ARCADIA-CSI

Cognition and Silent Infarcts

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Overview

Study population

ARCADIA-MRI

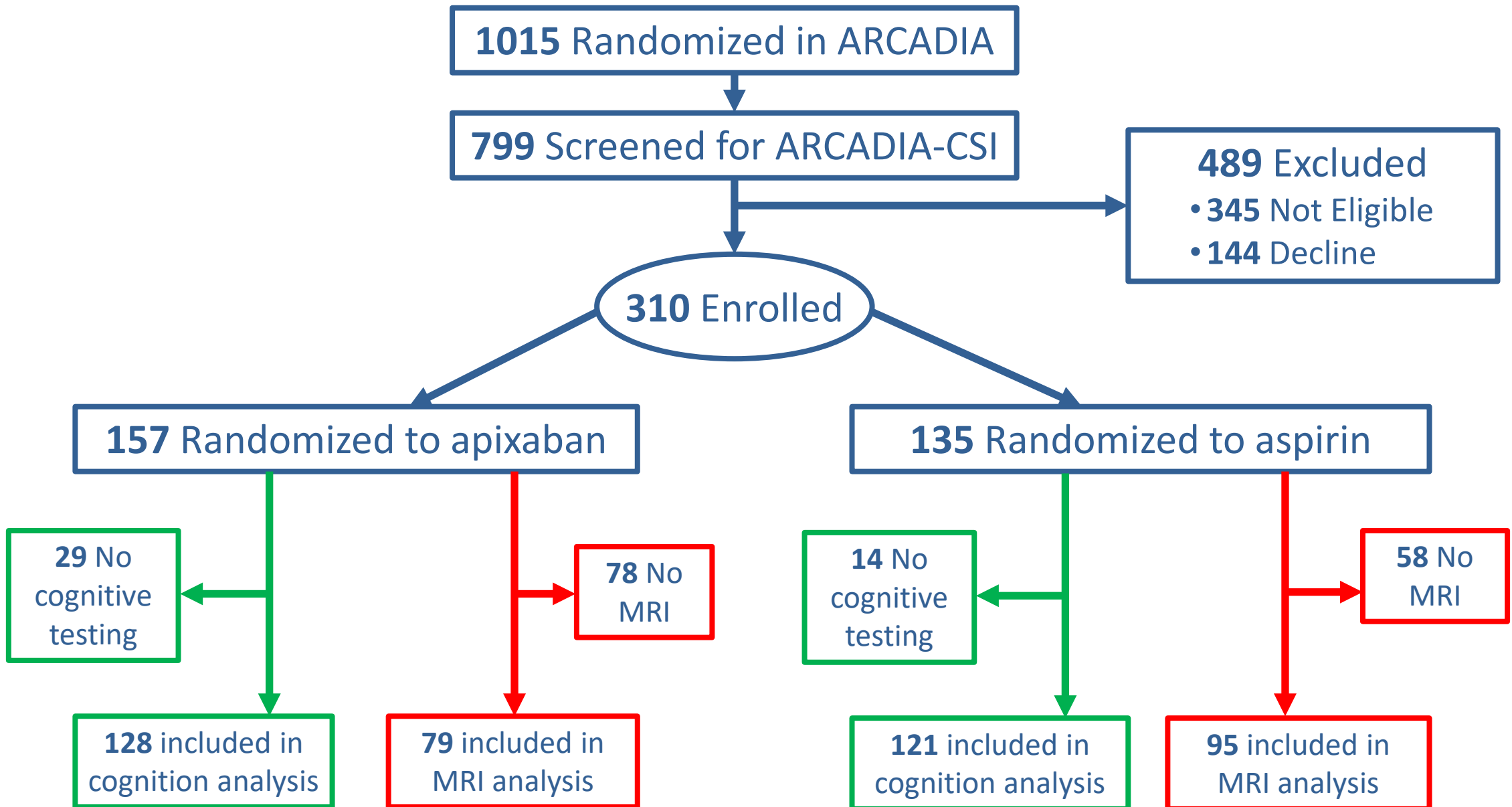ARCADIA-Cognition

Study population

Inclusion and Exclusion

Inclusion Criteria

- Randomized in ARCADIA

- Able to undergo MRI

- Able to provide informed consent

Exclusion Criteria

- ARCADIA study drug permanently discontinued

- Diagnosis of dementia

- Active illicit drug use

- Admission for depression

- <8 years of education

- TBI with >30 min loc

ARCADIA-MRI

Background

- Covert infarcts are common
  - Prevalence 30-50%
  - Incidence up to 19% annually after TIA
- Covert infarcts are important
  - Associated with increased risk of cognitive impairment and dementia
  - Associated with increased risk of clinical stroke
- Two secondary stroke prevention studies have focused on covert infarcts
  - NAVIGATE-ESUS and PACIFIC-Stroke
  - Annual rate of covert infarcts 10-22%

