Cerebral Amyloid Angiopathy

A Clinical Update

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Outline

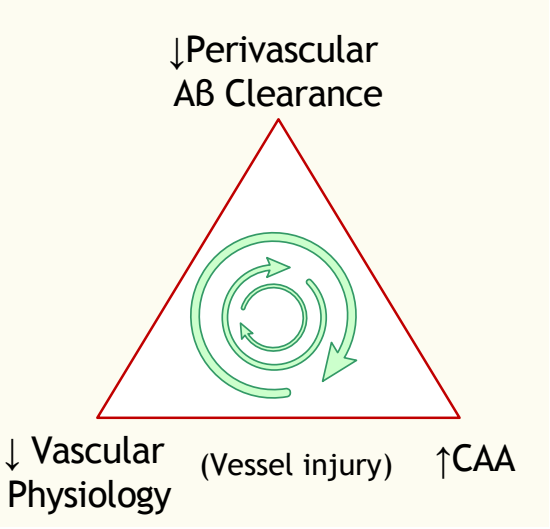
- Updates on clinical-MRI diagnosis: the Boston Criteria
- Clinical questions, frameworks on CAA and AFib

Why should we diagnose CAA?

- High risk of future lobar ICH – *but in selected patients*
- Implications for OAC decisions in Afib
- Presentations w/o ICH, e.g. CAA-TFNEs often misdiagnosed as TIAs
- Key vascular contributor to Cognitive impairment/Dementia
- Core risk factor for ARIA in anti-amyloid trials in AD
- New emerging syndromes, i.e. iatrogenic CAA
- Research/RCTs patient selection

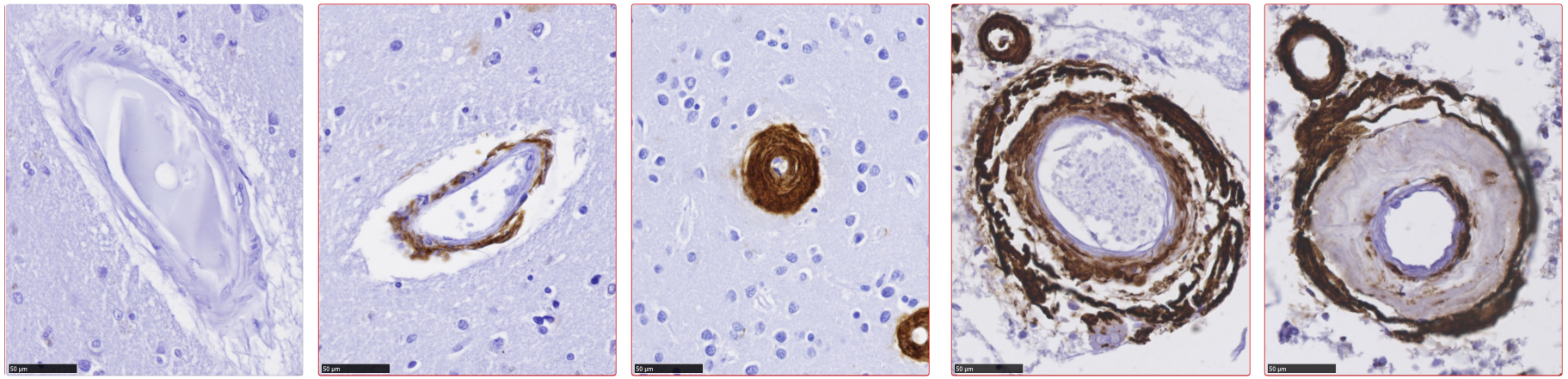
Cerebral Amyloid Angiopathy (CAA):

