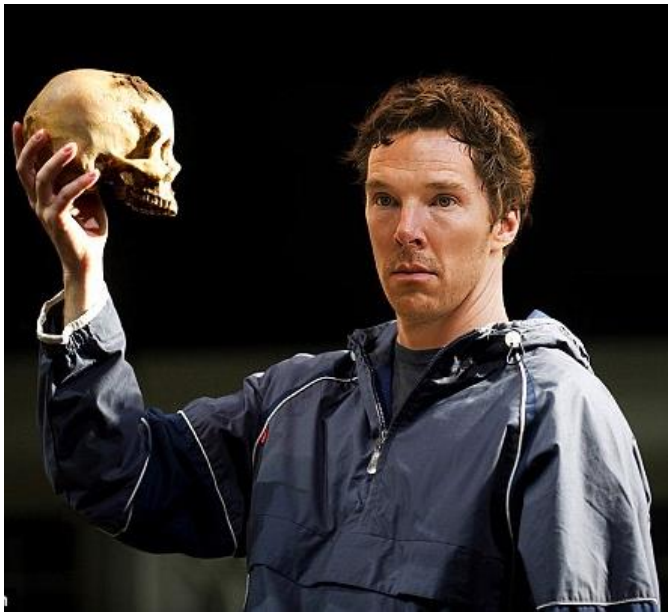
CAA in the Era of Ischemic Stroke Treatments



Steven M. Greenberg, MD, PhD
JPK Stroke Research Center
Massachusetts General Hospital
& Harvard Medical School

Virginia Systems Stroke Task Force
Quarterly Meeting July 15, 2022

Thanks to….

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International CAA Association, Boston Criteria v2.0

Andreas Charidimou David Werring Eric Smith

Mark van Buchem Rustam al-Shahi Salman

for the Boston Criteria v2.0 Investigators

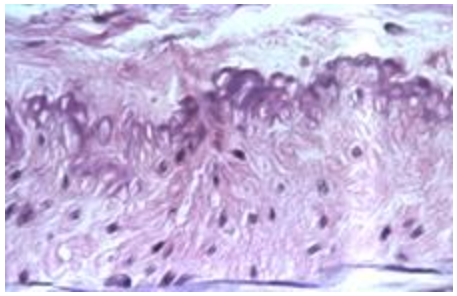
CAA in the Era of Ischemic Stroke Treatments

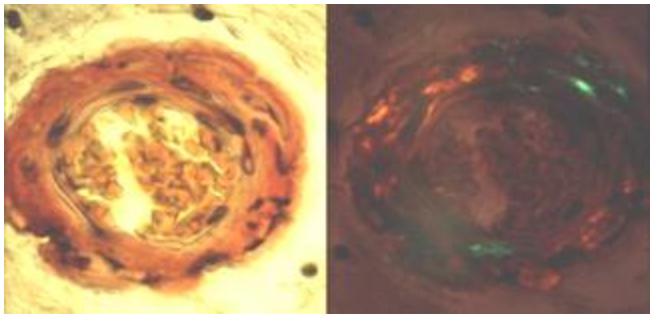
1. What is CAA? Criteria for Diagnosis
2. Implications of CAA for anticoagulation
3. Implications for thrombolysis

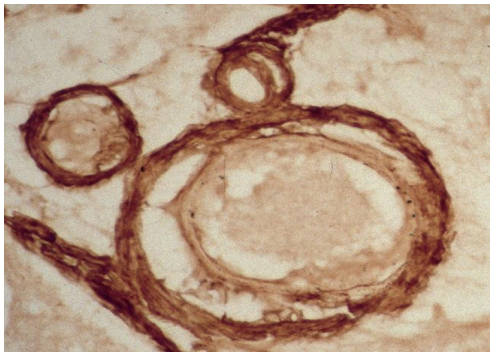
CAA in the Era of Ischemic Stroke Treatments

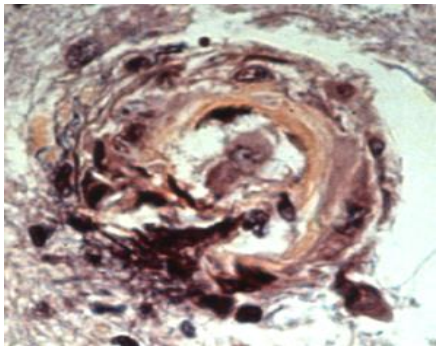
1. What is CAA? The Boston Criteria for Diagnosis
   - Defined by deposition of ß-amyloid peptide in arterioles and capillaries of leptomeninges and cortex
   - Moderate-to-severe CAA present in ~35% of brains at autopsy
   - Major cause of spontaneous intracerebral hemorrhage
   - Common contributor to age-related cognitive decline

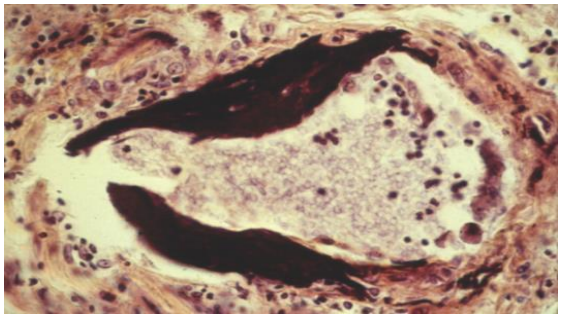
What is CAA?
Pathologic stages



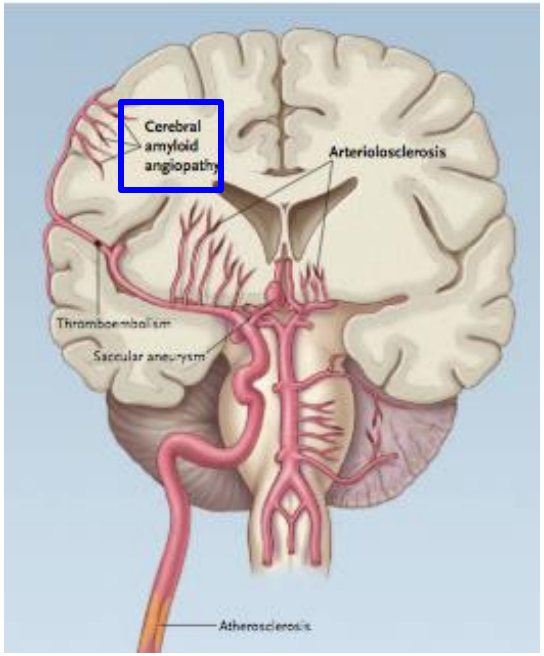


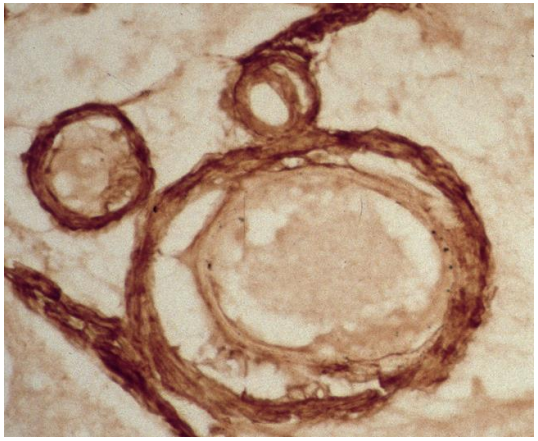


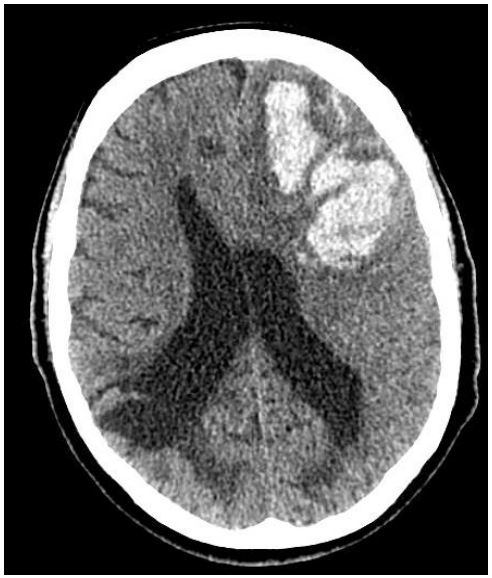




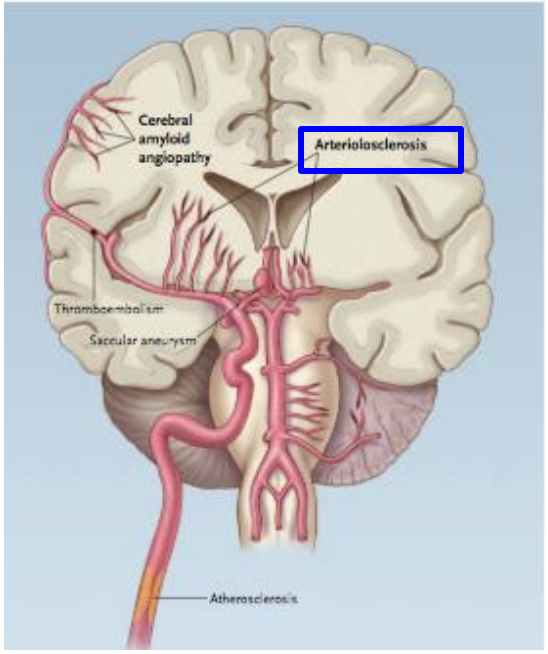
Cerebral amyloid angiopathy

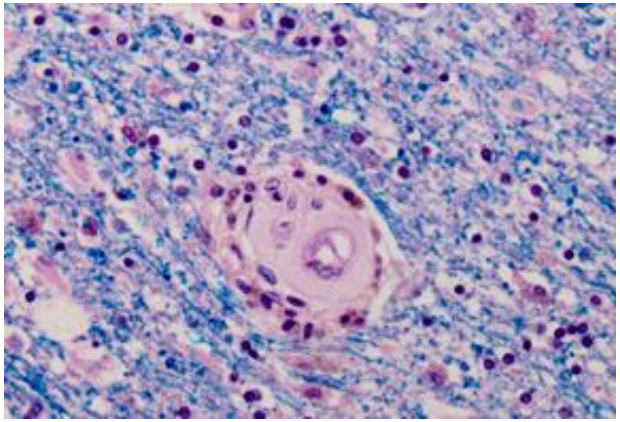


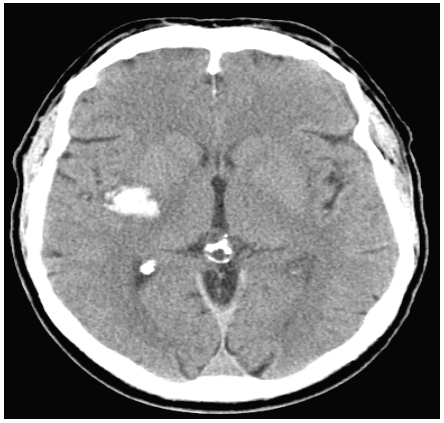


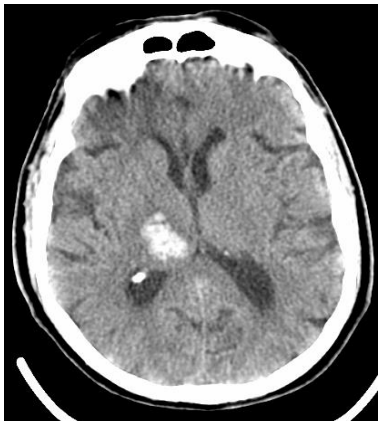


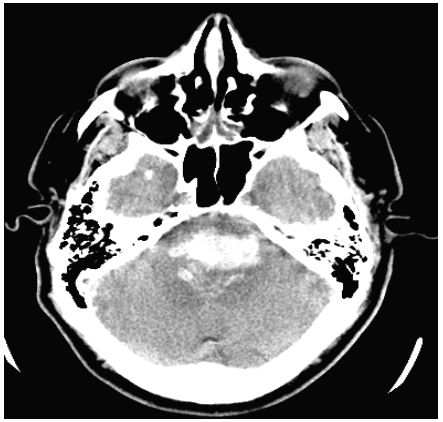
Arteriolosclerosis (HTN microangiopathy)