Timing of MRI Scans

ARCADIA
events

ARCADIA-CSI
events

Index stroke ⎯ Baseline Clinical MRI as SOC

Randomization ⎯
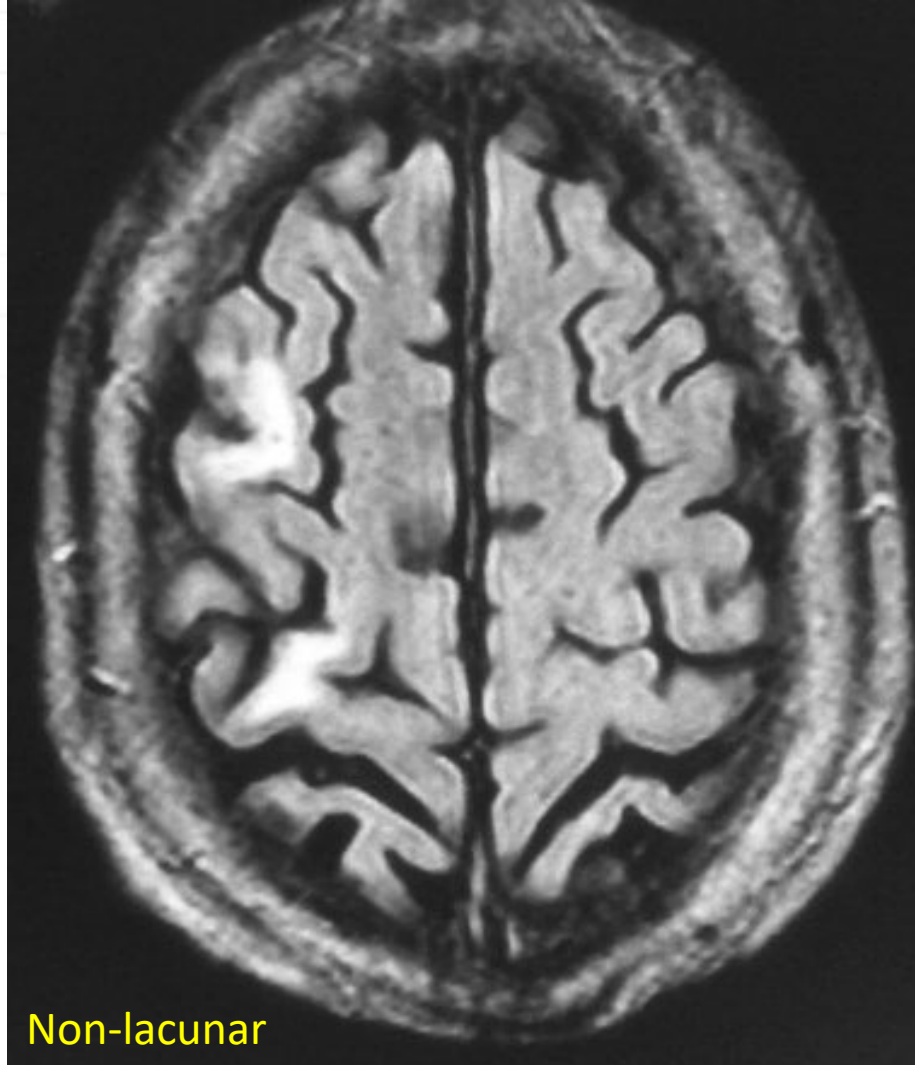
• ARCADIA-CSI Enrollment (anytime after ARCADIA randomization)
• Baseline Research MRI (only if no clinical MRI at time of index stroke)

F o l l o w - u p

Exit ⎯ Follow-up Research MRI

MRI Interpretation

- Follow-up scans rated for the presence of new silent infarcts

- Lacunar infarcts defined as round or ovoid subcortical lesions <15 mm in diameter

