



ARCADIA-CSI (Cognition and Silent Infarcts)

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Integration with Parent Trial

ARCADIA Parent Trial

- Apixaban vs. aspirin for secondary stroke prevention
- 1100 patients with cryptogenic stroke and atrioopathy
- 2.5 years of enrollment; 1.5-4 (median 3) yrs of f/u
- No data on cognitive and neuroimaging outcomes

ARCADIA-CSI Ancillary Study

- Adds key cognitive and neuroimaging outcomes
- Integrates seamlessly with ARCADIA study visits
- Low patient / investigator burden
- Potentially high impact



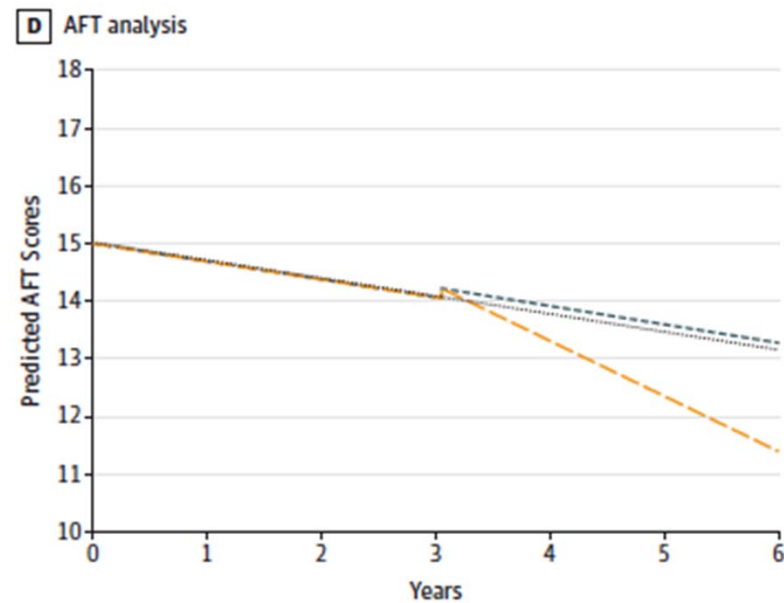


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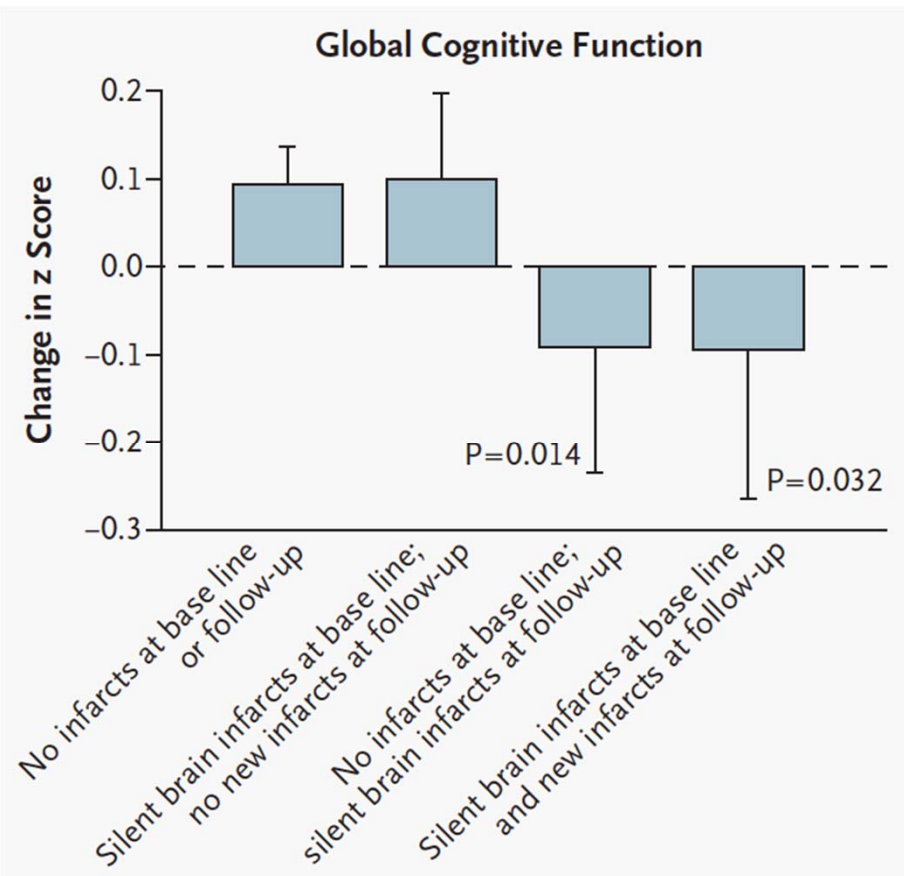


Post-stroke Cognitive Decline

- Cognitive decline accelerates after stroke
- Stroke doubles the risk of developing dementia
- 30% prevalence of dementia post-stroke