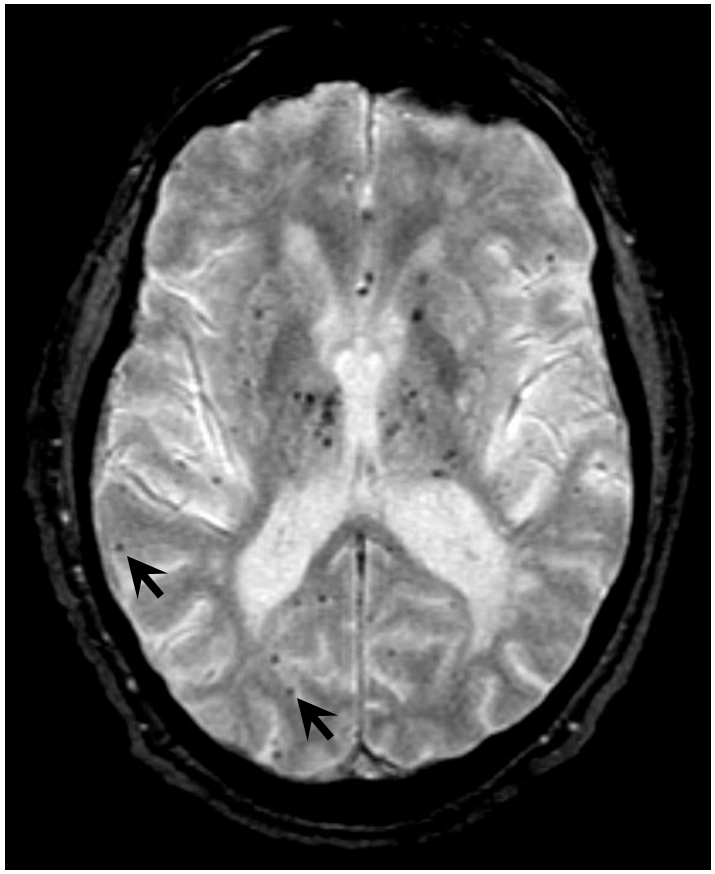




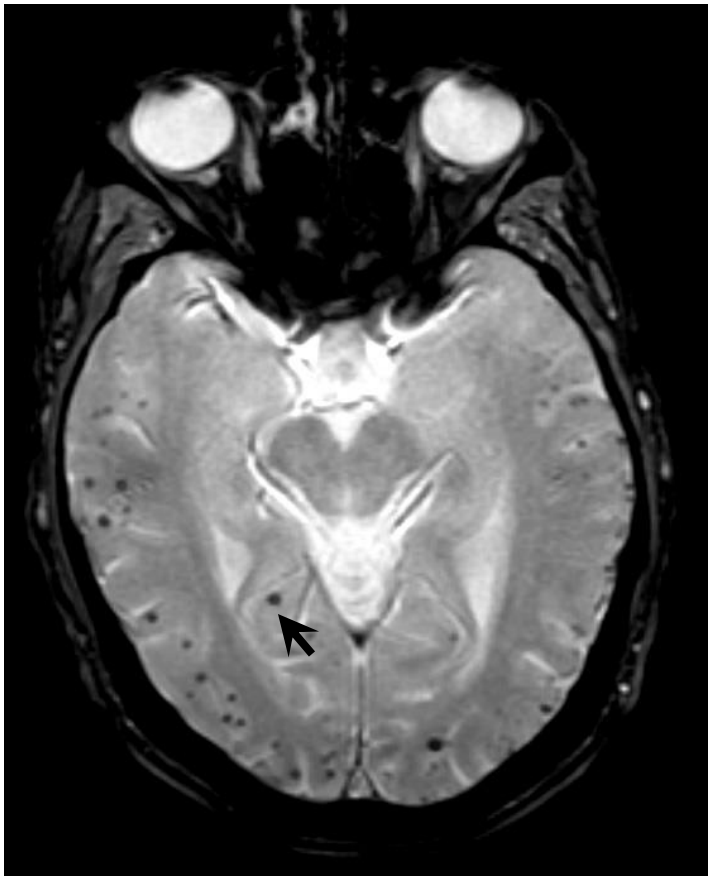


What is CAA?

Cerebral microbleeds



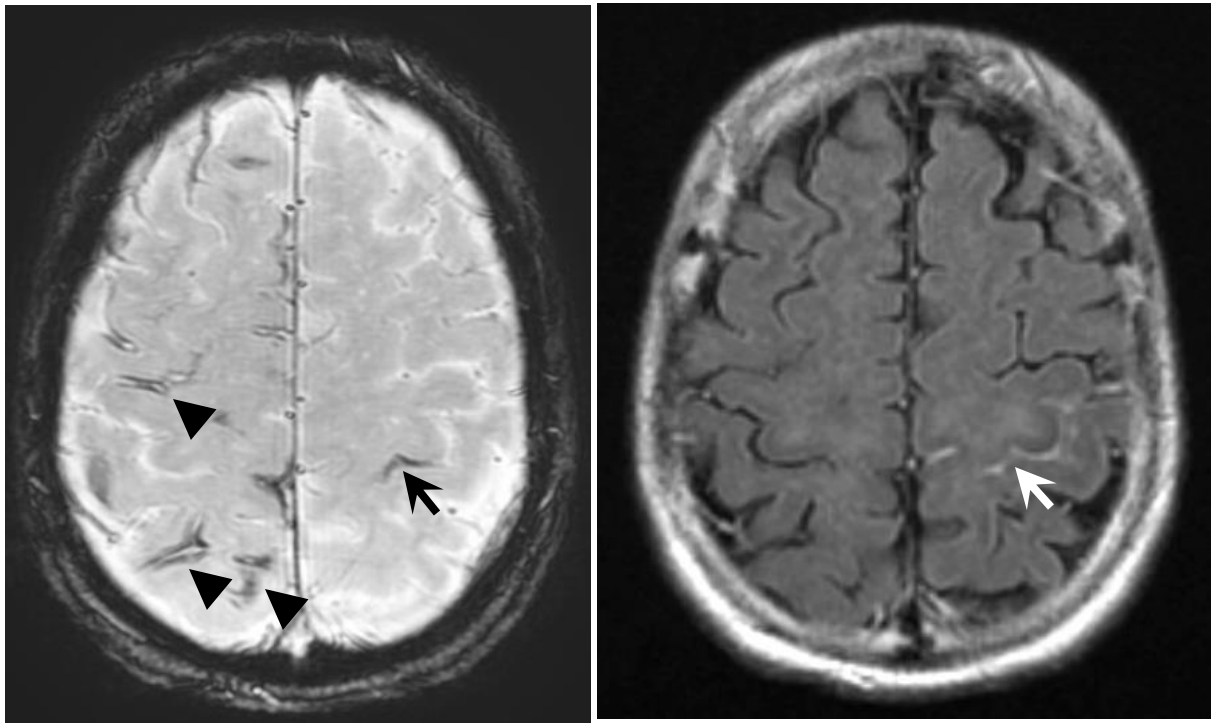
Probable HTN



Probable CAA

What is CAA?

Cortical superficial siderosis (cSS) & convexity subarachnoid hemorrhage (cSAH)

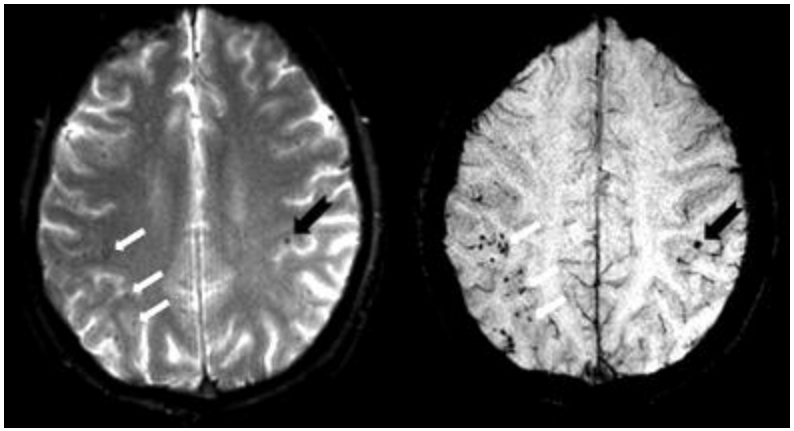


T2*

FLAIR

What is CAA?
T2*-weighted MRI for hemorrhage detection

- Conventional GRE methods
- Thinner scanning sections, increased magnetic field strength
- Image post-processing (susceptibility-weighted imaging, SWI)
- Multiple TE's (susceptibility-weighted angiography, SWAN)



Clinical T2* Thin Slice SWI

Nandigam, Greenberg, Dickerson
AJNR 2009;30:338

Boston Criteria for CAA-related Hemorrhage v1.5

Definite CAA

Full postmortem exam with severe CAA

Probable CAA with Supporting Pathology

Evacuated specimen showing CAA

Probable CAA (modified)

- Multiple (≥2) bleeds/microbleeds/cSS
- Strictly lobar/corticosubcortical location
- No other cause

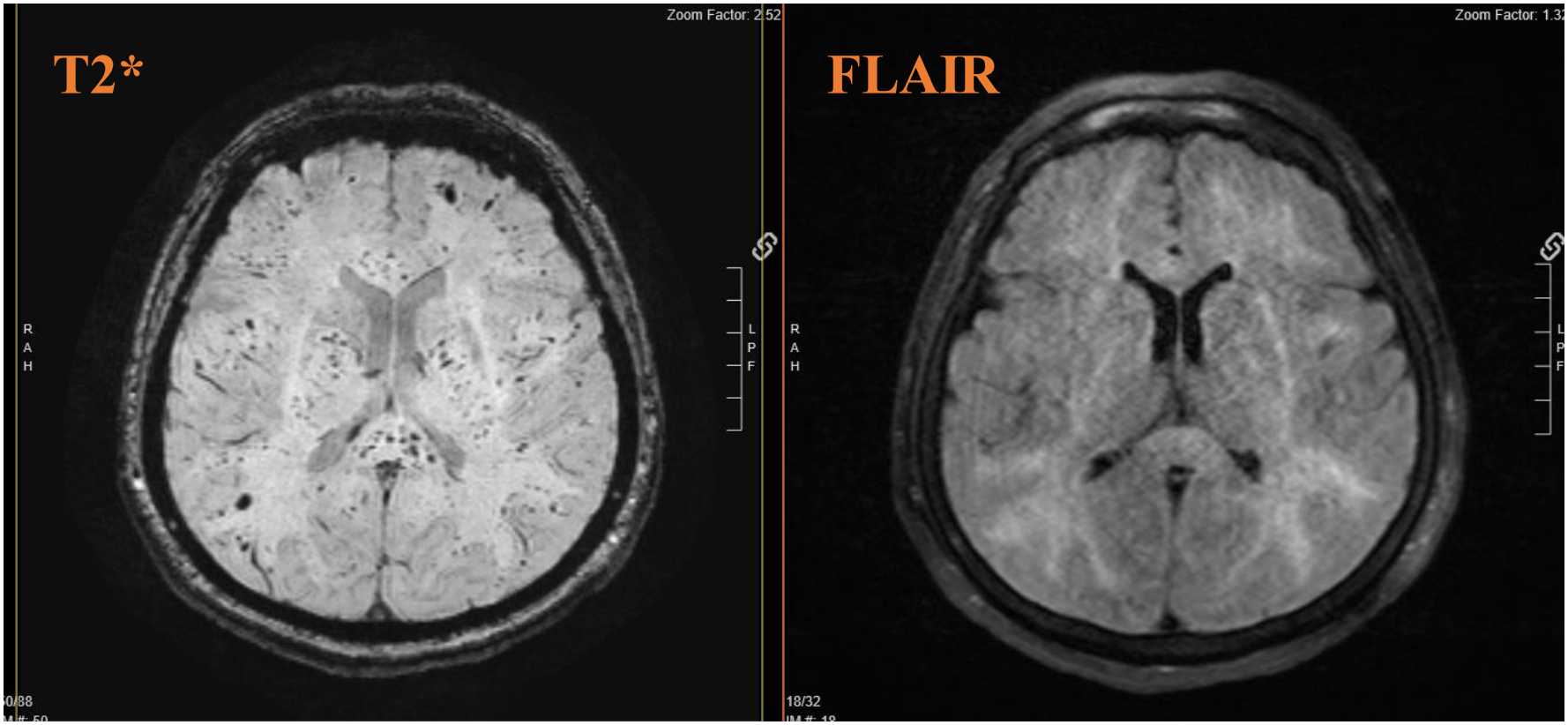
Possible CAA

Single lobar bleed, no other cause

Linn *Neurology* 2010;74:1346

What is CAA?