Non-lacunar
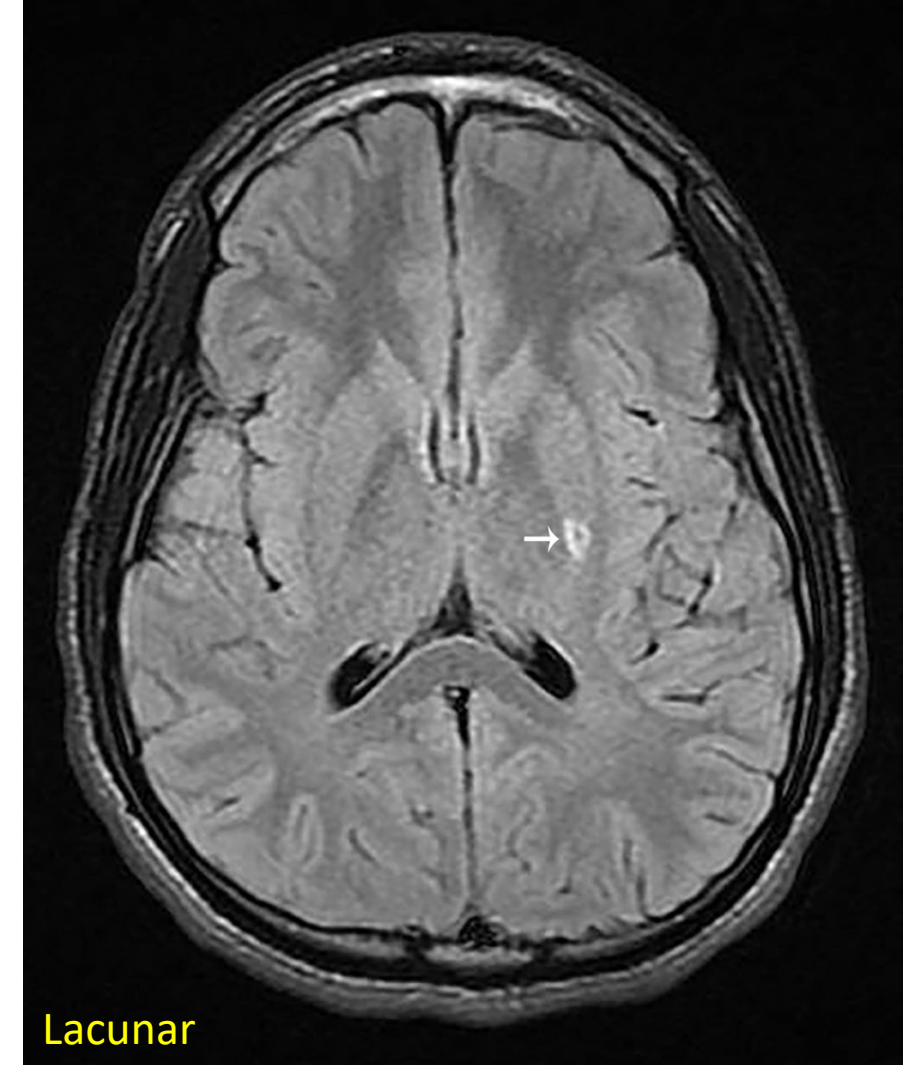
Lacunar

Statistical Analysis

- The relative risk of the incidence of one or more new non-lacunar covert infarcts during follow-up was estimated using Poisson regression with adjustment for follow-up time and inverse probability weighting to account for missing follow-up MRI studies
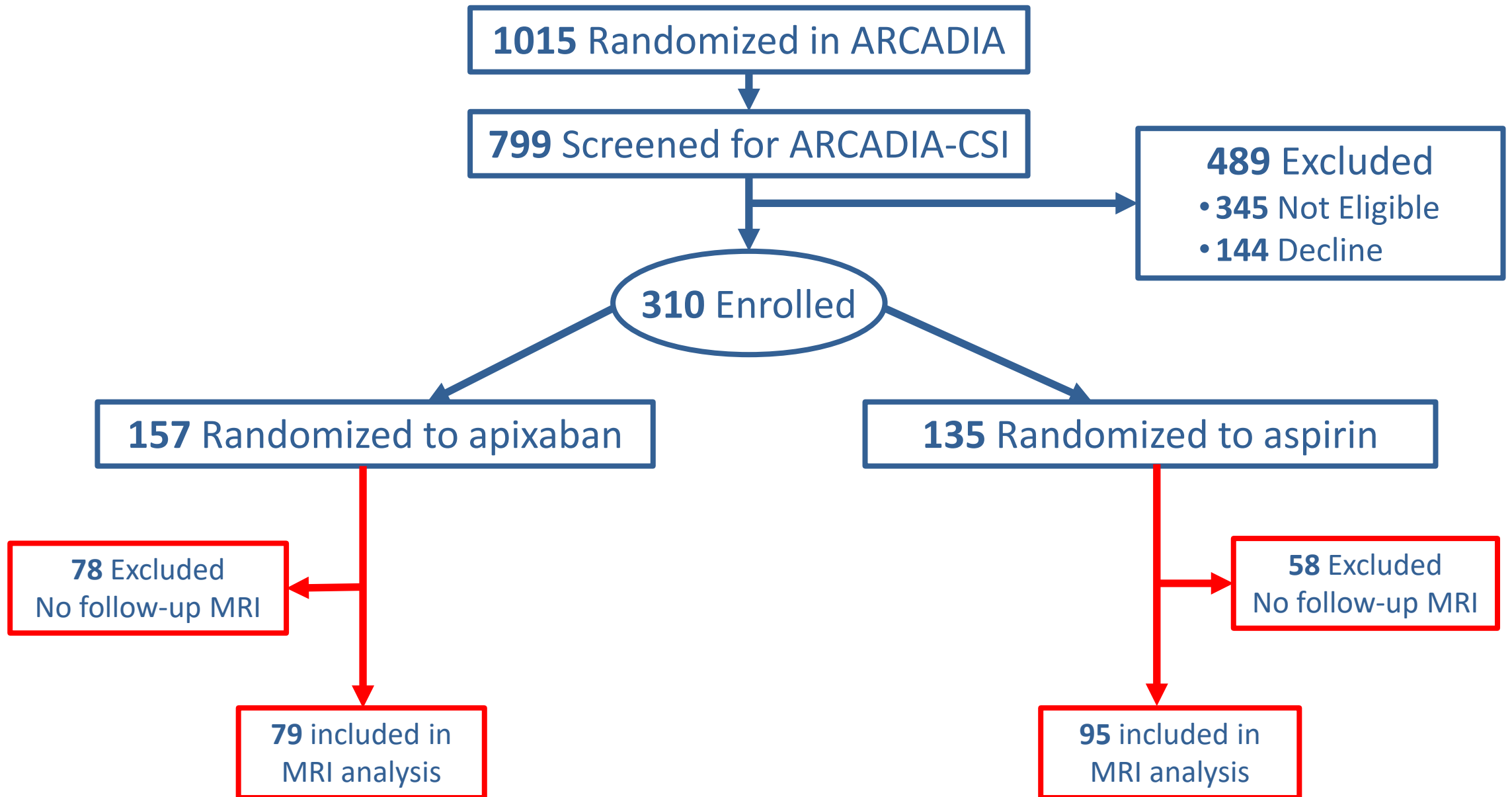
Baseline Characteristics of Enrolled Patients

	Included (n=174)	Excluded (n=136)
Age, Mean (SD)	66.3 (10.6)	67.2 (9.7)
Female, no. (%)	83 (47.7)	72 (52.9)
Black, no. (%)	33 (19.0)	30 (22.1)
Hypertensive, no. (%)	128 (73.6)	104 (76.5)
Diabetic, no. (%)	44 (25.3)	43 (31.6)
Prior stroke or TIA (before index), no. (%)	36 (20.7)	27 (19.9)
Modified Rankin Scale, Median (IQR)	1 (0-2)	1 (0-2)
NIHSS, Median (IQR)	0 (0-2)	1 (0-3)
Fazekas score, Median (IQR)	2 (1-3)	2 (1-3)

