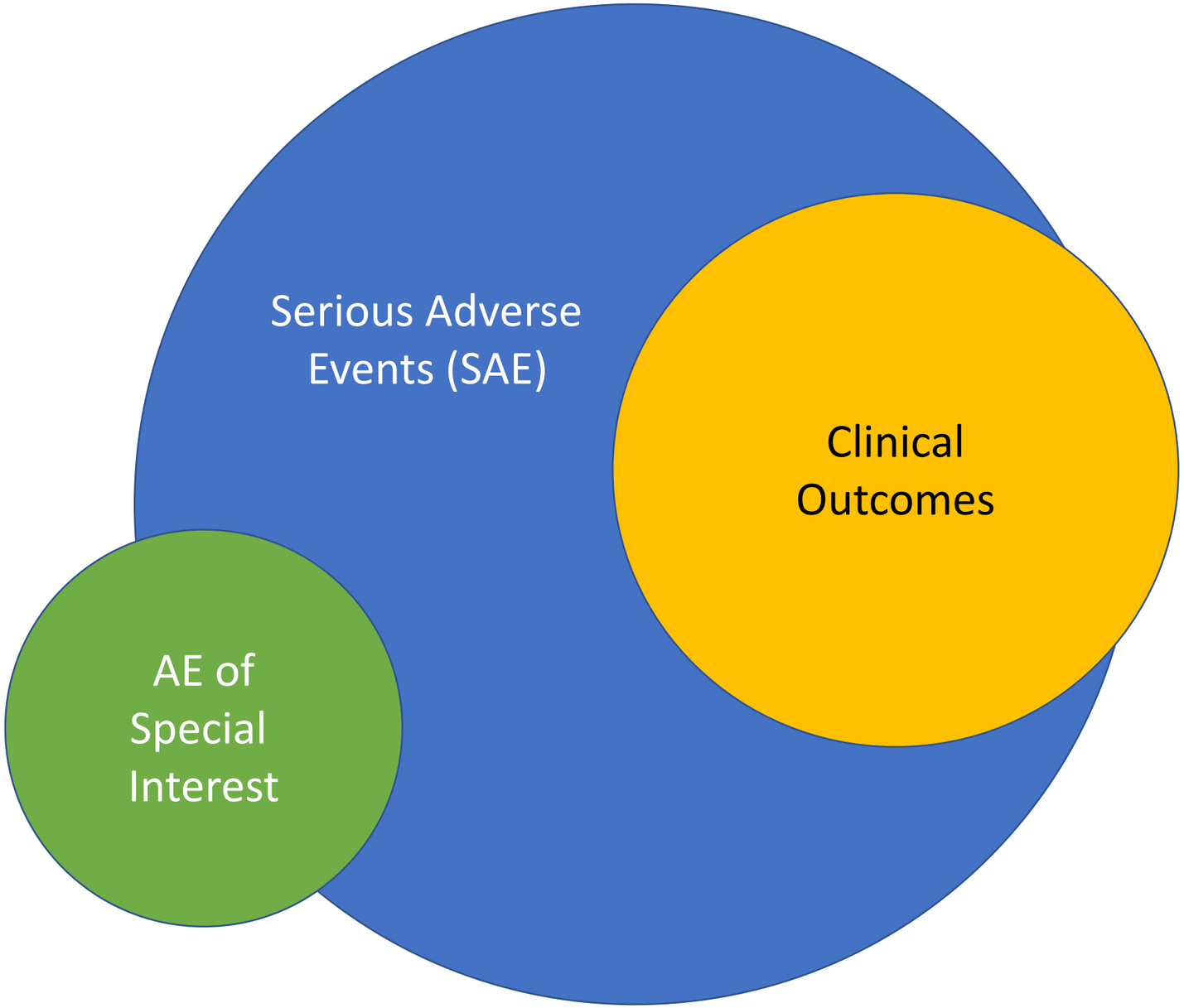
- Site reports AE by submitting in WebDCU™ **Adverse Event CRF**
- NCC Project Manager (PM) will be notified of submission and review CRF for completeness and correctness
- Once PM determines CRF is complete, the following will happen concurrently:
  - PM will generate a safety report within WebDCU™ for reporting to BMS (provider of study drug).
  - An automatic email notification will be sent to the independent Medical Safety Monitor (MSM)

Processing of Reports

- MSM reviews the event and indicates whether the event is:
  - Serious
  - Unexpected
  - Related to study intervention