COVID19- (not CAA-) related microbleeds

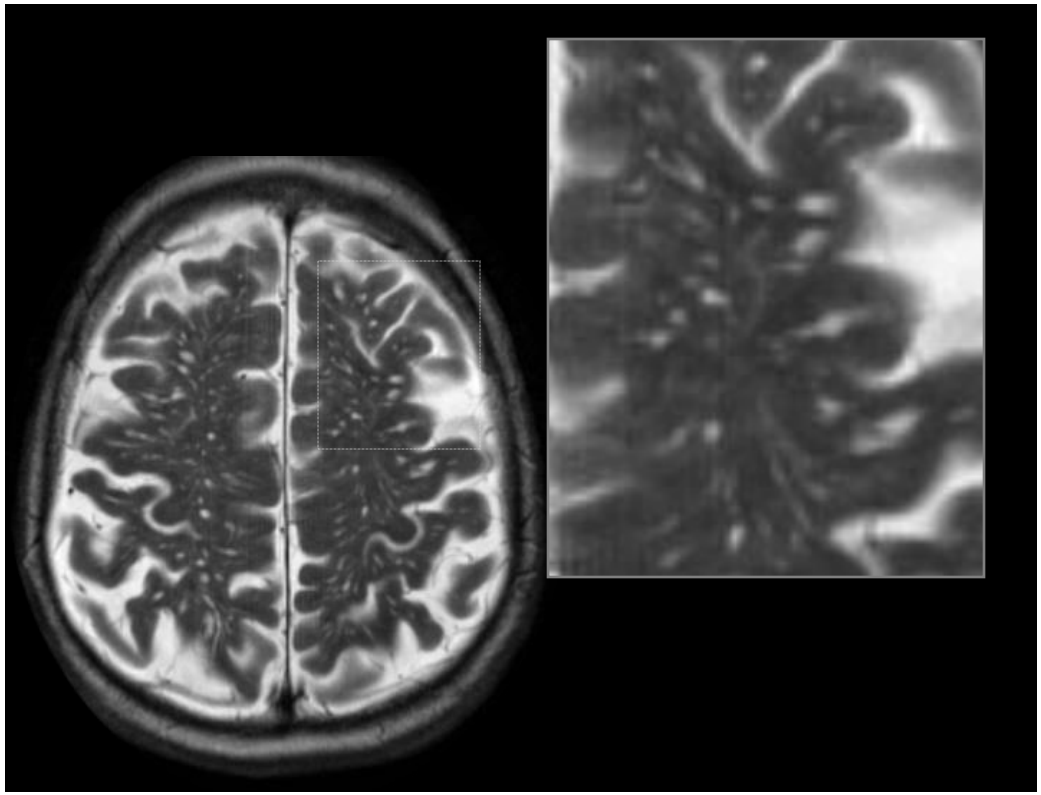


71 yr old woman admitted with COVID19 pneumonia, persistent agitation and encephalopathy

What is CAA?

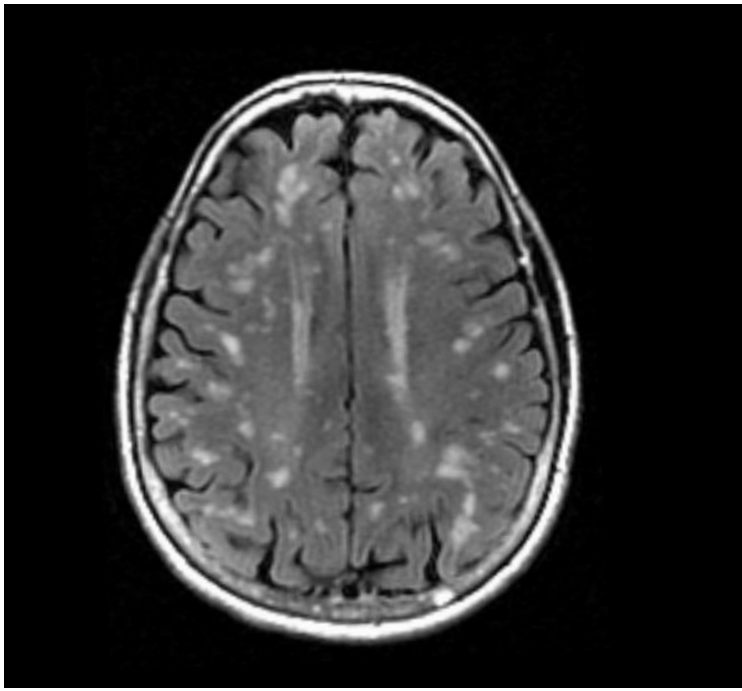
Emerging white matter lesions

Centrum semiovale
enlarged perivascular spaces



Charidimou, Werring *Neurology* 2014;82:57

Multiple subcortical spot
WMH pattern



Charidimou, Gurol *Neurology* 2016;86:505

What is CAA?
Boston Criteria v2.0

Probable CAA

- ≥2 strictly lobar hemorrhagic lesions in any combination: ICH, CMBs, cSS/cSAH foci

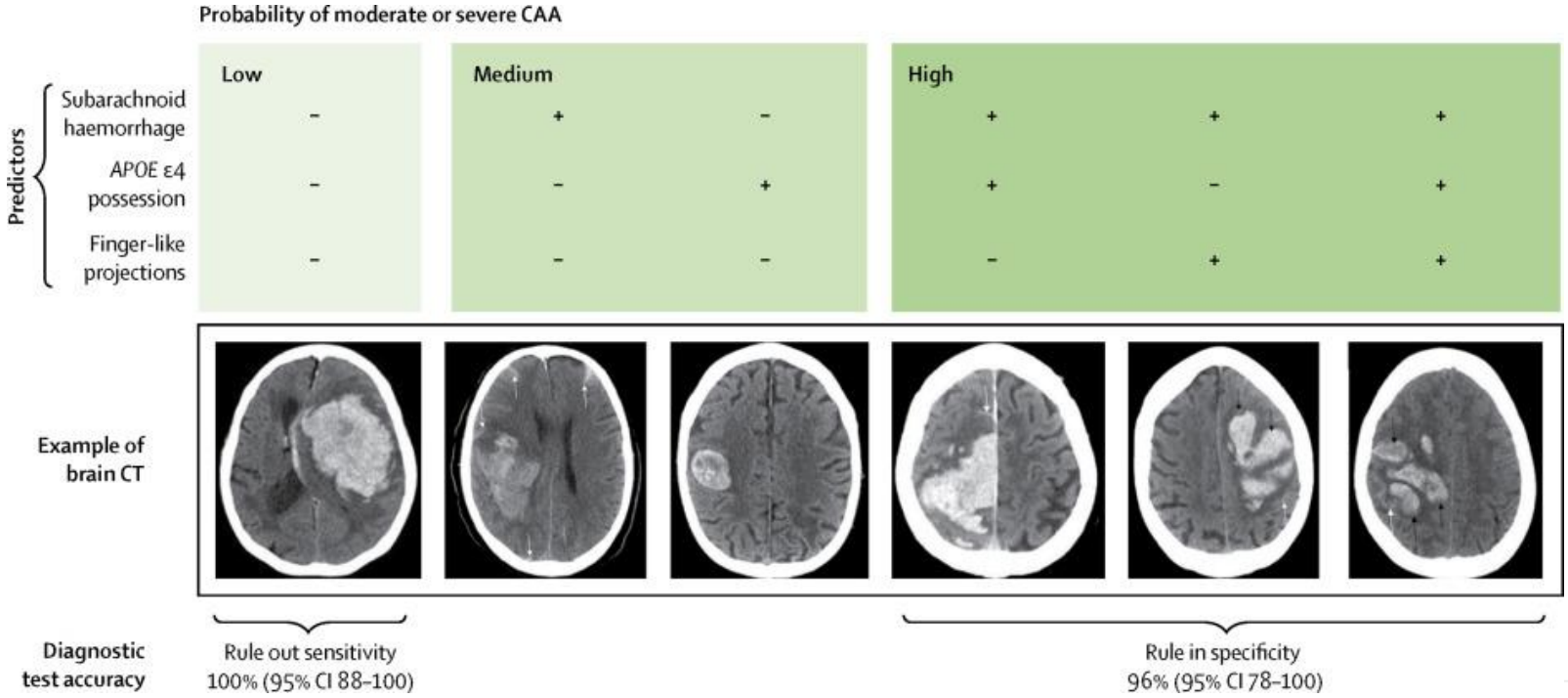
OR

- 1 strictly lobar hemorrhagic lesion + 1 WM feature (Severe CSO-PVS or multispot WMH pattern)

	Derivation (1994-2012) n=159	Temporal validation (2012-2018) n=59	Geographical validation n=123
Sensitivity	74.8% (65.4-82.7)	87.5% (73.2-95.8)	72.9% (62.9-81.5)
Specificity	84.6% (71.9-93.1)	100% (82.4-100)	85.2% (66.3-95.8)
AUC	0.797 (0.732-0.861)	0.938 (0.886-0.989)	0.791 (0.709-0.872)
PPV	90.9% (82.9-96)	100% (90-100)	94.6% (86.7-98.5)
NPV	62% (49.7-73.2)	79.2% (47.8-92.9)	46.9% (32.5-61.7)

Charidimou, Greenberg *Lancet Neurol* 2022; 21: 714

Can I diagnose CAA?
Edinburgh CT Criteria for CAA-ICH



	β coefficient (SE)	Odds ratio (95% CI)	p value
Intercept	–2·55 (0·89)	· ·	0·0040
APOE ε4 carrier	3·11 (1·01)	22 (4–862)	0·0020
Subarachnoid haemorrhage	2·31 (0·94)	10 (2–299)	0·014
Finger-like projections	3·20 (1·58)	27 (3–not reached)	0·043

Rodrigues, Al-Shahi Salman
Lancet Neurol 2018;17:232

CAA in the Era of Ischemic Stroke Treatments

1. What is CAA? Criteria for Diagnosis

- One of two common age-related small vessel diseases
- Boston criteria v2.0
  - Multiple strictly lobar bleeds/microbleeds/cSS
  - CSO-EPVS, WMH multispots
- Edinburgh CT criteria (ICH only)

CAA in the Era of Ischemic Stroke Treatments

1. What is CAA? Criteria for Diagnosis
2. Implications of CAA for anticoagulation

Implications for anticoagulation

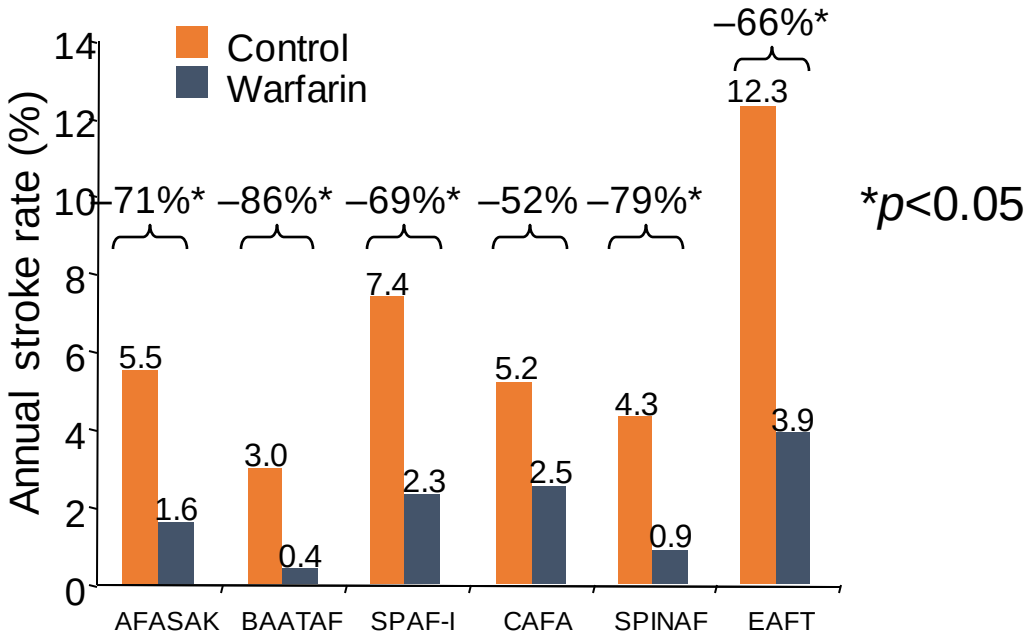
"If you are treating even one patient in your practice with anticoagulation, you should wake up once a week or so in a cold sweat."