Baseline Characteristics of Included Patients

	Apixaban (n=79)	Aspirin (n=95)
Age, Mean (SD)	66.3 (10.2)	66.3 (11.0)
Female, no. (%)	37 (46.8)	46 (48.4)
Black, no. (%)	13 (16.5)	20 (21.1)
Hypertensive, no. (%)	57 (72.2)	71 (74.7)
Diabetic, no. (%)	16 (20.3)	28 (29.5)
Prior stroke or TIA (before index), no. (%)	12 (15.2)	24 (25.3)
Modified Rankin Scale, Median (IQR)	1 (0-2)	1 (0-2)
NIHSS, Median (IQR)	0 (0-2)	1 (0-2)
Fazekas score, Median (IQR)	2 (1-3)	2 (1-3)

Study Characteristics of Included Patients

	Apixaban (n=79)	Aspirin (n=95)	P-value
Time from ARCADIA randomization to ARCADIA-CSI consent, median (IQR), days	179 (48, 364)	93 (37, 362)	0.47
Time from baseline to follow-up MRI, median (IQR), days	800 (479-1311)	822 (487-1238)	0.65
Discontinued study drug prematurely, no. (%)*	14 (17.7)	13 (13.7)	0.46

*A subject was considered to have "Discontinued study drug prematurely" if they discontinued study drug permanently before the date that sites were notified of trial end (12/21/22) and more than seven days before their censor date in the parent trial.

Primary Analysis

Difference in non-lacunar covert infarcts between treatment arms

Primary Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct				

Primary Analysis

Difference in non-lacunar covert infarcts between treatment arms

Primary Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)			

Primary Analysis

Difference in non-lacunar covert infarcts between treatment arms

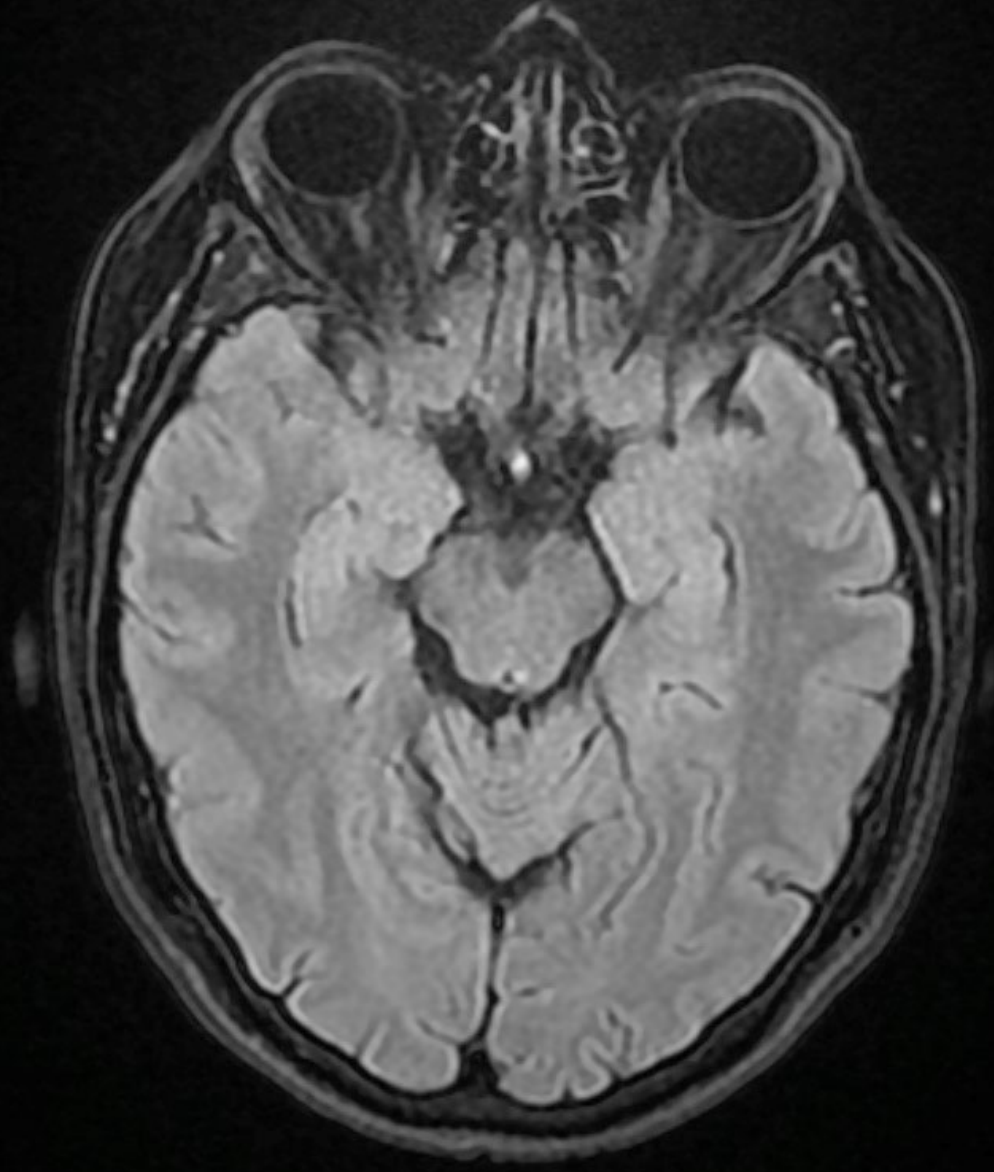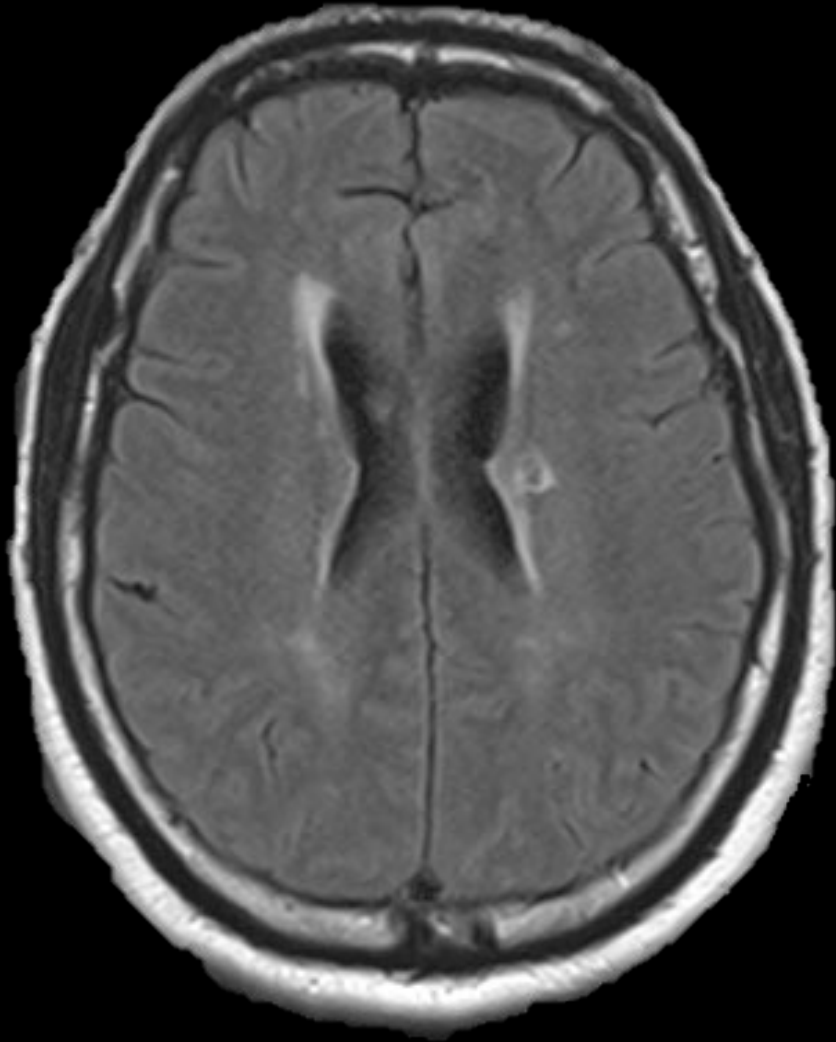| Primary Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)		