- MSM, NCC PM or both may request additional documentation from the site to process or update a report

Adverse Events (AE)



Clinical Outcomes

- All are reported on the AE CRF
- All are called out in the AE CRF for tracking
- All are related to efficacy and safety endpoints
- Several trigger additional questions
- Efficacy endpoints are adjudicated

Clinical Outcomes

- Stroke
- Symptomatic hemorrhagic transformation of ischemic stroke
- Intracranial hemorrhage (subdural or epidural) excluding stroke
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Clinical Outcomes

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- Myocardial infarction
- Systemic embolism
- Symptomatic deep vein thrombosis
- Symptomatic pulmonary embolism

Outcome-Specific Questions on CRF

Examples

- Stroke
  - If stroke → ischemic type or not
  - If ischemic → complete online Causative Classification System for Ischemic Stroke
- Atrial fibrillation or flutter
  - If atrial fibrillation or flutter → how detected and longest duration

Clinical Outcomes

- Stroke
- Symptomatic hemorrhagic transformation of ischemic stroke
- Intracranial hemorrhage (subdural or epidural) excluding stroke
- Transient ischemic attack
- Major hemorrhage excluding intracranial hemorrhage
- Minor hemorrhage
- Atrial fibrillation or flutter
- Myocardial infarction
- Systemic embolism
- Symptomatic deep vein thrombosis
- Symptomatic pulmonary embolism

Events to be adjudicated

- Stroke
- Symptomatic hemorrhagic transformation of an ischemic stroke
- Transient ischemic attack
- Systemic embolism
- Death

Adjudication process

- Two neurologists with expertise in vascular neurology
- Each independently reviews information on event
  - If they agree, responses submitted
  - If they disagree, they confer and seek consensus
- Try to maintain blinding to study drug

Follow up after an event

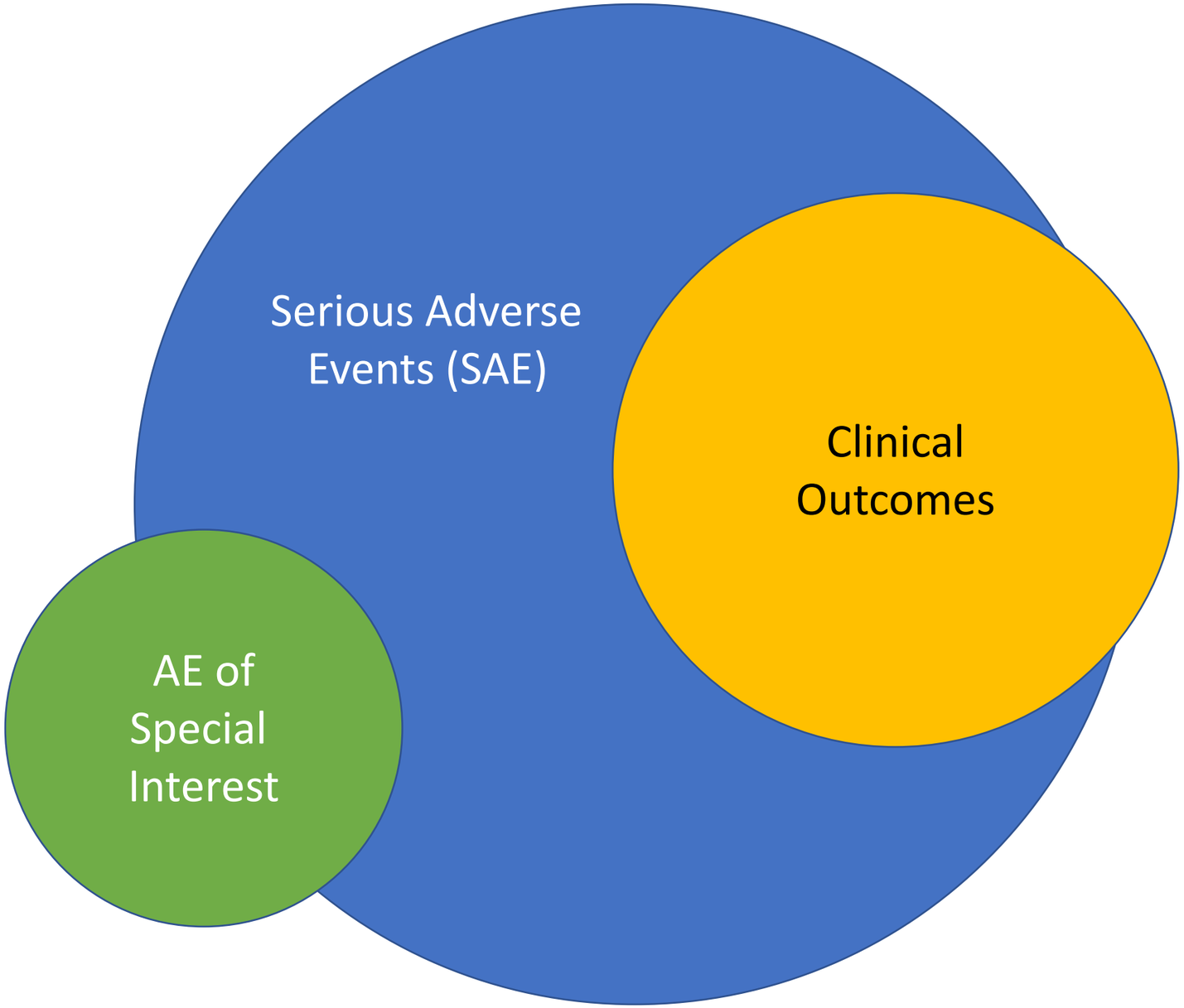
- For primary efficacy endpoint, stroke, follow up for only 30 days after the event.
- For any other event, follow until the end of the study regardless of whether or not still on study drug, honoring intention-to-treat design
- For example, atrial fibrillation, major hemorrhage, systemic embolism.