-C. Miller Fisher, MD c. 1995

Implications for anticoagulation
Established indications

- Nonvalvular atrial fibrillation
- Valvular atrial fibrillation (defined as moderate-to-severe mitral stenosis or mechanical heart valve)
- Hypercoagulable state
- ?Heart failure (EF<35%)

Implications for anticoagulation
Benefits: Prevention of AFib-related stroke



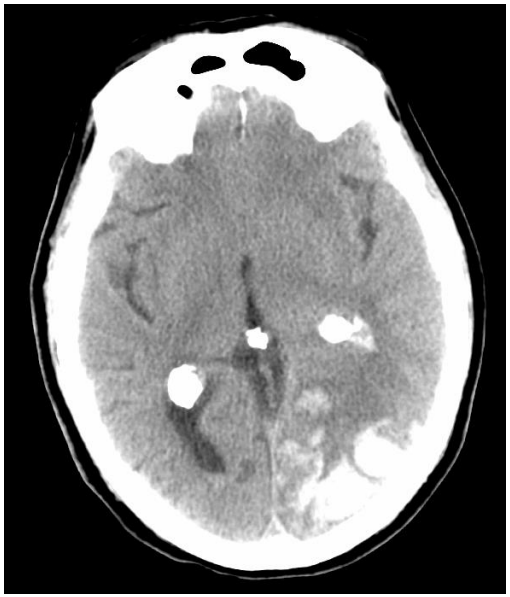
*$p<0.05$

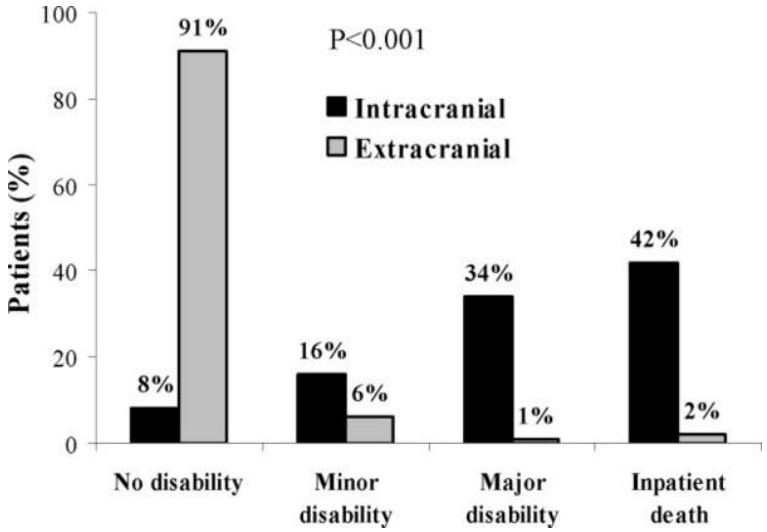
	Relative Risk Reduction
Warfarin (INR 1.8-4.2)	68% (50-79%)
Aspirin (75-325 mg)	21% (0-38%)

Go *Progr Cardiovasc Dis* 2005;48:108 Pooled analysis *Arch Intern Med* 1994;154:1449

Implications for anticoagulation
Risks: Intracranial hemorrhage

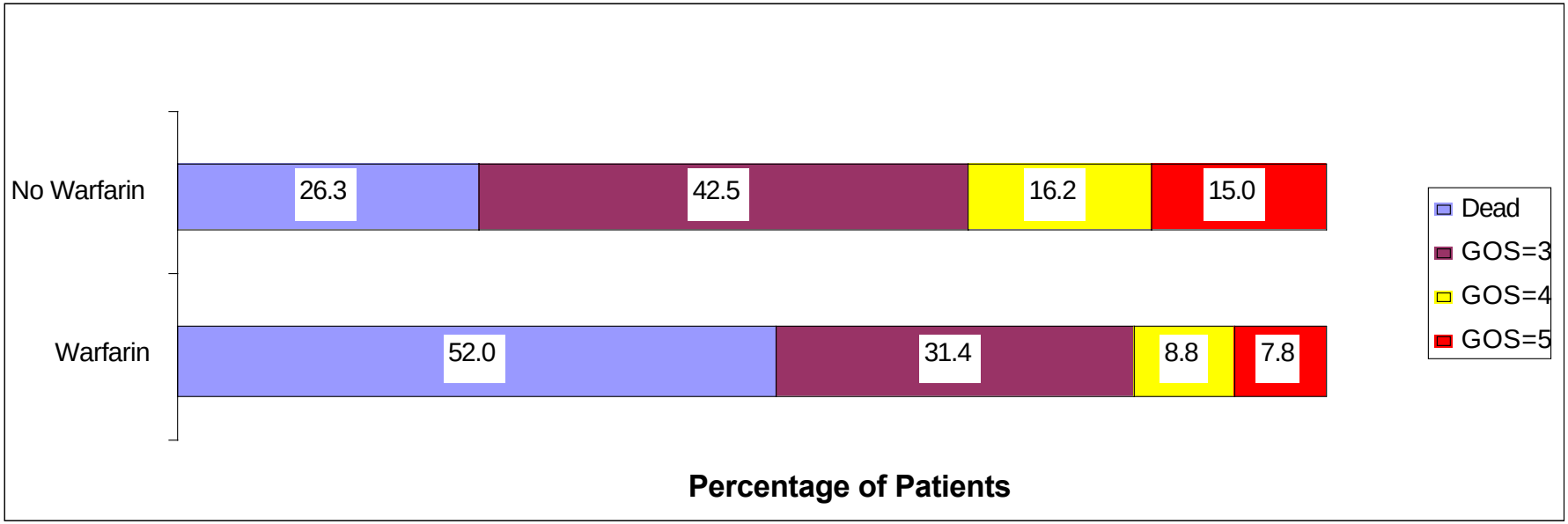
- Intracerebral hemorrhage
- Subdural hemorrhage
- "Major" extracranial hemorrhage, e.g. requiring transfusion





Fang *Am J Med* 2007;120:700

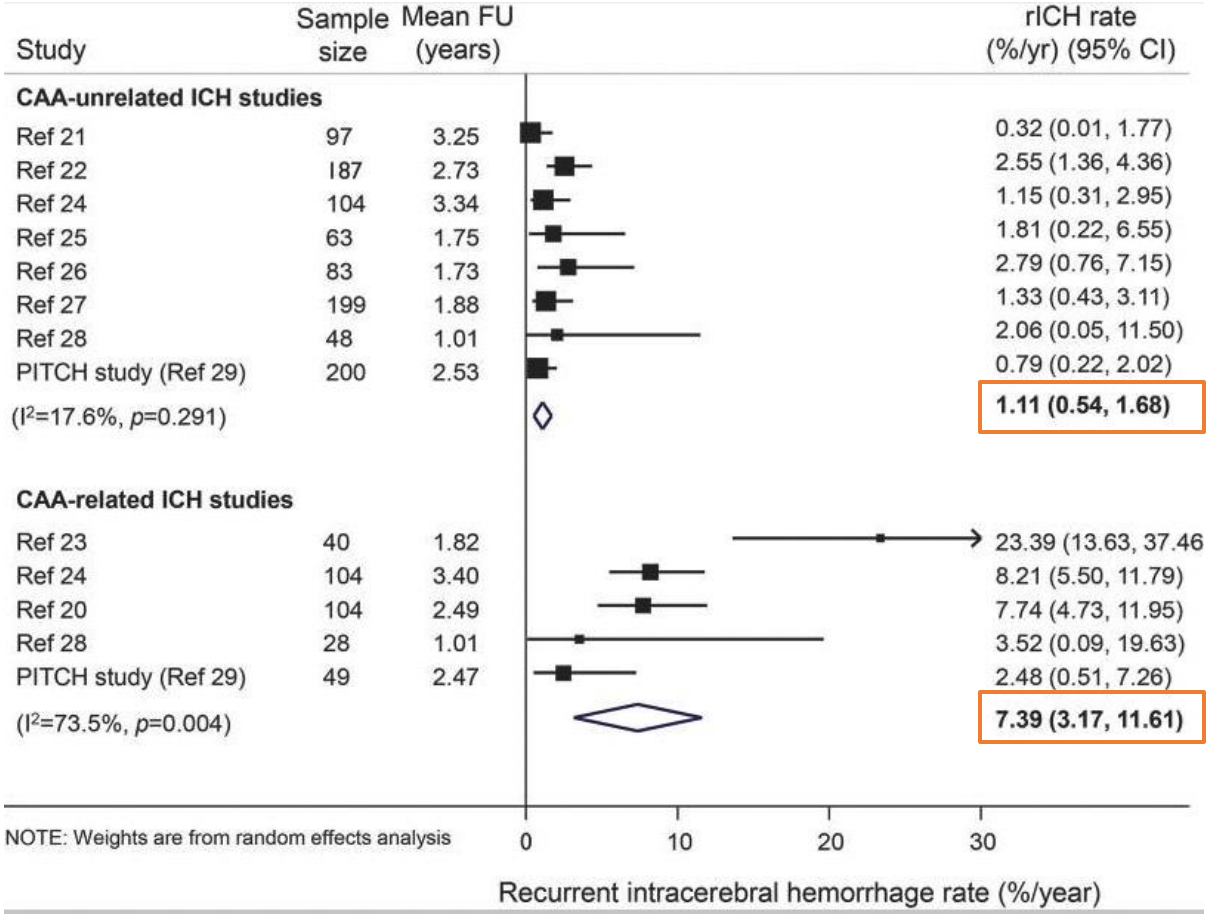
Implications for anticoagulation
ICH 3-month outcome

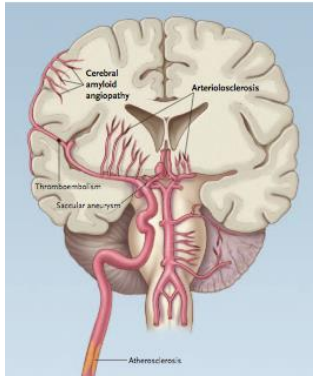


Rosand *Arch Int Med* 2004;164:880

Implications for anticoagulation

ICH recurrence CAA >> arteriolosclerosis





Charidimou, Werring *Neurology* 2017; 89:820

Implications for anticoagulation

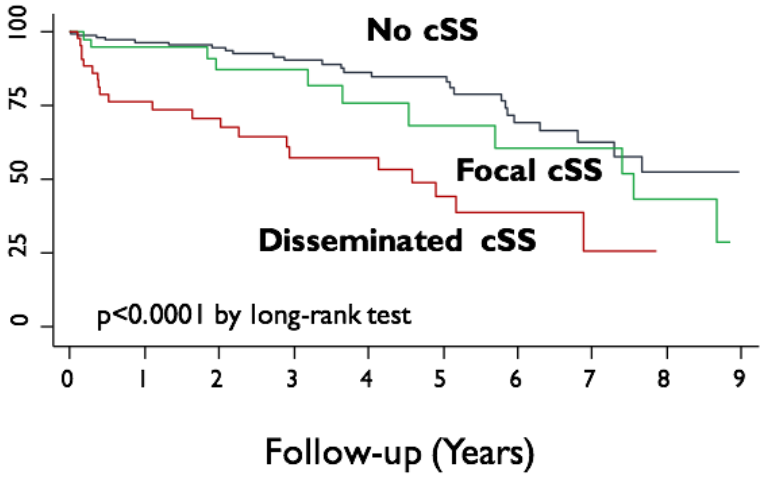
Predictors of CAA-related recurrence

Increased risk

- CAA
- Prior ICHs
- Disseminated cSS
- Abundant microbleeds
- Higher blood pressures
- (APOE ε2/ε4)

Decreased risk

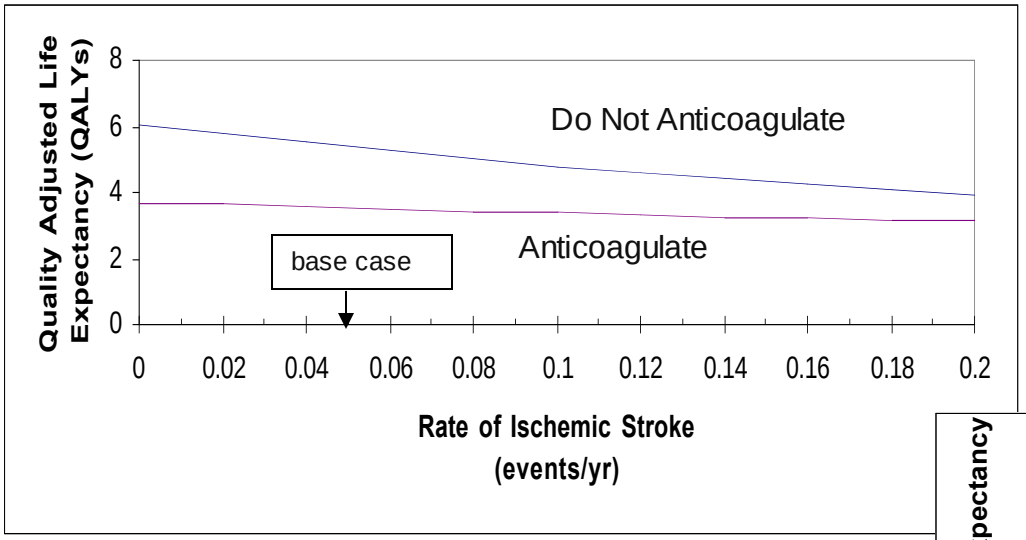
- Microbleeds only



Charidimou *Int J Stroke* 2019;14:723

Can Patients be Anticoagulated After CAA-ICH?