Silent Infarcts



- Common
 - Prevalence 30-50%
 - Incidence up to 19% annually after TIA
- Accelerate cognitive decline
- Double risk of dementia
- Secondary stroke prevention studies have not focused on preventing silent infarcts and cognitive decline

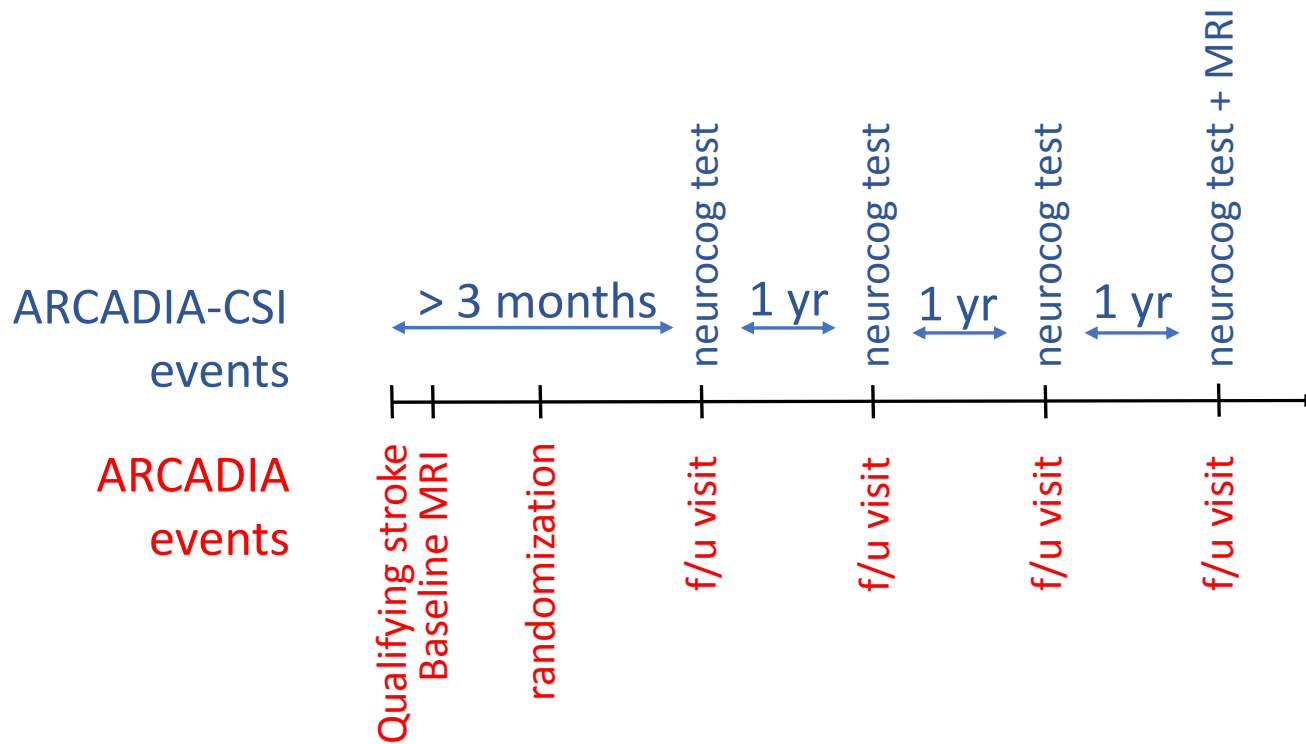


Aims

1. To determine the effect of anticoagulation (vs antiplatelet therapy) on the slope of cognitive function after stroke (primary clinical outcome)
2. To determine the effect of anticoagulation (vs antiplatelet therapy) on the incidence of silent infarcts after stroke (primary imaging outcome)
3. To determine (a) the imaging and clinical predictors of cognitive decline after stroke and (b) how much of the treatment effect on cognitive function is explained by a reduction in silent infarcts



Schedule of Events





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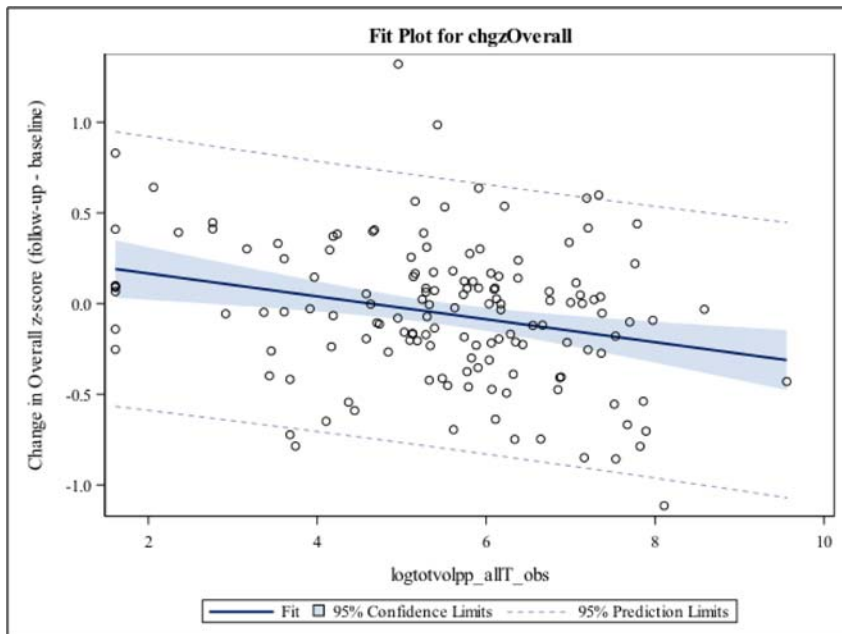
Annual neurocognitive test