Pathogenesis



Protein-elimination failure arteriopathy

No CAA | Mild CAA | Moderate CAA | Severe CAA



Amyloid-β deposition

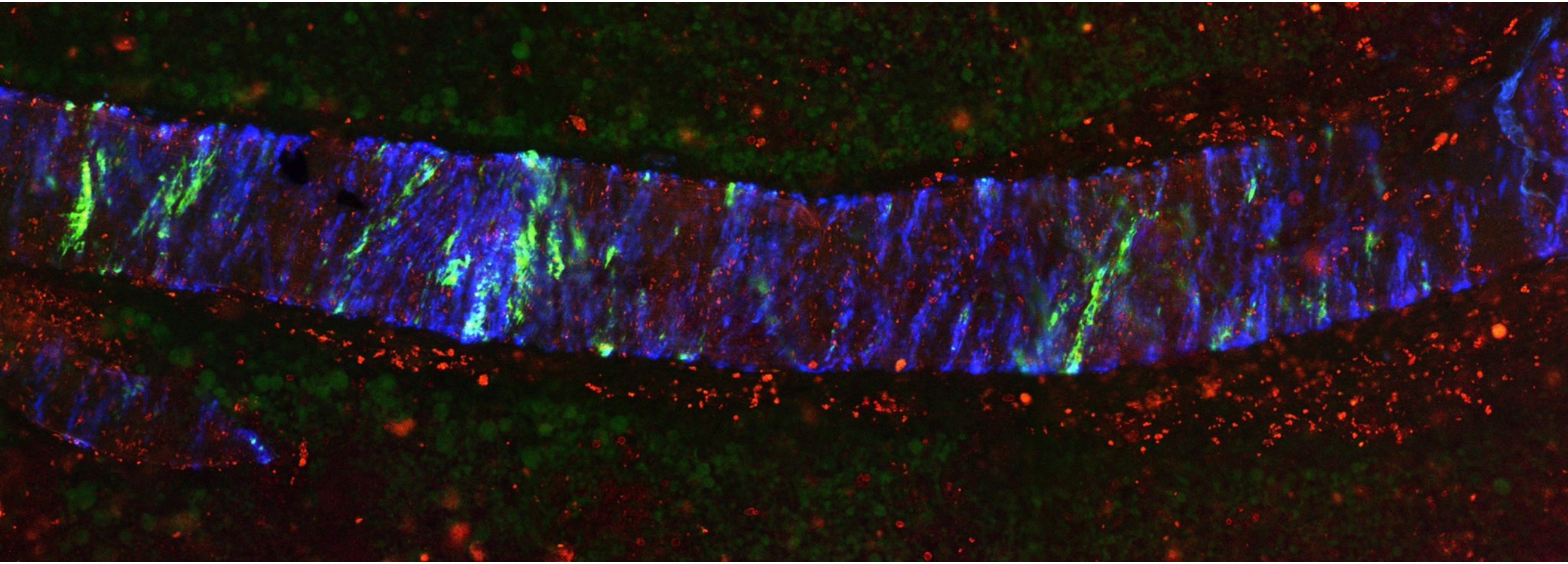
"Double barreling"
Vessel wall cracks

Fibrinoid necrosis