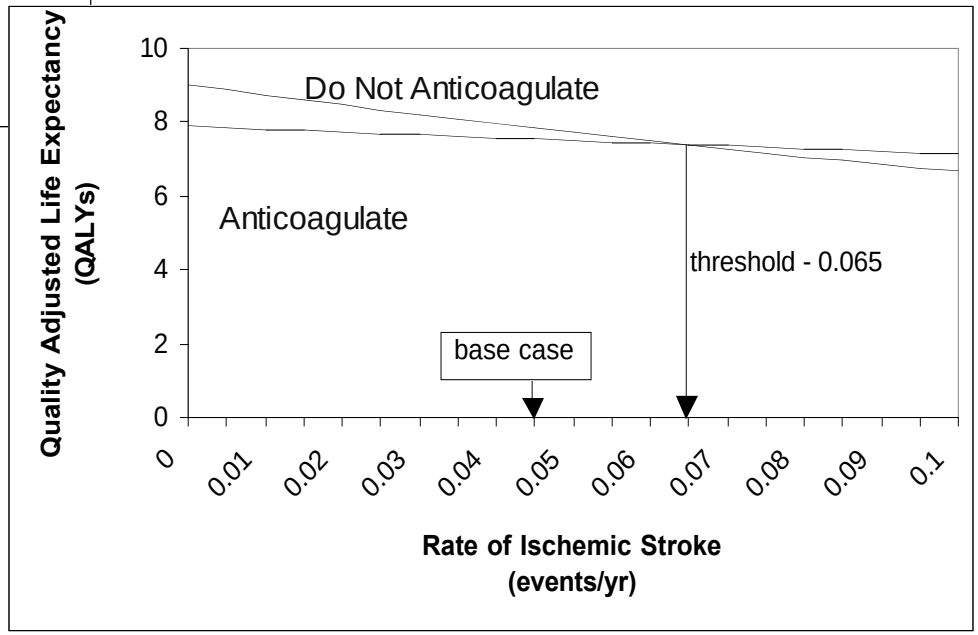
Decision analysis says *no*



Eckman *Stroke* 2003;34:1710

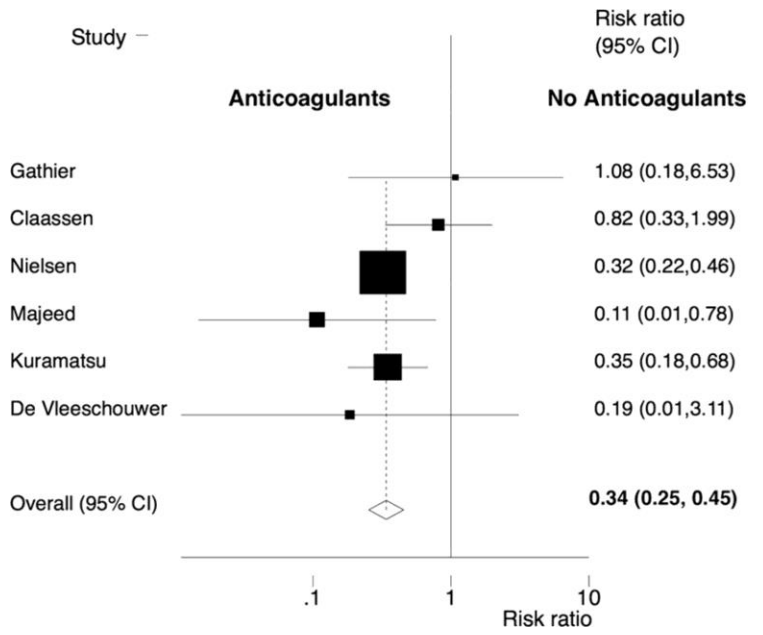
Lobar ICH

Deep hemispheric ICH



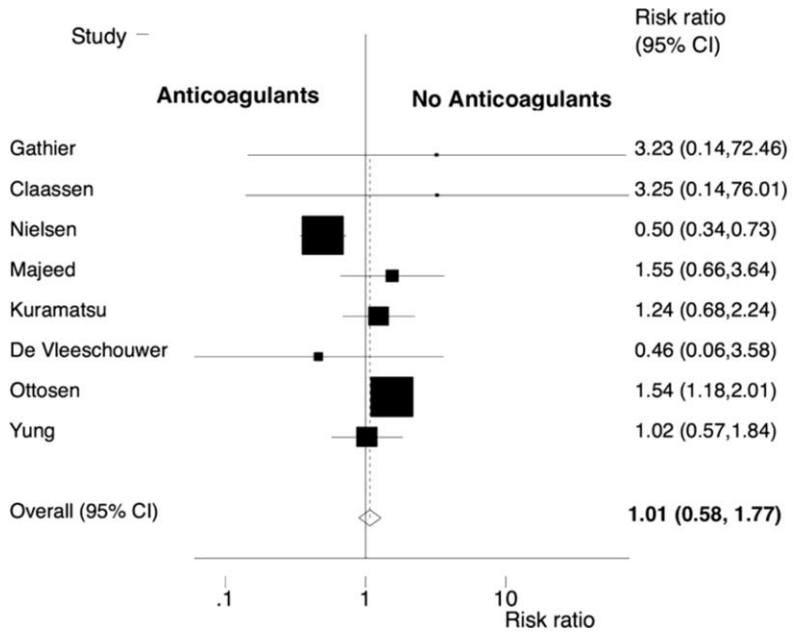
Can Patients be Anticoagulated After CAA-ICH?

Retrospective series say *maybe*



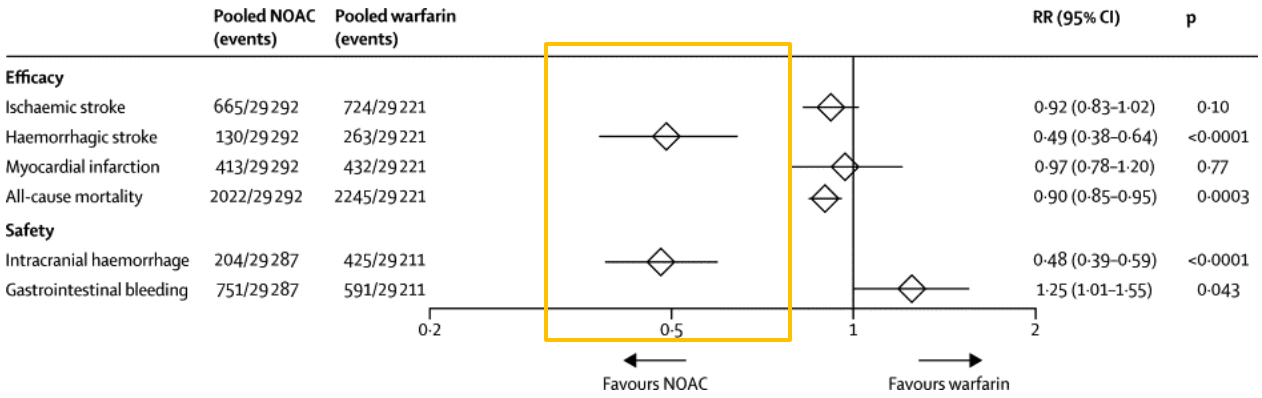
Thromboembolic stroke

Recurrent ICH

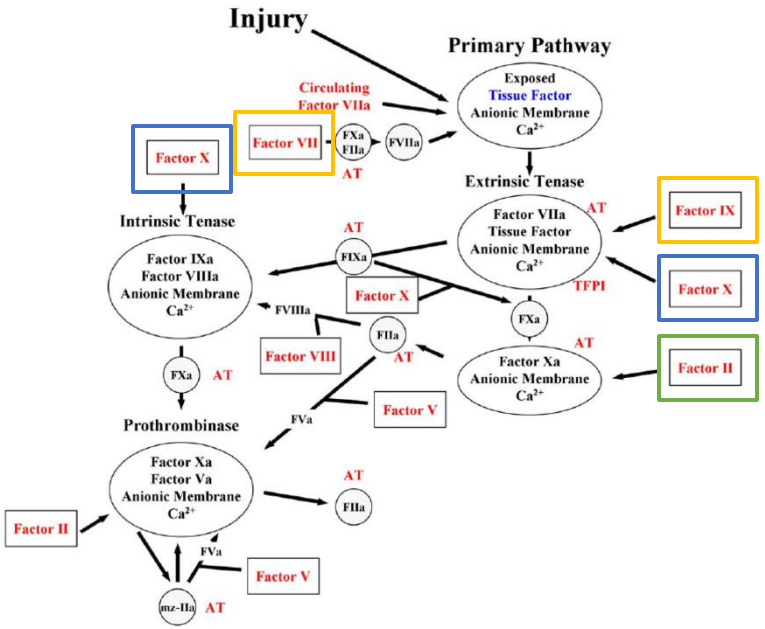


Murthy, Kamel *Stroke* 2017; 48:1594

Implications for anticoagulation
DOACs vs warfarin: reduced ICH

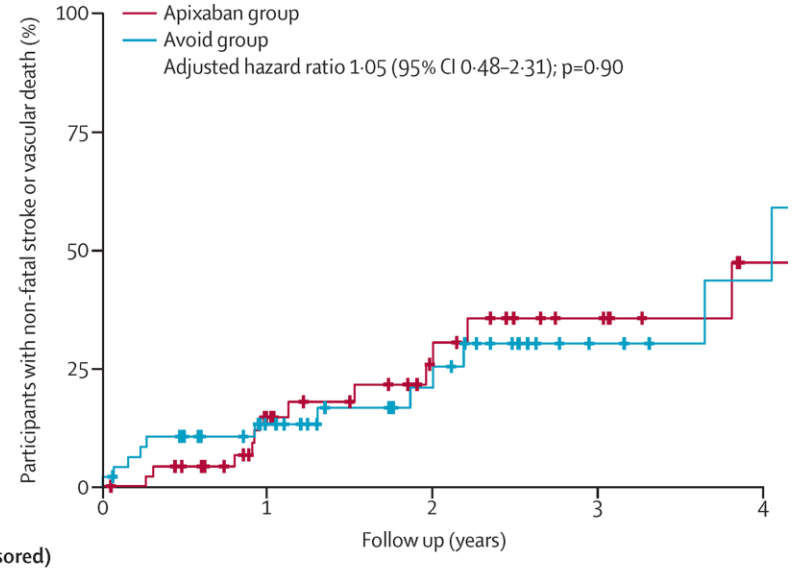


Ruff *Lancet* 2014;383:955



Acronym	Methods	Population	Experimental arm	Control arm
APACHE-AF 	PROBE RCT	≥18 years with anticoagulant-associated ICH, AF and CHA2DS2-VASc score≥3	**Apixaban**	APT or no antithrombotic
NASPAF-ICH 	PROBE RCT	≥45 years with Prior ICH and high-risk AF indicated by CHADS65	**Any NOAC**	Aspirin
SoSTART 	PROBE RCT	Spontaneous ICH, AF, and CHA2DS2-VASc score≥2	**Any OAC**	APT or no antithrombotic
STATICH 	PROBE RCT	Spontaneous ICH	**APT or any OAC**	No antithrombotic
A_3ICH 	PROBE RCT	ICH, AF, and a CHA2DS2-VASc score≥2	i) **Apixaban** ii) **LAAO**	APT or no antithrombotic
PRESTIGE AF 	PROBE RCT	ICH, AF CHA2DS2-VASc score≥2	**Any NOAC**	APT or no antithrombotic
ASPIRE 	Double-Blind RCT	ICH, AF CHA2DS2-VASc score≥2	**Apixaban**	Aspirin
ENRICH-AF 	PROBE RCT	ICH, AF CHA2DS2-VASc score≥2	**Edoxaban**	APT or no antithrombotic

Anticoagulation after ICH
APACHE-AF trial



Patients at risk (censored)					
Apixaban group	50 (0)	34 (10)	22 (19)	13 (26)	6 (32)
Avoid group	51 (0)	35 (10)	23 (20)	10 (31)	7 (33)
Cumulative number of events					
Apixaban group	0	6	9	11	12
Avoid group	0	6	8	10	11

	Apixaban group (n=50)		Avoid anticoagulation group (n=51)	
	Patients with first event	All events	Patients with first event	All events
Primary outcome				
Non-fatal stroke or vascular death	13 (26%)	14	12 (24%)	12
Secondary outcomes				
Major haemorrhagic events	6 (12%)	6	3 (6%)	3
Intracerebral haemorrhage	4 (8%)	4	1 (2%) *	1
Subarachnoid haemorrhage	0	0	0	0
Traumatic intracranial haemorrhage	0	0	0	0
Major extracranial haemorrhage	2 (4%)	2	2 (4%)	2
Clinically relevant non-major bleeding	1 (2%)	1	0	0
Major occlusive events	6 (12%)	7	11 (22%) †	12
Ischaemic stroke	6 (12%)	7	6 (12%)	6
Myocardial infarction	0	0	2 (4%)	2
Pulmonary embolism ‡	0	0	4 (8%)	4
Systemic embolism	0	0	0	0
Unclassified stroke	0	0	0	0
Any stroke	10 (20%)	11	7 (14%)	7
Vascular death	5 (10%)	5	7 (14%)	7
All-cause death	9 (18%)	9	11 (22%)	11