Primary Analysis

Difference in non-lacunar covert infarcts between treatment arms

Primary Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 – 0.83)	0.02

Baseline

Baseline

Secondary Outcome

Composite of ≥1 non-lacunar covert infarct or a non-lacunar clinical stroke

Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 − 0.83)	0.02
≥1 non-lacunar covert infarct or a non-lacunar clinical stroke	7 (9%)	25 (26%)	0.36 (0.17 − 0.79)	0.01

Additional Outcomes

Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 – 0.83)	0.02
≥1 non-lacunar covert infarct or a non-lacunar clinical stroke	7 (9%)	25 (26%)	0.36 (0.17 – 0.79)	0.01
Additional Outcomes				
Non-lacunar clinical stroke	3 (4%)	8 (8%)	0.52 (0.15 – 1.77)	0.30

Additional Outcomes

Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 − 0.83)	0.02
≥1 non-lacunar covert infarct or a non-lacunar clinical stroke	7 (9%)	25 (26%)	0.36 (0.17 − 0.79)	0.01
Additional Outcomes				
Non-lacunar clinical stroke	3 (4%)	8 (8%)	0.52 (0.15 − 1.77)	0.30
≥1 lacunar covert infarct	8 (10%)	12 (13%)	0.80 (0.34 − 1.86)	0.60

Additional Outcomes

Outcome	Apixaban (n=79)	Aspirin (n=95)	RR (95% CI)	P-value
≥1 non-lacunar covert infarct	4 (5%)	17 (18%)	0.29 (0.10 – 0.83)	0.02
≥1 non-lacunar covert infarct or a non-lacunar clinical stroke	7 (9%)	25 (26%)	0.36 (0.17 – 0.79)	0.01
Additional Outcomes				
Non-lacunar clinical stroke	3 (4%)	8 (8%)	0.52 (0.15 – 1.77)	0.30
≥1 lacunar covert infarct	8 (10%)	12 (13%)	0.80 (0.34 – 1.86)	0.60
≥1 lacunar or non-lacunar covert infarct	12 (15%)	25 (26%)	0.57 (0.31 – 1.07)	0.08

Limitations / Discussion

- High percentage (44%) of enrolled patients did not return for their follow-up MRI

- Patients included in the ARCADIA-MRI analysis were less likely to discontinue study drug prematurely (15.5%) than patients who were screened but not enrolled (50.8%)

Conclusion

Among patients with a cryptogenic stroke and atrial cardiopathy, apixaban as compared to aspirin:

- prevents non-lacunar covert infarcts

- does not prevent lacunar covert infarcts

ARCADIA-Cognition

ARCADIA – CSI: (Cognition Substudy)

Cognition and Covert Infarction

Vermeer SE et al. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke. Jan 2002;33(1):21-5.