Conclusion

Report

- All serious adverse events
- Four events of special interest to pharma
- Eleven clinical outcomes
  - Adjudication of four efficacy endpoints and death

Adverse Events (AE)



ARCADIA Monitoring and Regulatory Requirements

Erin Klintworth, NDMC Site Monitoring Manager

ARCADIA

NIH StrokeNet
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Purpose of Monitoring

- Ensure protection of human subjects
- Ensure study data is accurate, complete and verifiable from source documents
- Ensure compliance with protocol, GCP and applicable regulations

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ARCADIA Data Monitoring

- NDMC is responsible for data monitoring activities
- Monitoring strategy relies heavily on central monitoring
  - Programmed logic checks within WebDCU™
  - Data Manager reviews entered data
  - Statistical analysis to identify errors and trends

Q01	Date of birth *Paient must be 45 years of age or older to be eligible*	31-May-2006	PV *Q01 must be greater than or equal to 45 or this is a protocol violation*

On-site and Remote monitoring

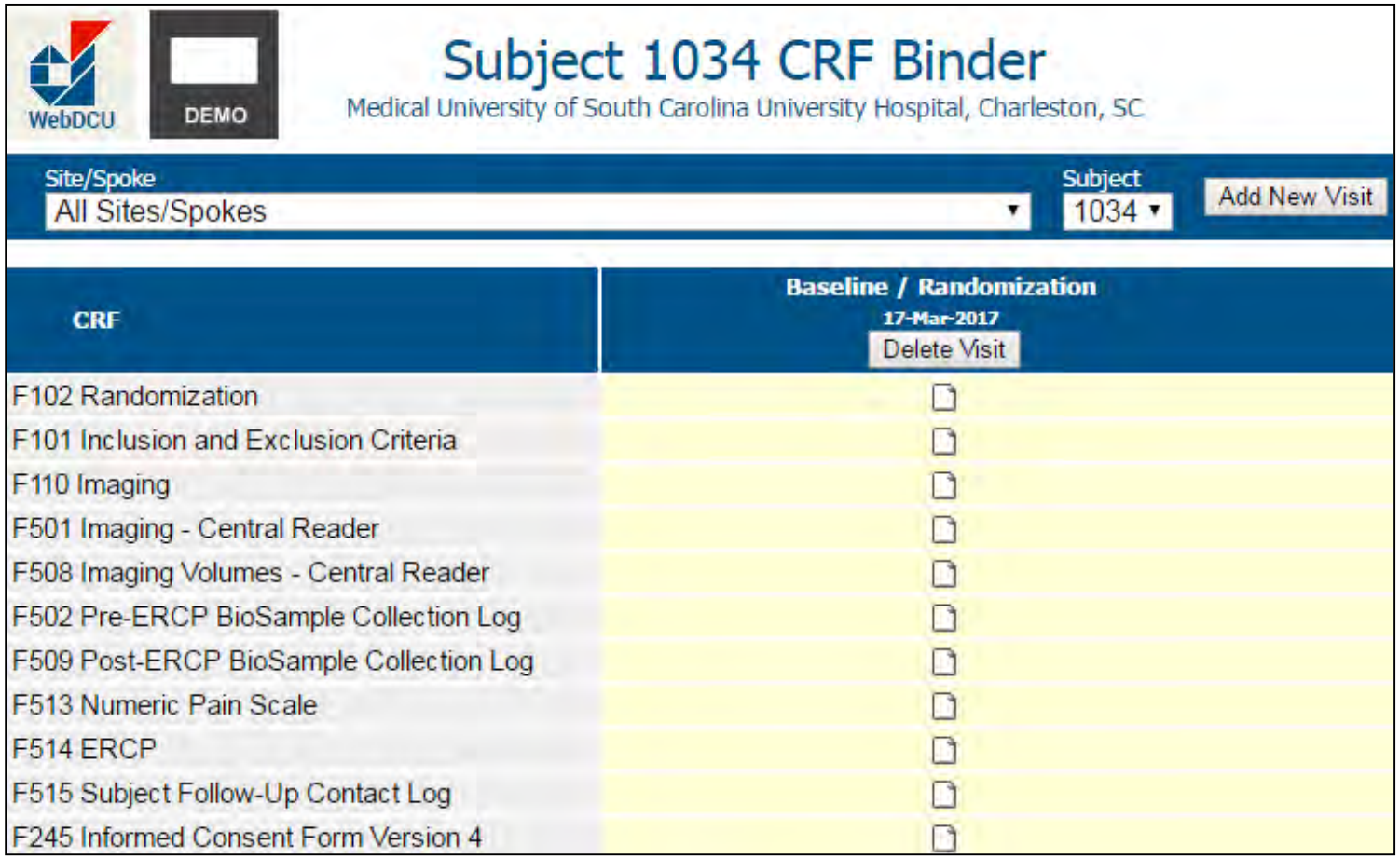
- Monitoring visits may be conducted remotely (via remote access to electronic medical records).
- Frequency and timing of visits determined by central monitoring findings, enrollment rate, unique attributes of study and/or site.
- Each site will be monitored in the early stages of the study after a small number of subjects are enrolled.
- All work performed, issues identified, and action items will be included in a Monitoring Report available to sites via WebDCU™

Preparing for a monitoring visit (on site or remote)

- Sites will be contacted well in advance of the monitoring visit to allow time for preparation.
- A coordinator should be available to answer questions during visit
- Site should secure monitor access to source records (e.g. – obtain EMR access for monitor) prior to visit
- If on-site visit, site should arrange for monitor access to pharmacy (if applicable).
- Site PI should be available to meet with the monitor during the visit