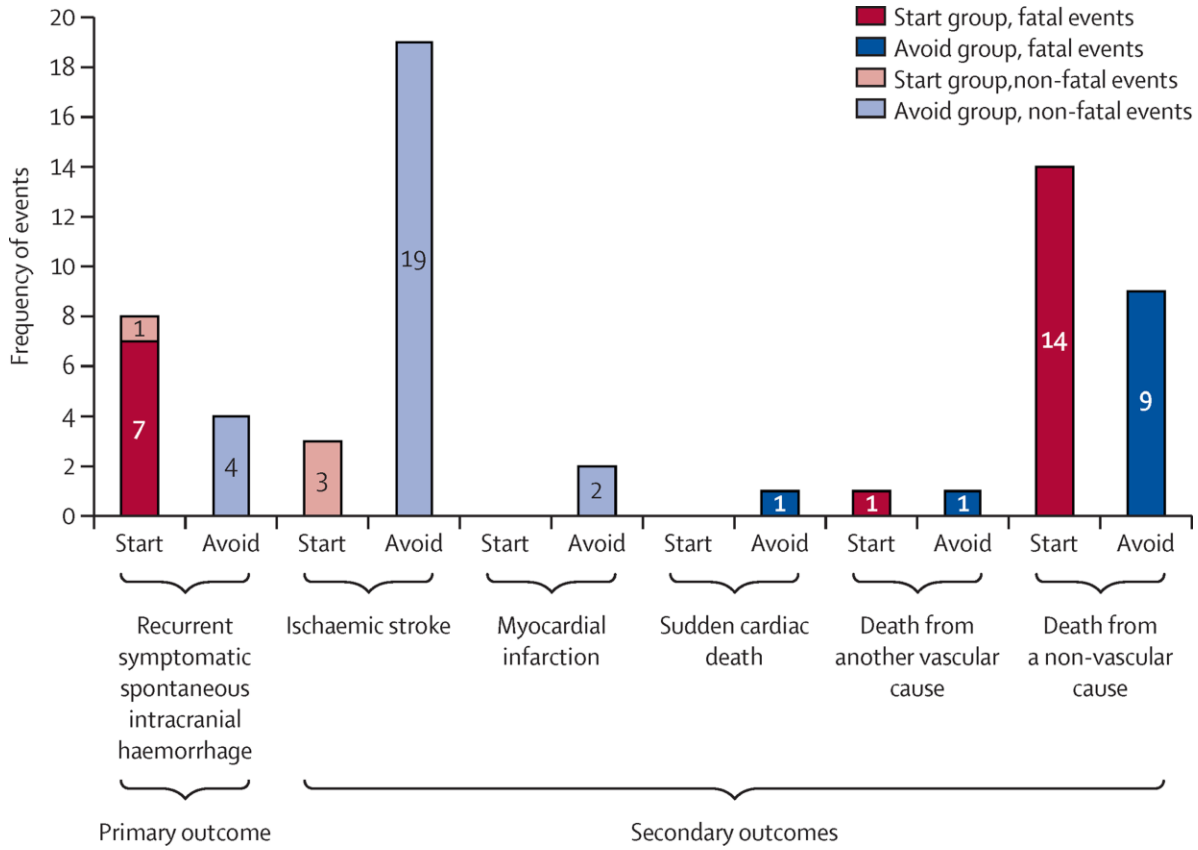
* Event occurred while on treatment with rivaroxaban that had been prescribed because of pulmonary embolism at an earlier timepoint during follow-up.

† One patient had a pulmonary embolism and then an ischaemic stroke later.

‡ Not prespecified as a secondary outcome.

Schreuder, Klijn *Lancet Neurol* 2021;20:907

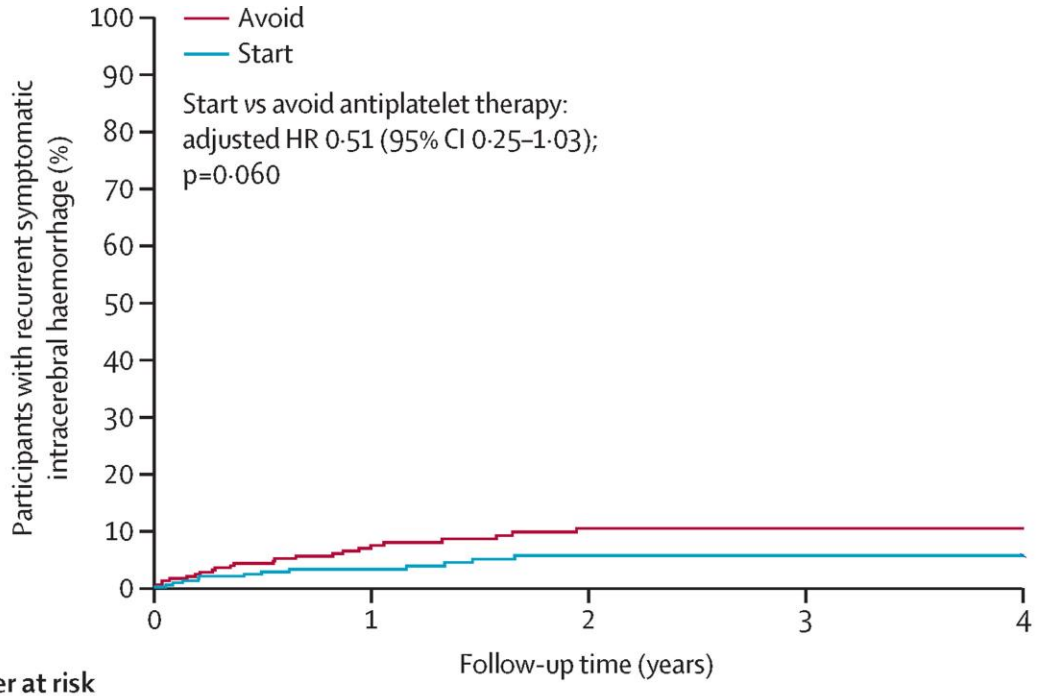
Anticoagulation after ICH
SoSTART trial



taking an oral anticoagulant), whereas after allocation to avoid oral anticoagulation, none of the four primary outcomes were fatal (two participants were taking an oral anticoagulant; figure 2 ; appendix pp 16–19

Al-Shahi Salman/SoSTART collaborators *Lancet Neurol* 2021;20:842

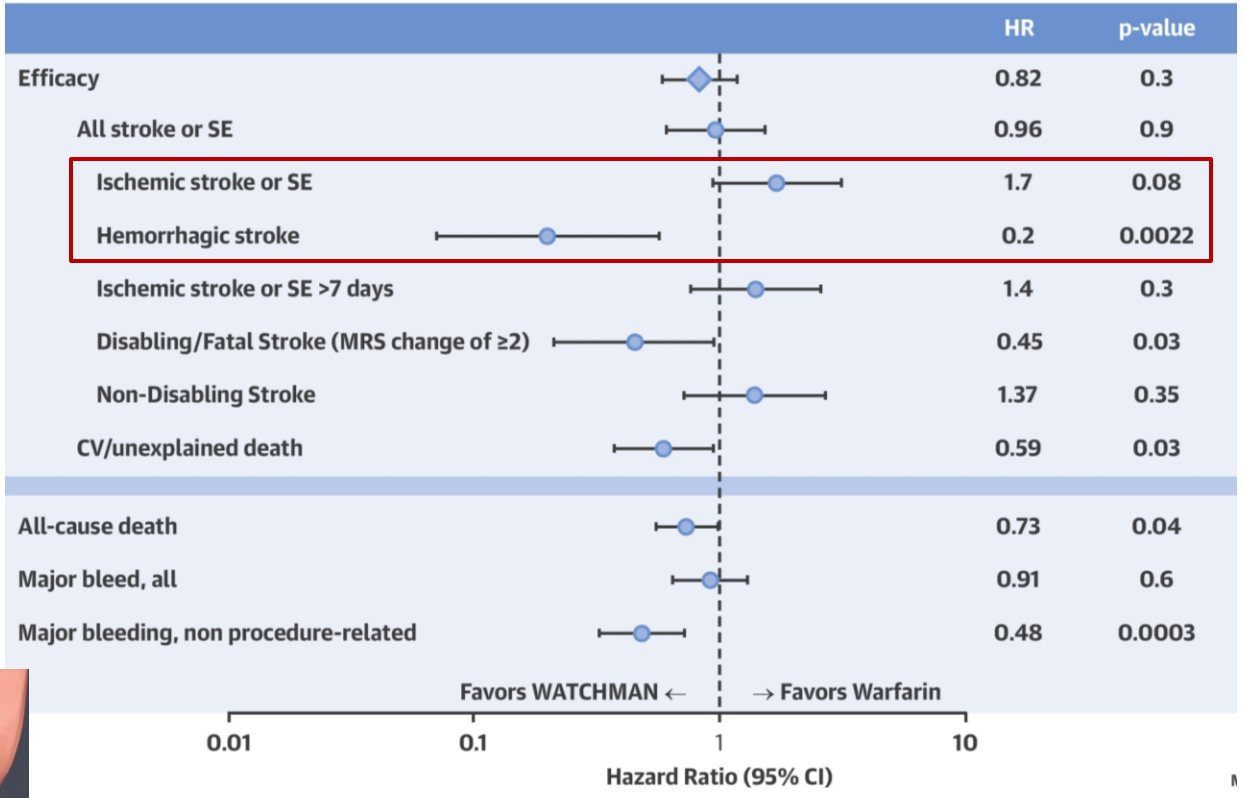
Antiplatelets after ICH
RESTART trial

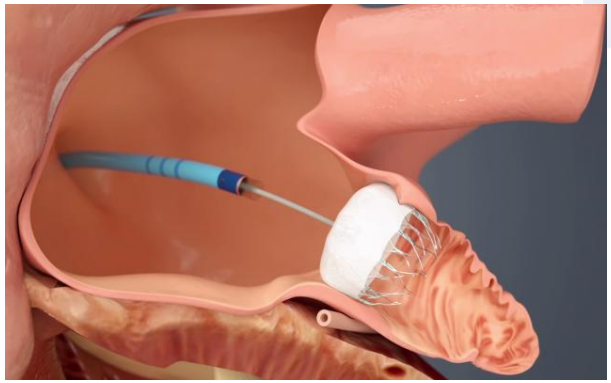


Number at risk (number of cumulative events)					
Avoid	268 (0)	184 (18)	121 (23)	73 (23)	22 (23)
Start	268 (0)	190 (8)	122 (12)	72 (12)	25 (12)

Al-Shahi Salman/RESTART collaborators *Lancet* 2019;393:2613

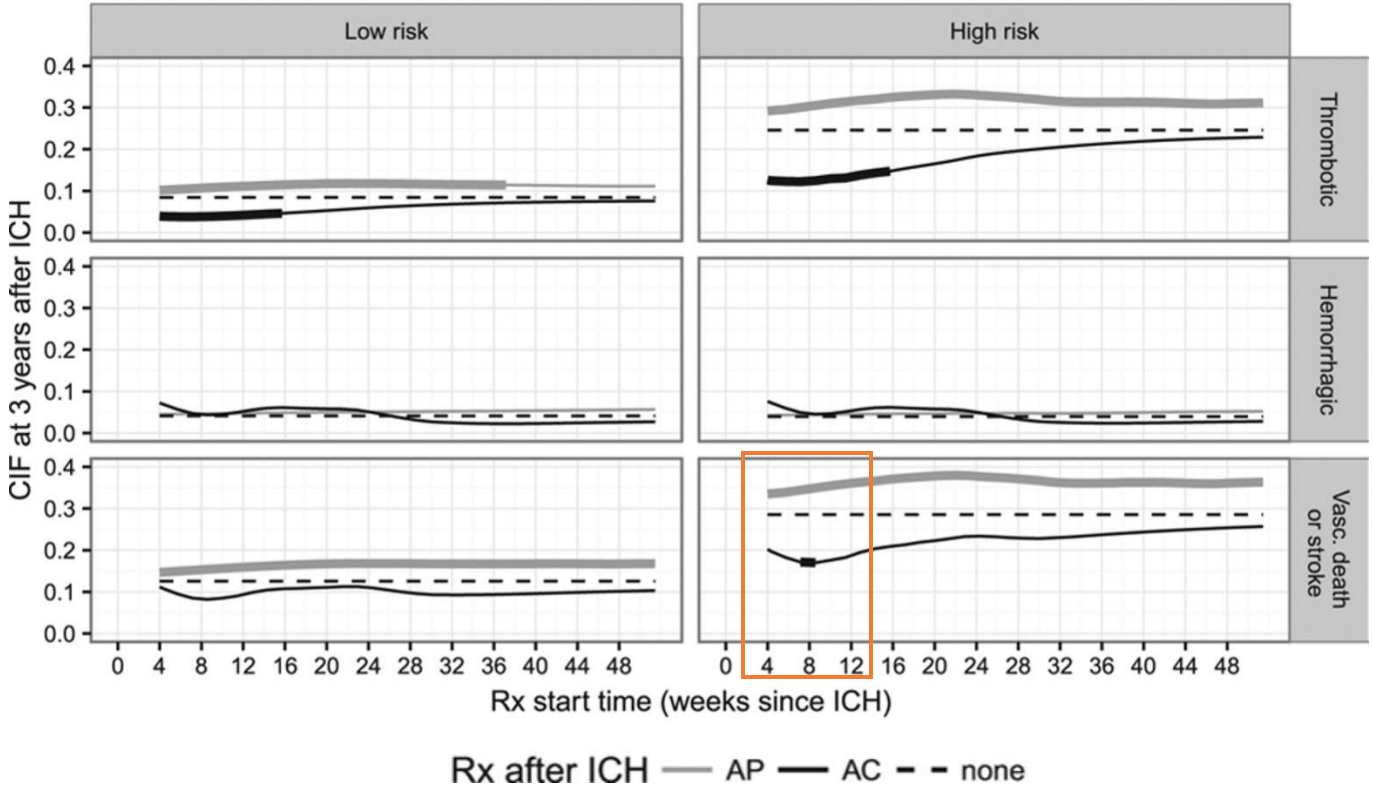
Alternatives to anticoagulation
Left atrial appendage closure