Vermeer SE, Longstreth WT, Jr., Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol. Jul 2007;6(7):611-9. doi:10.1016/S1474-4422(07)70170-9
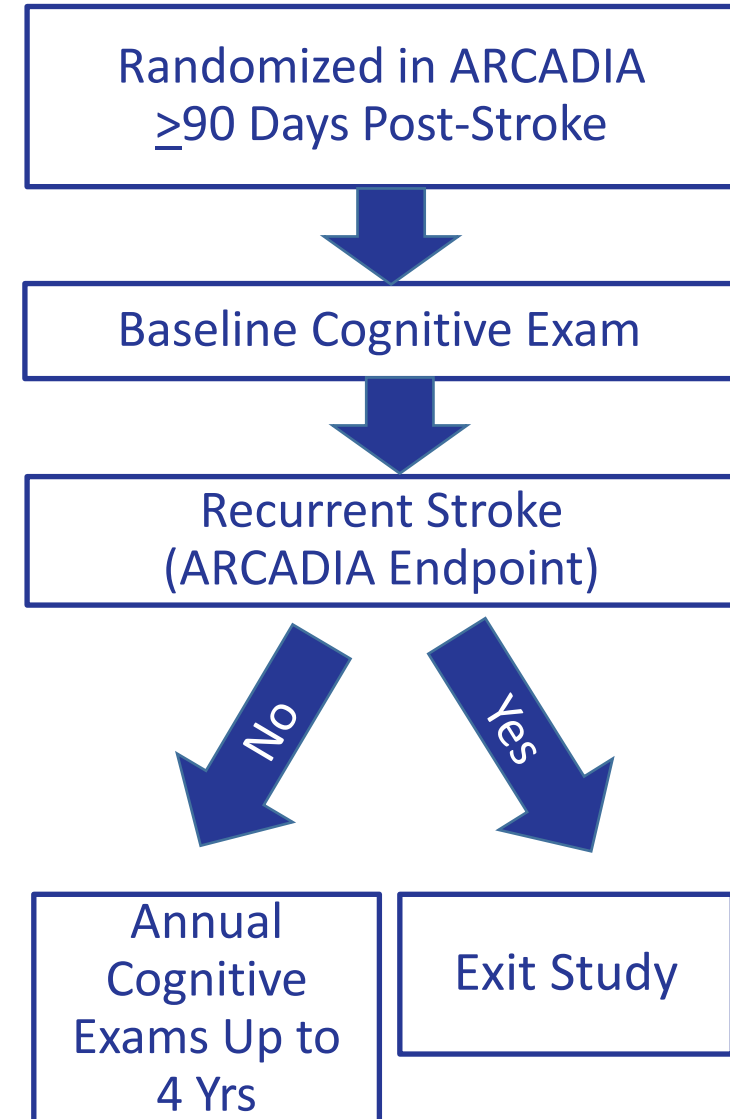
Iatrogenic Etiology: CABG (Tachibana, 2021), TAVR (Lazar, 2018), AF Ablation (Hahne, 2016)
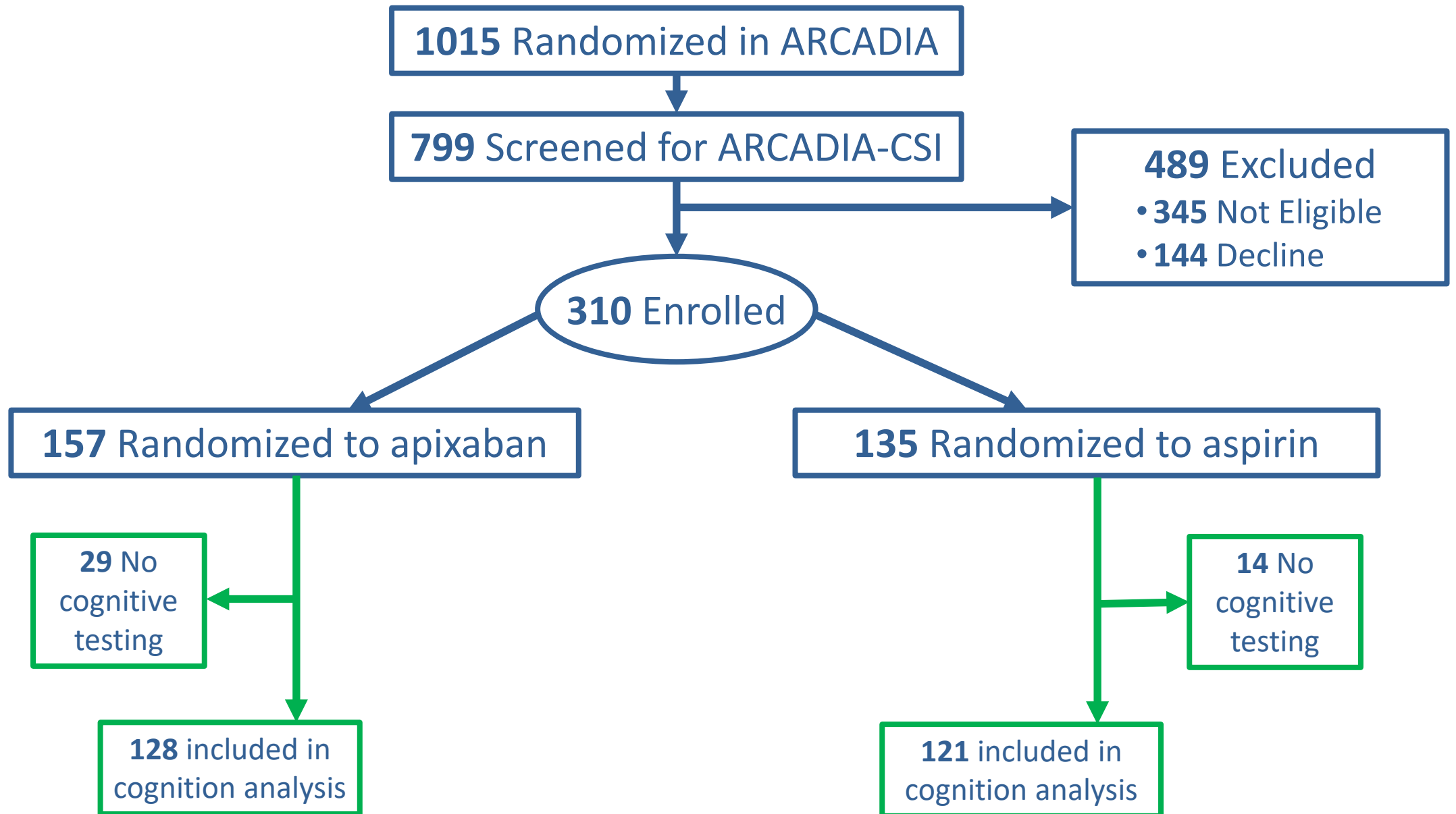
Specific Aim 2: Determine the effect of apixaban (vs aspirin) on the longitudinal rate of change (i.e., slope) of global cognitive function after stroke (primary clinical outcome).