Remote monitoring of Informed Consent Document

- Informed consents will be uploaded by sites into WebDCU™ and remotely reviewed by NDMC study team members.



ARCADIA Regulatory Document Requirements

- ARCADIA Regulatory Document Parameters document details documents required for this trial.

ARCADIA Regulatory Document Parameters for WebDCU™ V1 APR. 25 2017							
Document	**Study Team Member Role**	**DOA Responsibilities**	**Document Type**	**Effective Date**	**Expiration Date**	**Can be waived?**	**Instructions**
Curriculum Vitae	Principal Investigator, Sub-Investigator	People who: Obtain Informed Consent, Determine Eligibility, Administer modified Rankin Scale, Administer NIH Stroke Scale (A, B, D, E)	People	Signature date	5 years from signature date	No	Document must be signed and dated. Provide Source in a PDF attachment
Medical/ Professional License	Principal Investigator, Sub-Investigator, Primary Pharmacist, Primary Study Coordinator, Study Coordinator	People who: Obtain Informed Consent, Determine Eligibility, Administer modified Rankin Scale, Administer NIH Stroke Scale, study drug accountability (A, B, D, E)	People	Issuance date on license, if present. Otherwise use date of upload.	Expiration date on license	Yes - if person is not a licensed medical/ professional	Current copies are required for all PIs, Co-Inv. Pharmacists and applicable study coordinators. Upload a PDF copy of the current license into WebDCU. Copies of online verifications are acceptable.
StrokeNet CIRB Financial Interest Disclosure Form	Principal Investigator, Sub-Investigator, Primary Study Coordinator, Study Coordinator	People who: Obtain Informed Consent, Determine Eligibility, Perform Randomization, Administer modified Rankin Scale, Administer NIH Stroke Scale, Administer other study-specific assessments, Complete CRFS & Respond to Queries, Report Adverse Events (A, B, C, D, E, F, I, J)	People	Signature date	Date of the next StrokeNet CIRB Annual Review	No	Document must be signed and dated. This document must be completed yearly, at the time of CIRB annual review. This document is not required for participating VA sites.