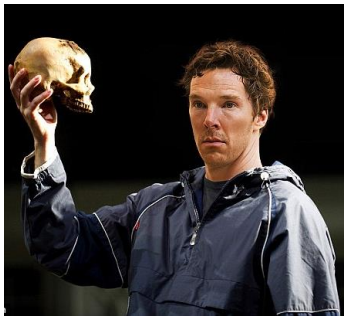
Reddy *J Am Coll Cardio* 2017;70:2964

Resuming Anticoagulation after Brain Hemorrhage
If yes when?



Pennlert *Stroke* 2017;48:314

CAA in the Era of Ischemic Stroke Treatments



1. What is CAA? Criteria for Diagnosis

2. Implications of CAA for anticoagulation
   - Each decision is personalized weighing of risks vs benefits
   - Diagnosis of CAA markedly increases ICH risk, with variation according to CAA features
   - Depending on embolic vs hemorrhagic risk, DOAC, antiplatelet, or LAAC may be rational options. Warfarin probably not.
   - Defined treatment period less risky than indefinite
   - Minimize other sources or risk eg BP control <130/80 mmHg
   - No recommendation that MRI should be performed pre-anticoagulation

CAA in the Era of Ischemic Stroke Treatments

1. What is CAA? Criteria for Diagnosis
2. Implications of CAA for anticoagulation
3. Implications for thrombolysis
   - Acute ICH = absolute contraindication
   - Remote ICH generally considered relative contraindication
   - No consensus re microbleeds

Implications for thrombolysis
Microbleeds and tPA-related parenchymal hematoma

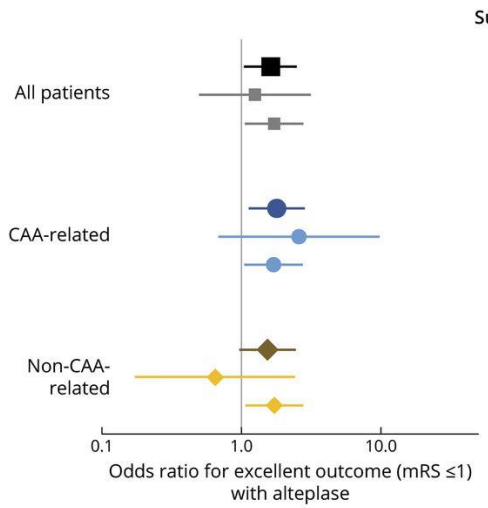
Table 4. Adjusted ORs (95% CI) for CMB Distribution and the Risk of ICH After Intravenous Thrombolysis

	Symptomatic ICH (per ECASS-2 Definition) OR (95% CI)		PH (vs No or Non-PH ICH)* (per ECASS-2 Definition) OR (95% CI)		PHr (Remote Parenchymal ICH vs No or Nonremote ICH) OR (95% CI)	
CAA-related CMBs Models	n=1458		n=1311		n=1458	
CAA-related CMBs presence Model	1.14 (0.49–2.67)		1.78 (1.05–3.00)†		3.26 (1.54–6.91)‡	
Main Model (CAA-related CMBs categorized by burden)						
Single CMB	0.65 (0.19–1.19)		1.42 (0.75–2.68)		2.18 (0.85–5.61)	
2–4 CMBs	2.67 (0.74–9.66)	Overall *P*=0.113	2.39 (0.91–6.27)	Overall *P*=0.06	4.89 (1.51–15.82)†	Overall *P*=0.001
≥5 CMBs	2.31 (0.24–22.19)		4.77 (1.03–22.05)†		16.40 (2.87–93.58)‡	
Log CMBs number model	1.49 (0.74–2.98)		2.06 (1.32–3.21)‡		3.77 (2.12–6.71)§	
Non-CAA–related CMBs models	n=1538		n=1386		n=1538	
Non-CAA–related CMBs presence model	1.62 (0.89–2.96)		1.77 (1.55–2.70)†		2.99 (1.56–5.72)‡	
Main model (Non-CAA–related CMBs categorized by burden)						
Single CMB	1.20 (0.46–3.15)		0.94 (0.45–1.97)		1.35 (0.40–4.60)	
2–4 CMBs	2.79 (1.23–6.34)†	Overall *P*=0.123	2.06 (1.06–4.01)†	Overall *P*=0.006	3.62 (1.48–8.84)†	Overall *P*=0.003
5–10 CMBs	0.58 (0.08–4.38)		3.16 (1.45–6.86)‡		3.95 (1.24–12.56)†	
>10 CMBs	1.87 (0.41–8.51)		2.63 (0.99–7.01)		5.61 (1.71–18.36)‡	
Log CMBs number model	1.25 (0.88–1.76)		1.47 (1.16–1.87)‡		1.85 (1.37–2.50)§	

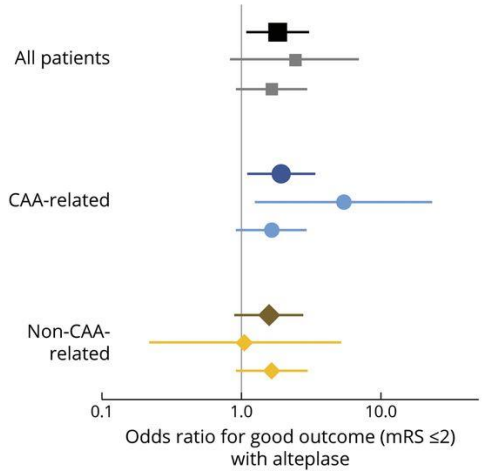
Charidimou, Werring *Stroke* 2017;48:2084

Implications for thrombolysis

Microbleeds and tPA-related outcome



Subgroup	Placebo	Alteplase	OR (95% CI)	p*
All patients				
All	**99/222 (44.6%)**	**124/227 (54.6%)**	**1.61 (1.07–2.43)**	**0.022**
≥1 CMB	19/44 (43.2%)	25/52 (48.1%)	1.26 (0.51–3.09)	0.546
No CMB	80/178 (44.9%)	99/175 (56.6%)	1.72 (1.09–2.72)	
CAA-related				
All	**86/200 (43.0%)**	**112/205 (54.6%)**	**1.79 (1.16–2.75)**	**0.008**
≥1 CMB	6/22 (27.3%)	13/30 (43.3%)	2.60 (0.70–9.60)	0.553
No CMB	80/178 (44.9%)	99/175 (56.6%)	1.71 (1.08–2.70)	
Non-CAA-related				
All	**93/200 (46.5%)**	**111/197 (56.3%)**	**1.54 (1.00–2.37)**	**0.048**
≥1 CMB	13/22 (59.1%)	12/22 (54.5%)	0.65 (0.18–2.39)	0.169
No CMB	80/178 (44.9%)	99/175 (56.6%)	1.72 (1.09–2.72)	

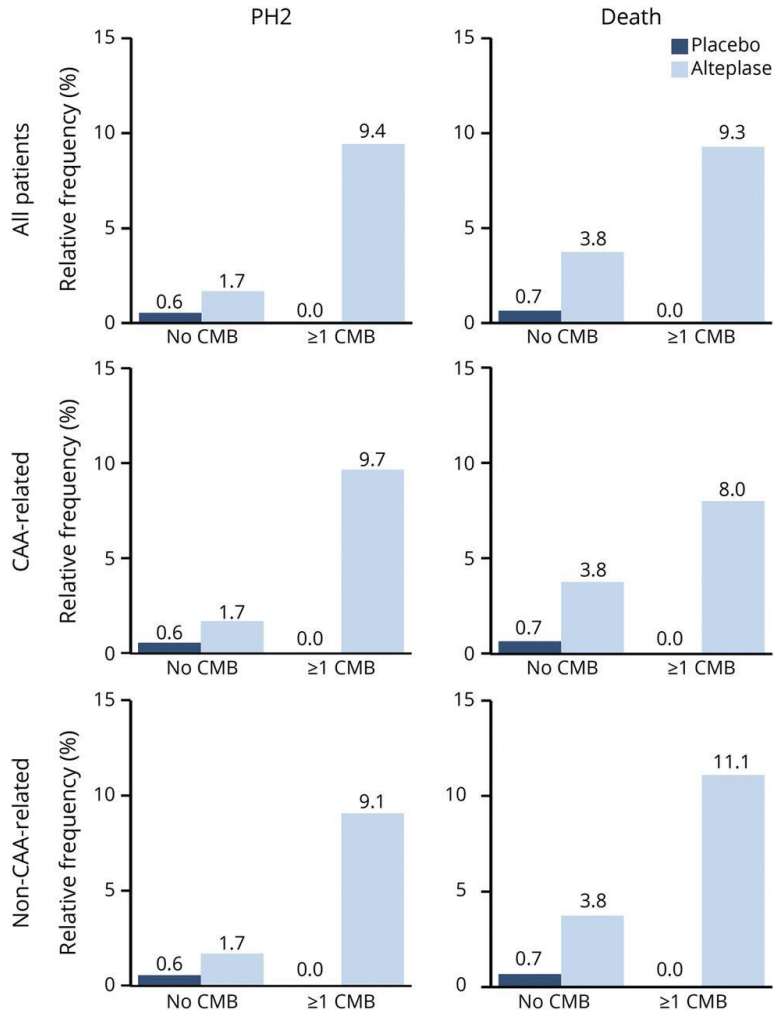


All patients				
All	**151/222 (68.0%)**	**173/227 (76.2%)**	**1.79 (1.08–2.95)**	**0.023**
≥1 CMB	25/44 (56.8%)	37/52 (71.2%)	2.40 (0.85–6.81)	0.528
No CMB	126/178 (70.8%)	136/175 (77.7%)	1.64 (0.93–2.89)	
CAA-related				
All	**135/200 (67.5%)**	**156/205 (76.1%)**	**1.91 (1.13–3.25)**	**0.016**
≥1 CMB	9/22 (40.9%)	20/30 (66.7%)	5.35 (1.27–22.58)	0.131
No CMB	126/178 (70.8%)	136/175 (77.7%)	1.63 (0.93–2.87)	
Non-CAA-related				
All	**142/200 (71.0%)**	**153/197 (77.7%)**	**1.55 (0.91–2.64)**	**0.104**
≥1 CMB	16/22 (72.7%)	17/22 (77.3%)	1.04 (0.22–5.00)	0.595
No CMB	126/178 (70.8%)	136/175 (77.7%)	1.64 (0.93–2.88)	