ARCADIA – CSI: (Cognition Substudy)

ARCADIA-CSI Cognitive Test Battery (Administered via Phone by the UAB Survey Research Unit)	
Test	**Domain**
CERAD Word List Learning	Learning
Digit Span	Attention
CERAD Delayed Recall	Memory
Animal Fluency	Executive Function
Letter Fluency	
Oral Trail Making*	

Randomized in ARCADIA ≥90 Days Post-Stroke

↓

Baseline Cognitive Exam

↓

Recurrent Stroke (ARCADIA Endpoint)

No ↙   ↘ Yes

Annual Cognitive Exams Up to 4 Yrs

Exit Study

ARCADIA – CSI: (Cognition Substudy)

Baseline Characteristics/Follow-up Visits	Apixaban (n = 128)	Aspirin (n = 121)
Age at time of CSI consent, Mean (SD)	66.7 (10.3)	66.8 (10.6)
Female, no. (%)	64 (50.0)	65 (53.7)
Black, no. (%)	20 (15.6)	28 (23.1)
Hypertensive, no. (%)	96 (75.0)	89 (73.6)
Diabetic, no. (%)	31 (24.2)	35 (28.9)
Education n (%)	- - -	- - -
<High School	3 (2.3)	5 (4.1)
High School Graduate or GED	34 (26.6)	26 (21.5)
Partial College or Specialized Training	40 (31.3)	30 (24.8)
College Graduate	26 (20.3)	31 (25.6)
Graduate Professional Degree	25 (19.5)	29 (24.0)
Cognitive Exams Completed (%)		
Baseline	127 (99.2)	120 (99.2)
Follow-Up Visit 1	95 (74.2)	93 (76.9)
Follow-Up Visit 2	53 (41.4)	55 (45.5)
Follow-Up Visit 3	18 (14.1)	20 (16.5)
Follow-Up Visit 4		1 (1.0)

ARCADIA – CSI: (Cognition Substudy)
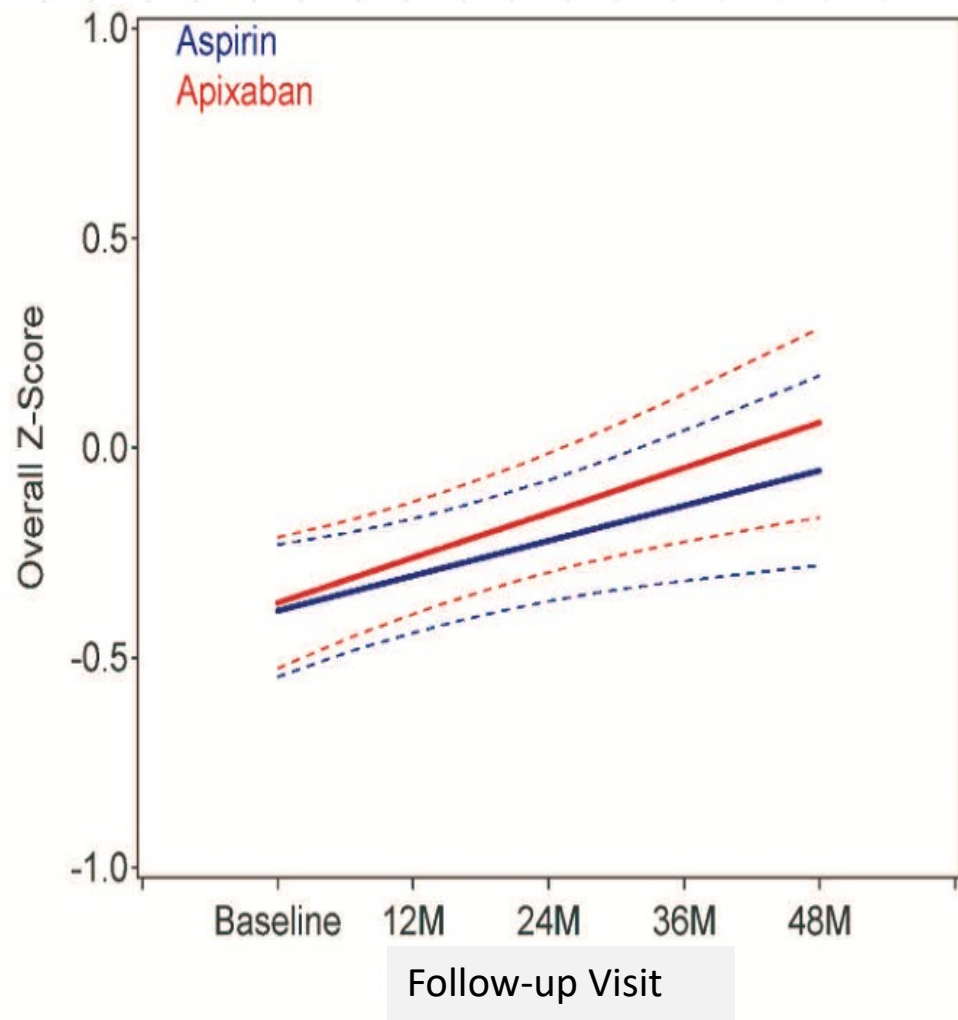
	Apixaban (n=128)	Aspirin (n=121)
ARCADIA Index stroke to first Cognitive exam (days), median (IQR)	264 (IQR: 141, 539)	249 (IQR: 138, 504)
First cognitive exam to last cognitive Exam (days), median (IQR)	374 (IQR: 0, 738)	413 (IQR: 225, 734)