Site Regulatory Documents

- cIRB approvals (protocol, informed consents, recruitment materials, amendments)
- Local IRB acknowledgement
- Protocol signature page
- Federalwide Assurance
- Data Use Agreement (VA sites only)
- Pharmacy License

ARCADIA
Protocol NCT03192215
Version 1.1
7 July 2017

ARCADIA

AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke
Protocol Identifying Number: NCT03192215

PROTOCOL ACCEPTANCE FORM / SIGNATURE PAGE

Version: 1.1
Date: 7 July 2017

By signing below I confirm that:

1. I have read this protocol and it contains all necessary details for conducting this study

AND

2. I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

Principal Investigator's Signature _____ Date _____

Principal Investigator's Name (Print) _____

Site Name _____

People Regulatory Documents

- Documents required for each team member vary based on their assigned role/responsibility

Person	Curriculum Vitae	Human Subjects Protection Training Certification	Medical/Professional License	mRS Certification	NIHSS Certification	Protocol Training	Sample Handling and Shipping Certification	StrokeNet CIRB Financial Interest Disclosure Form	Study Coordinator Training
PI									
Sub-I									
Coordinator									
Sub-I									
Pharmacist									

Regulatory Document Requirements

- Required documents must be uploaded to WebDCU™ **BEFORE** your site can be released to enroll.
- Documents that will expire while the trial is ongoing (e.g. certain trainings, licensure, IRB approvals) must be updated in WebDCU™ prior to expiration.

Recruitment Strategies

David Tirschwell

ARCADIA

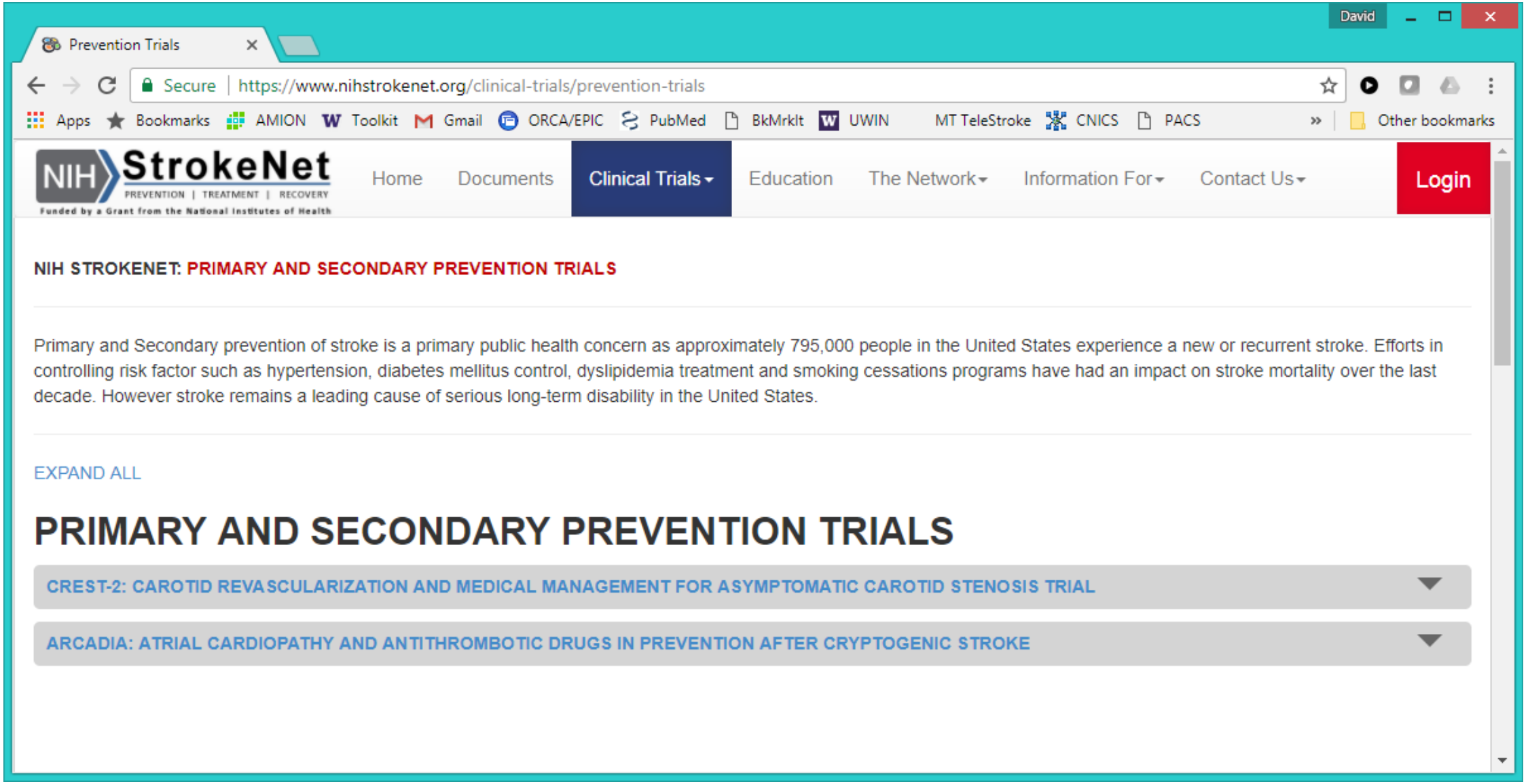
NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Agenda