WAKE-UP Trial Schlemm *Neurology* 2022;98:e302

Implications for thrombolysis

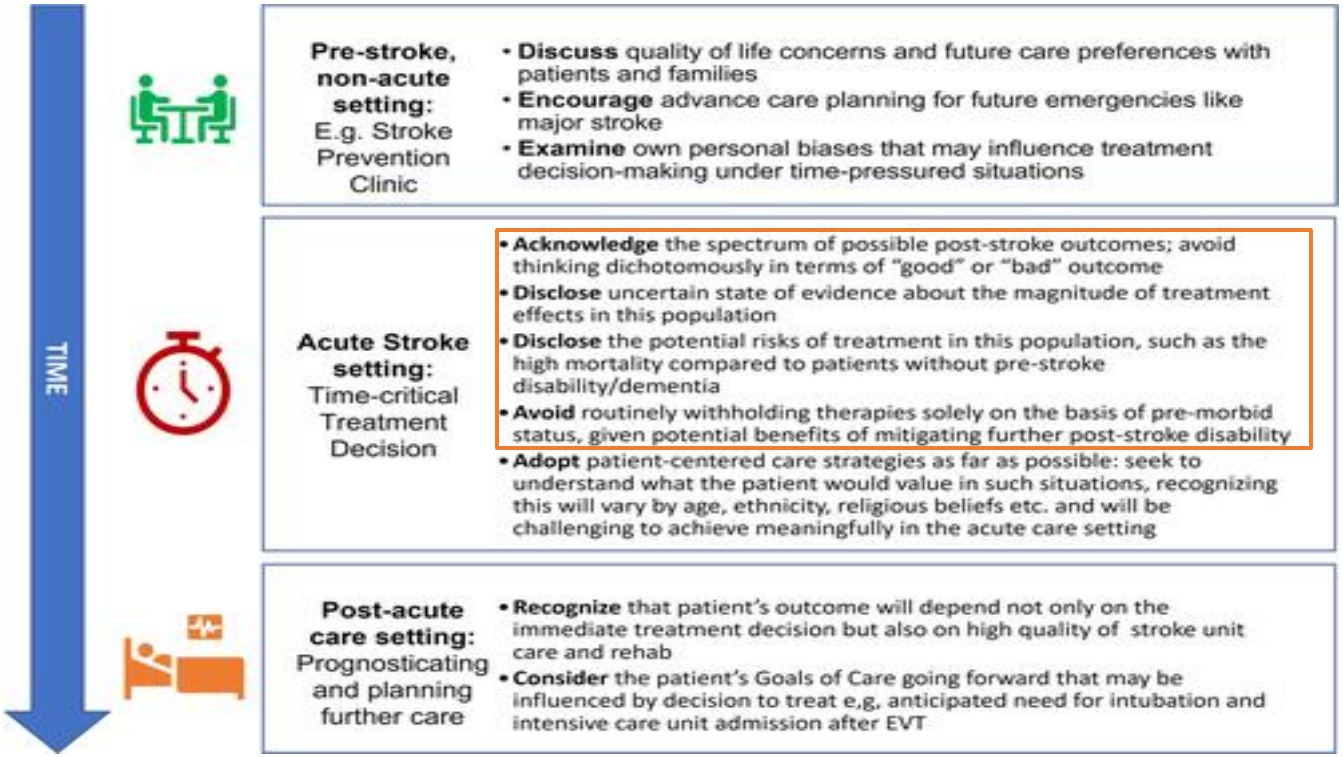
Microbleeds and tPA-related outcome



WAKE-UP Trial Schlemm *Neurology* 2022;98:e302

Implications for thrombolysis

Dementia and decision to treat



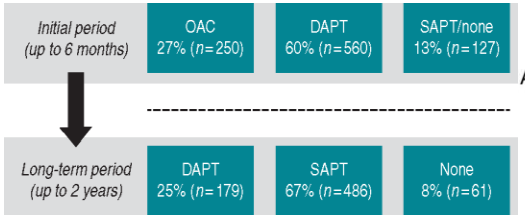
AHA Scientific Statement Ganesh *Stroke* 2022;53:e204

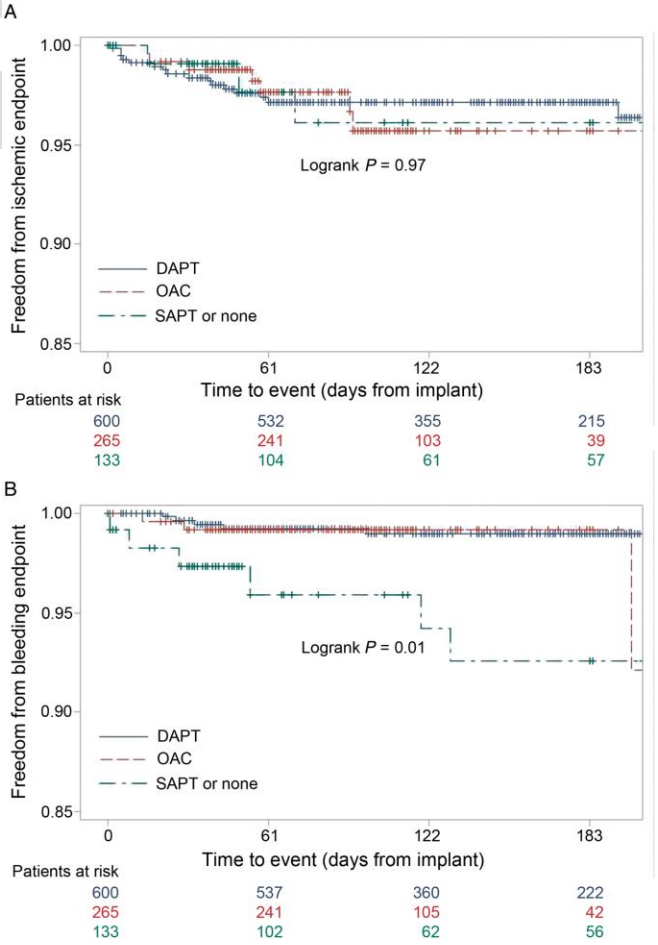
CAA in the Era of Ischemic Stroke Treatments

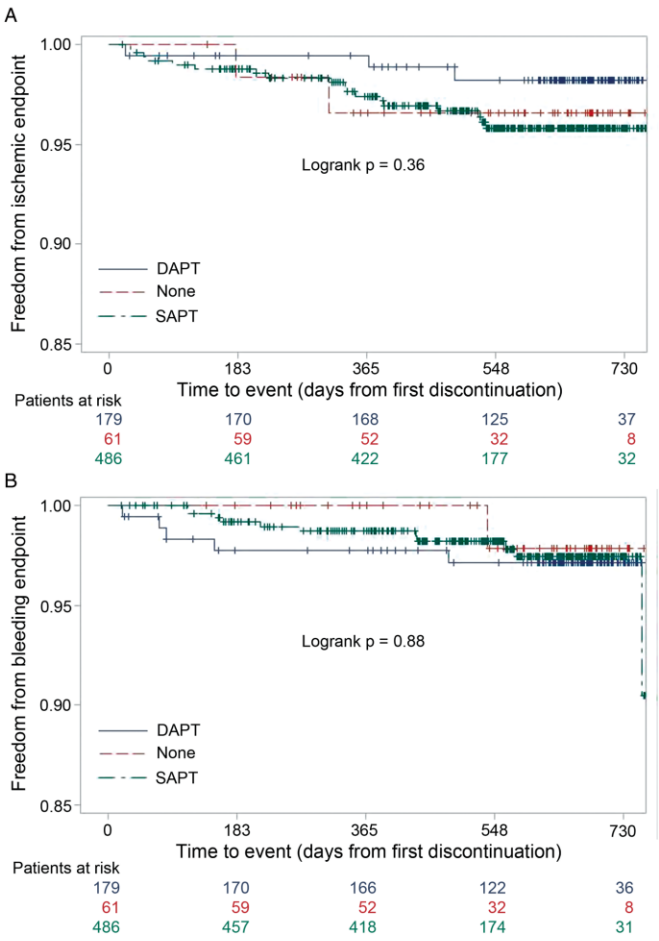
1. What is CAA? Criteria for Diagnosis
2. Implications of CAA for anticoagulation
3. Implications for thrombolysis
   - CAA-related cerebral microbleeds likely increase risk of thrombolysis-induced ICH but generally do not offset benefit
   - Thrombectomy without thrombolysis may avoid added risk
   - Do not withhold acute stroke therapy solely because of microbleeds or cognitive impairment

icaaconference.org

Left atrial appendage closure
Post-procedure antithrombotic regimen







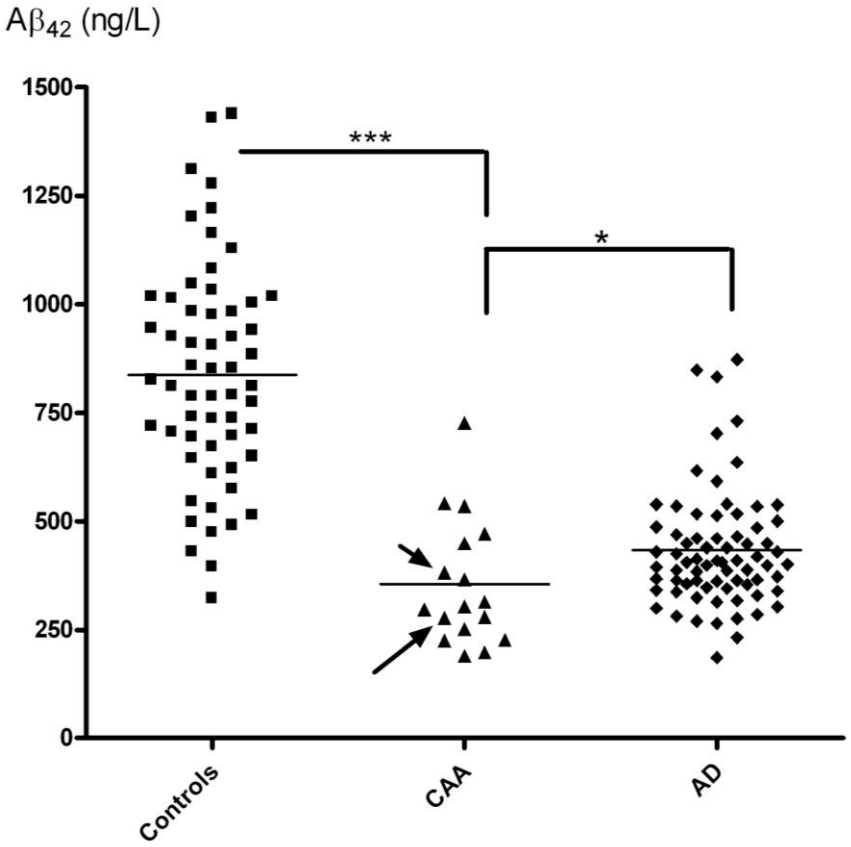
Initial period

Long-term period

Ledwoch *Europace* 2020;22:1036

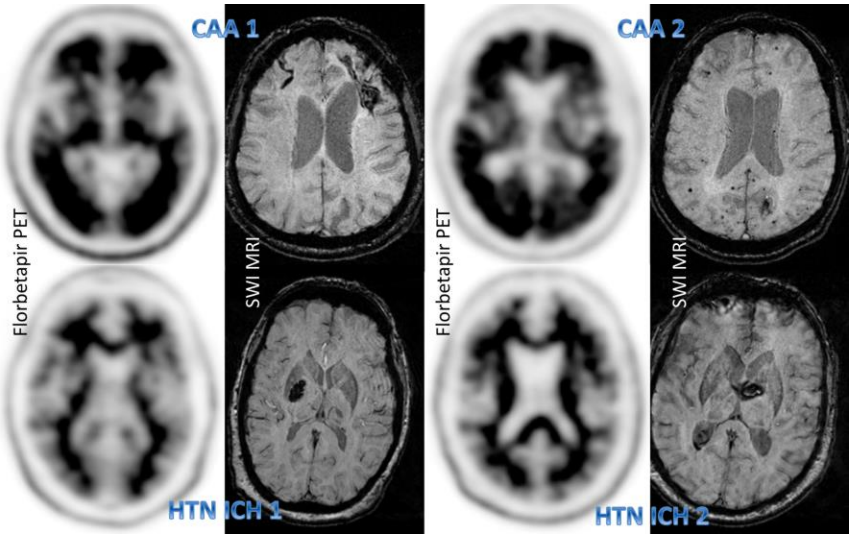
Can I diagnose CAA?
ß-amyloid detection

CSF Amyloid



Verbeek *Ann Neurol* 2009;66:245

Amyloid PET Imaging



Gurol *Neurology* 2016;87:2043

Guidelines for Anticoagulation in AFib

$CHADS_2 \geq 2$	Warfarin INR 2-3
$CHADS_2 = 1$	ASA or Warfarin
$CHADS_2 = 0$	ASA

ACCP: Singer *Chest* 2008;143:546S

Class I

For patients with AF and an elevated CHA2DS2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended.

Class IIb

For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA2DS2-VASc score of 1 in men or 2 in women, prescribing an oral anticoagulant to decrease thromboembolic stroke risk may be considered.

Class IIa

For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA2DS2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy.

ACC/AHA: January *Circulation* 2019;140:e125