Estimated Annual Change	
Aspirin	Apixaban
0.084 (0.018 – 0.149)	0.107 (0.041– 0.174)
P = 0.62	

ARCADIA – CSI: (Cognition Substudy)

Estimated Annual Change by Cognitive Test

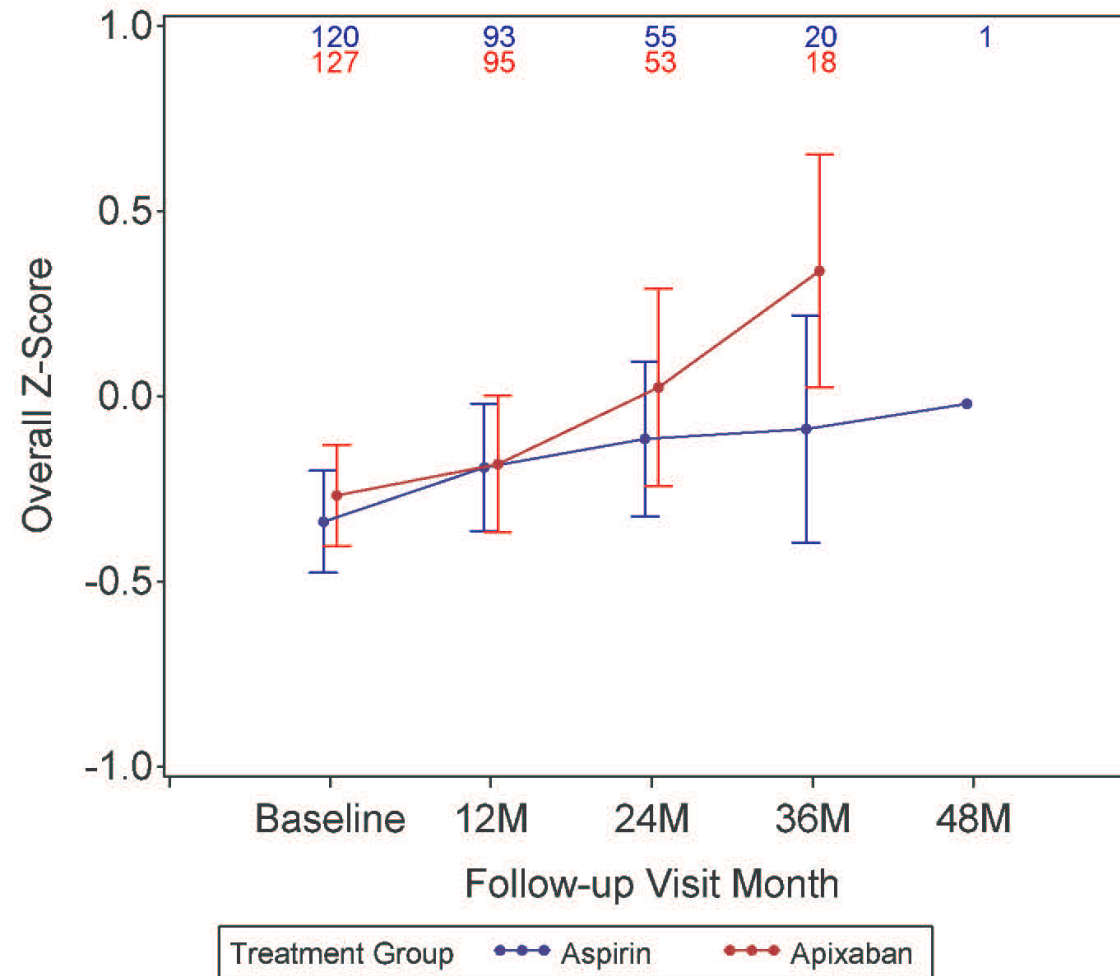|	Aspirin	Apixaban	P-value
Verbal Fluency	0.089 (0.022 – 0.156)	0.109 (0.040 – 0.177)	0.69
Digit Span	0.069 (-0.008 – 0.147)	0.046 (-0.033 – 0.124)	0.67
Animal Naming	0.026 (-0.053 – 0.104)	0.109 (0.030 – 0.189)	0.14
Word List Learning	0.096 (0.008 – 0.185)	0.094 (0.005 – 0.183)	0.97
Word List Recall	0.057 (-0.038 – 0.153)	0.060 (-0.036 – 0.156)	0.97

ARCADIA – CSI: (Cognition Substudy)

Factor Affecting Cognitive Effects

- Duration of Follow-Up

- Number of Covert Infarcts

- Volume of Covert Infarcts

- Location of Covert Infarcts

- Time since index stroke

ARCADIA – CSI: (Cognition Substudy)

What if....