- Recruitment Plan overview
- Inpatient vs. outpatient recruitment
  - Start preparing now!
- Recruitment Challenges and Strategies – Scott Kasner
- Focus on Minority Recruitment – Bernadette Boden-Albala

Recruitment Plan

- Local PIs establishing close working relationships with local physicians and others providing care to patients with cryptogenic stroke;
- Provision of educational materials for lectures and other opportunities;
- Provision of pocket cards and other recruitment materials (e.g., trifold brochures);
- Translation of patient-facing materials into Spanish and other needed languages;
- Maintenance of a ARCADIA website;
- Listing of ARCADIA on clinicaltrials.gov;
- Minority recruitment plan;
- Inclusion of all sexes/genders and all race-ethnic groups;
- Absence of upper age limit;
- Active oversight and monitoring of recruitment by the ARCADIA leadership team;
- Termination of participation by sites that do not meet recruitment goals.


David
Prevention Trials
Secure
https://www.nihstrokenet.org/clinical-trials/prevention-trials
Apps
Bookmarks
AMION
Toolkit
Gmail
ORCA/EPIC
PubMed
BkMrklt
UWIN
MT TeleStroke
CNICS
PACS
Other bookmarks
NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health
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Education
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Contact Us
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NIH STROKENET: PRIMARY AND SECONDARY PREVENTION TRIALS
Primary and Secondary prevention of stroke is a primary public health concern as approximately 795,000 people in the United States experience a new or recurrent stroke. Efforts in controlling risk factor such as hypertension, diabetes mellitus control, dyslipidemia treatment and smoking cessations programs have had an impact on stroke mortality over the last decade. However stroke remains a leading cause of serious long-term disability in the United States.
EXPAND ALL
PRIMARY AND SECONDARY PREVENTION TRIALS
CREST-2: CAROTID REVASCULARIZATION AND MEDICAL MANAGEMENT FOR ASYMPTOMATIC CAROTID STENOSIS TRIAL
ARCADIA: ATRIAL CARDIOPATHY AND ANTITHROMBOTIC DRUGS IN PREVENTION AFTER CRYPTOGENIC STROKE

ARCADIA: ATRIAL CARDIOPATHY AND ANTITHROMBOTIC DRUGS IN PREVENTION AFTER CRYPTOGENIC STROKE

ATRIAL CARDIOPATHY AND ANTITHROMBOTIC DRUGS IN PREVENTION AFTER CRYPTOGENIC STROKE (ARCADIA)

Trial Summary:

In one-third of ischemic strokes, a specific cause cannot be identified. Many of these cryptogenic strokes appear to arise from a distant embolic source. Recent evidence suggests that some cryptogenic strokes arise from left atrial thromboembolism that goes unrecognized because it is not associated with atrial fibrillation/flutter (AF). Under the prevailing clinical paradigm, it is thought that AF is required for blood clots to form in the left atrium. Therefore, unless AF is apparent, patients do not receive anticoagulant therapy to prevent atrial thromboembolism. However, recent research indicates that embolization from the left atrium can occur when there are abnormal changes to atrial tissue and function even before there is AF. Such an "atrial cardiopathy" may explain many of the strokes that are currently of unknown cause. Since anticoagulant drugs such as apixaban have already proven more effective than standard aspirin therapy for preventing stroke from AF, the parallels between AF and atrial cardiopathy suggest that apixaban may also be more effective than aspirin for stroke prevention in patients with atrial cardiopathy and no AF.