- 22 minute phone battery
- Covers 4 key cognitive domains relevant to post-stroke cognition
- Centrally administered by trained interviewers to reduce interrater variability
- Tested in >30,000 subjects in REGARDS and CREST-2 studies
- Demonstrated sensitivity to cognitive change, cerebrovascular risk factors, large vessel disease.

Cerebral Protection in Transcatheter Aortic Valve Replacement: The SENTINEL Study

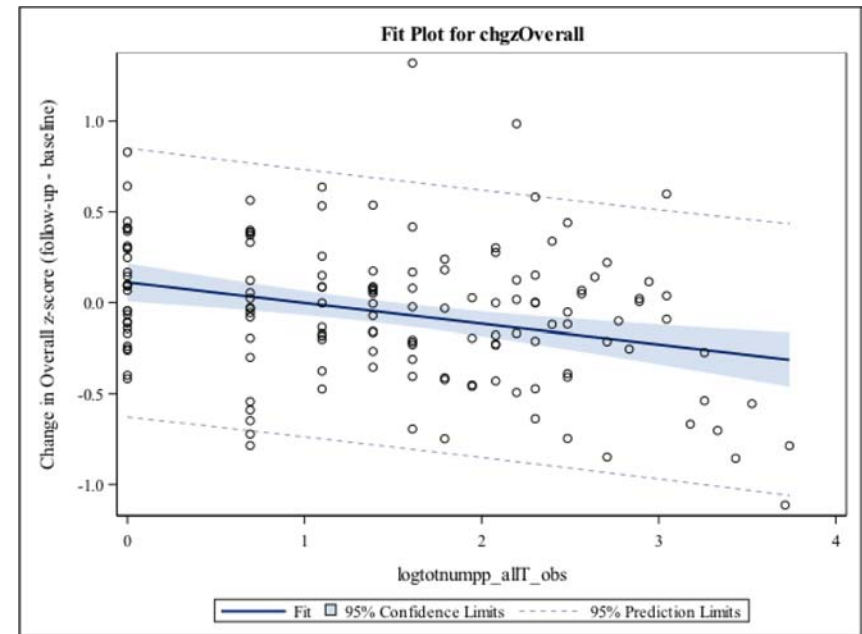


Correlation of Day 2-7 DW-MRI **Lesion Volume** with 30-Day Change in Neurocognitive Battery



$p = 0.0012$ $r = -0.26650$

Correlation of Day 2-7 DW-MRI **Lesion Number** with 30-Day Change in Neurocognitive Battery



$p = 0.0002$ $r = -0.30212$



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MRI

- Simple protocol with standard sequences
- Preferably on 3T (1.5T acceptable)
- 15 minute scanning time
- 30 minutes total time
- MUSC will collect and store the images
- Stanford Radiology Core will analyze the images:
 - New Silent infarcts
 - White matter disease burden
 - GRE lesions

Inclusion/Exclusion Criteria

Inclusion Criteria

- Randomized in ARCADIA
- >3 months post index stroke
- Able to undergo MRI
- Able to provide self-consent for ARCADIA-CSI enrollment in English
- Score of 0-1 on NIHSS language

Exclusion Criteria

- Pre-existing diagnosis of dementia
- Active illicit drug use
- Education less than 8 years



ARCADIA



Analysis

- **Sample:** 1100 patients in ARCADIA -> 85% (n=935) will meet ARCADIA-CSI eligibility -> 75% will be willing to consent (n=700) -> will easily meet our target enrollment of 500 patients
- **Cognitive outcome:** Random effects regression model with 90% power to detect a difference of 0.26 SD on the average z-score at 3 years
- **Radiological outcome:** Poisson regression model with 90% power to detect a 13% reduction (from 50 to 37%) in the incidence of silent infarcts over 3 years



ARCADIA

Impact of ARCADIA-CSI

- Large scale data of effect of anticoagulation on silent infarction and cognitive decline
- Results that are important regardless of the results of the parent trial
- Will provide deeper insight in the incidence of silent infarcts, the slope of post-stroke cognitive decline, and the relationship between them
- Will set the stage for future trials to prevent silent infarction and post-stroke cognitive decline