ARCADIA

ARCADIA is a randomized trial of apixaban versus aspirin specifically in patients with cryptogenic stroke who have evidence of atrial cardiopathy. This trial will address several important knowledge gaps. First, it will advance our understanding of stroke pathophysiology by assessing whether atrial cardiopathy is a valid therapeutic target, which may set the stage for a primary prevention trial. Second, this trial will advance our understanding of optimal secondary stroke prevention therapy.

Trial Design Summary:

ARCADIA is a multicenter, biomarker-driven, randomized, double-blind, active-control, phase 3 clinical trial of apixaban versus aspirin in patients who have evidence of atrial cardiopathy and a recent stroke of unknown cause. Atrial cardiopathy will be defined as one or more of the following biomarkers: P-wave terminal force in electrocardiogram lead V_1 >5,000 mV*ms, left atrial size index ≥3.0 cm/m^2 on echocardiogram, and serum NT-proBNP >250 pg/mL. The primary aim is to test the hypothesis that apixaban is superior to aspirin for the prevention of recurrent stroke in subjects with cryptogenic ischemic stroke and atrial cardiopathy.

ARCADIA will recruit 1,100 subjects over 2.5 years at 120 sites in the NINDS StrokeNet consortium. Subjects will be followed for a minimum of 1.5 years and a maximum of 4 years for the primary efficacy outcome of recurrent stroke and the primary safety outcomes of symptomatic intracranial hemorrhage and major hemorrhage other than intracranial hemorrhage.

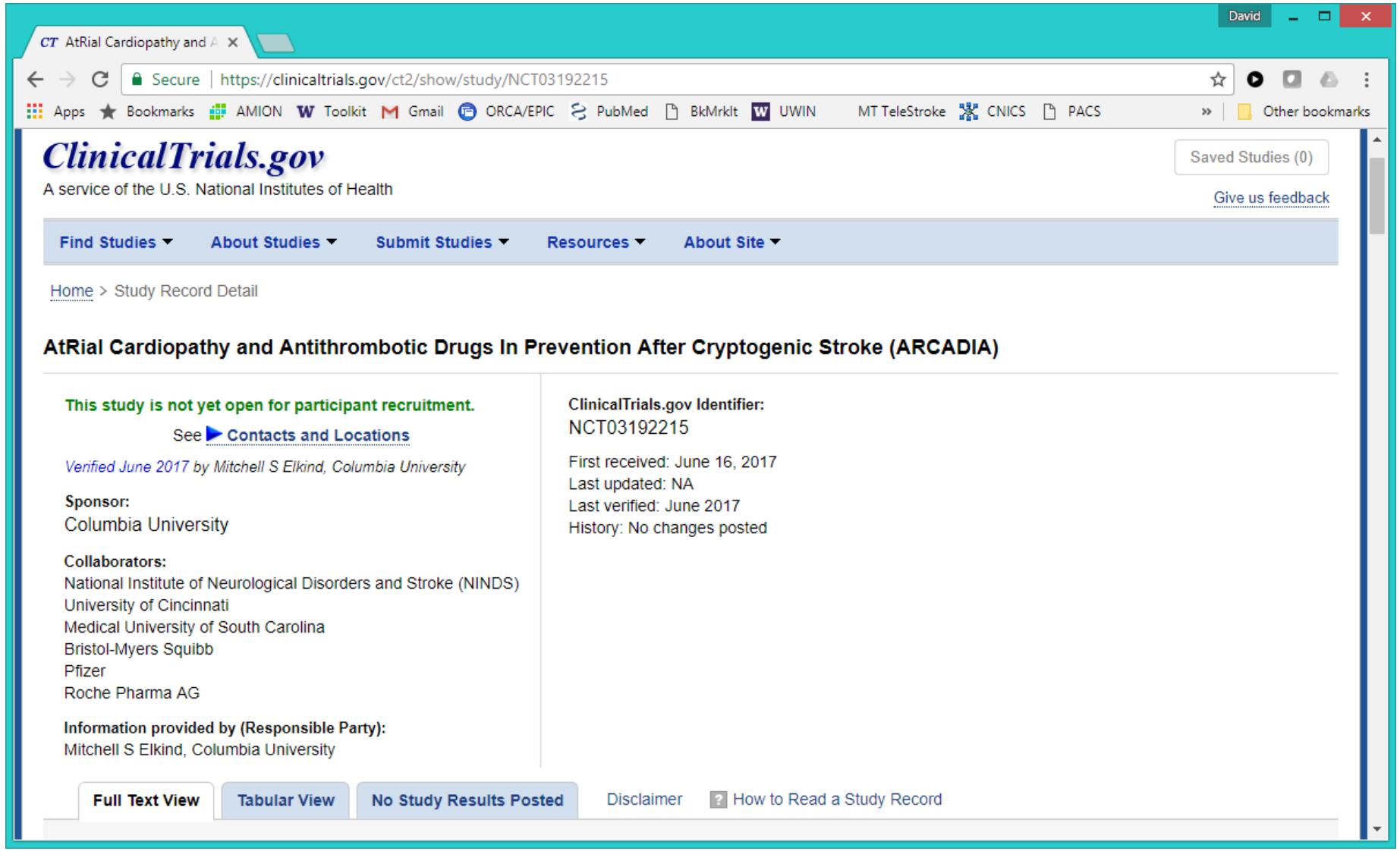
Sponsors and Collaborators:

Sponsor: Columbia University/Mitchell S.V. Elkind, MD, MS for the ARCADIA PIs
National Institute of Neurological Disorders and Stroke (NINDS)

Also supported by: BMS-Pfizer Partnership and Roche Diagnostics

Principal Investigators:

Mitchell S.V. Elkind, MD, MS, Columbia University
Hooman Kamel, MD, Cornell University
W.T. Longstreth Jr, MD, MPH, University of Washington
David L. Tirschwell, MD, MSC, University of Washington



- Objectives
- Outcome measures
- Eligibility
  - Inclusion
  - Exclusion
- Contacts
- Listing of study locations

https://clinicaltrials.gov/ct2/show/NCT03192215

Minority Recruitment Plan

- Inclusion or exclusion of subjects will not differ based on sex/gender/race/ethnicity
- Atrial cardiopathy may differ by these groups, screening data may elucidate
- Sites will be trained to use strategies to enhance recruitment of underrepresented minorities, including:
  - Training module based on toolkit on minority recruitment and retention from the national Initiative for Minority involvement in Neurological Clinical Trials (NIMICT);
  - Encourage community outreach to community centers and elder homes;
  - Use of flexible enrollment and follow-up office hours;
  - Translation of materials into local languages as needed;
  - Reimbursement for travel expenses to attend clinic.

Monitoring of Recruitment

- Screen failure logs will be reviewed monthly to identify recruitment problems.
- A Cumulative Recruitment Summary Report retrievable from WebDCU™ will detail the numbers of patients screened, enrolled, and randomized.
- Failure to recruit
  - Sites will be put on probation if they have not randomized any patients for 3 consecutive months.
  - Sites will be suspended if after an additional 3 month probation period they still do not have any randomized patients.
  - Sites may also be put on probation if they have 3 consecutive patients who meet randomization criteria based on screening biomarkers but are not randomized.

Inpatient recruitment

- Every ischemic stroke patient should be reviewed
- Randomization can be as early as 3-14 days, but you can start screening process as soon as patient arrives
- Most diagnostic testing is done by that time
- Plans for extended cardiac monitoring are NOT a barrier
- If qualify after screening, approach early

Outpatient recruitment

- Outpatient referrals to stroke clinic
- Stroke/Neurology colleagues in region can refer
  - Within your “system” or outside
- Primary care givers
- EM providers
- Volunteer to give talks at local meetings – we can provide slides
- After review of hospitalization records, consider prioritizing visit depending on time since stroke

Start planning now

- Expand your scope/screening populations
- How many hospitals in your system can you review patients from?
  - Remote access of EMR can facilitate
  - Start NOW on permission to access
- Creatively seek patients
  - ECAT cases with “stroke” indication reviewed each month
- Who will review charts? Do they have the ear of PI for questions?
- How will you NOT miss any patients?