CAA-related vasculopathies

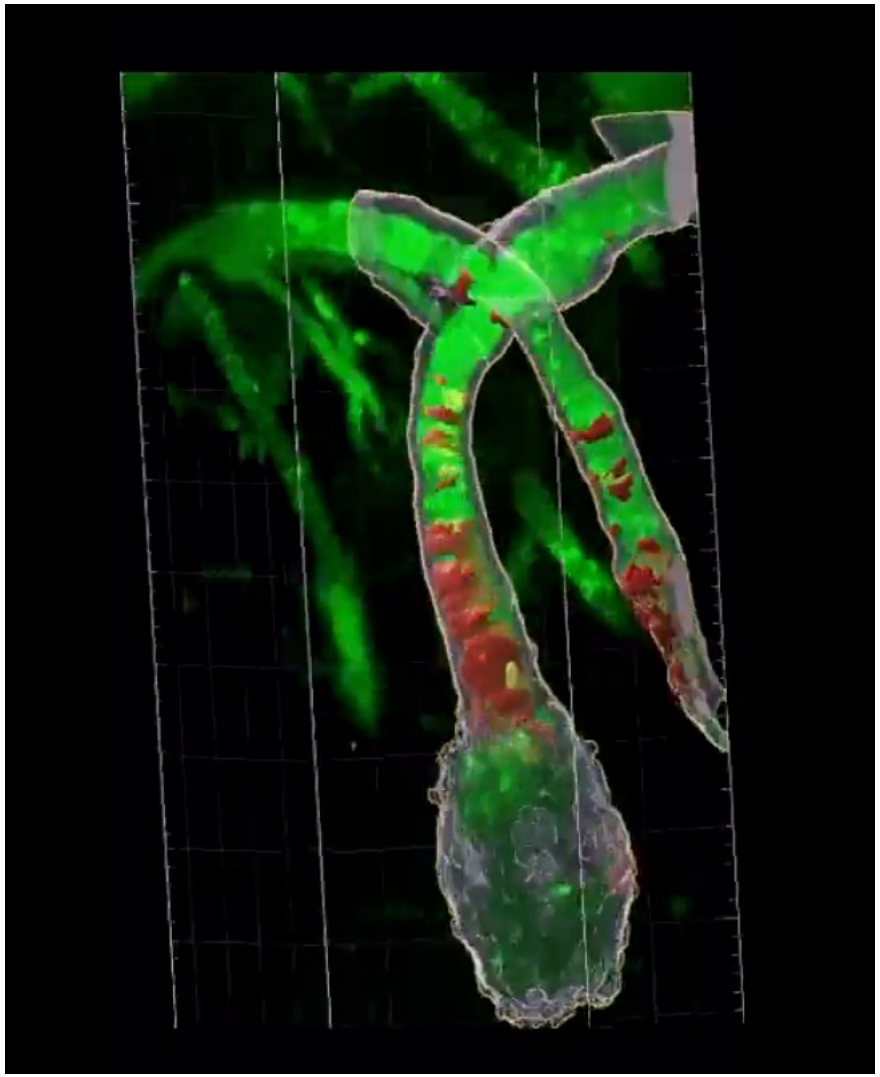
⇧ Bleeding Risk

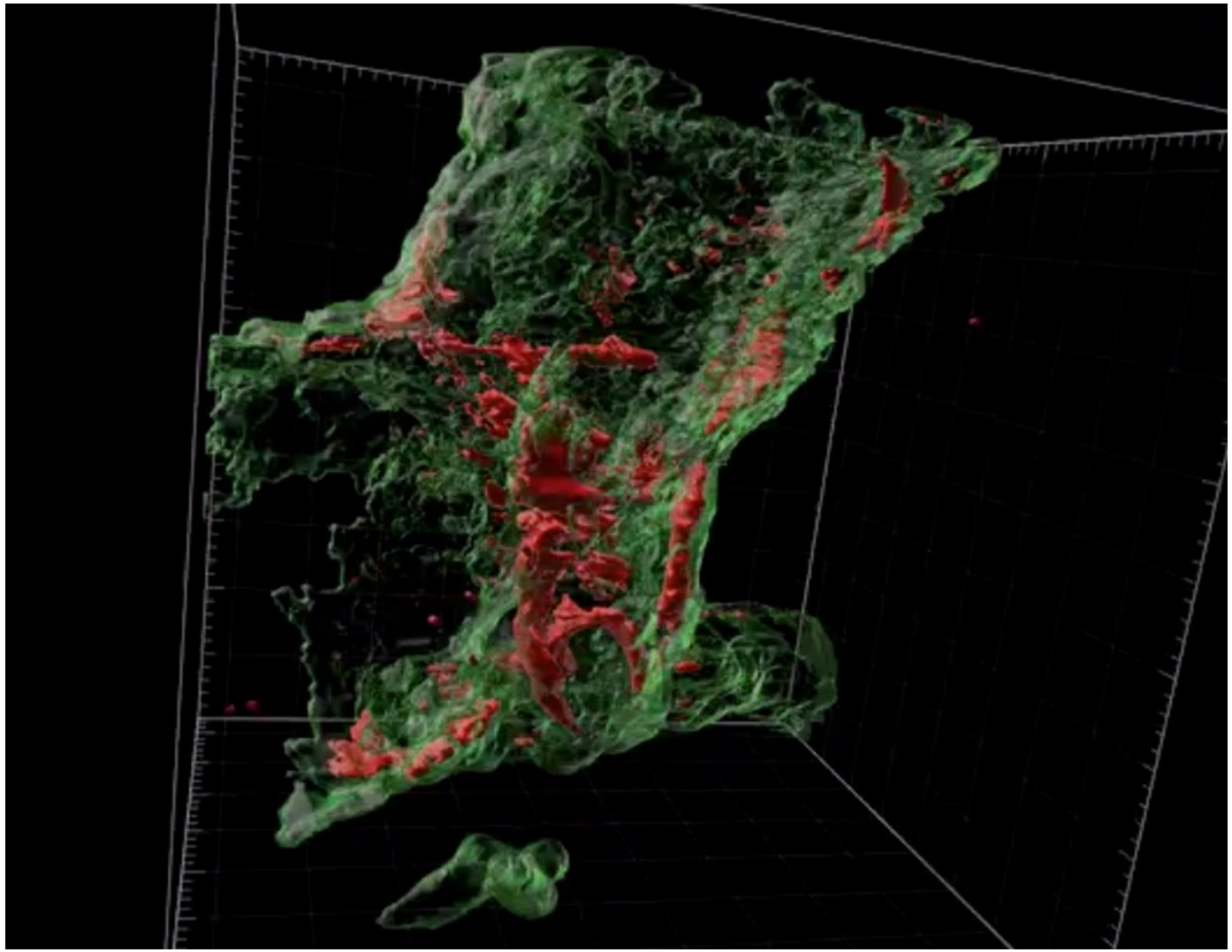
A small artery from the hippocampus of a human brain with CAA (amyloid in blue)



Via: SchragLab @LabSchrag

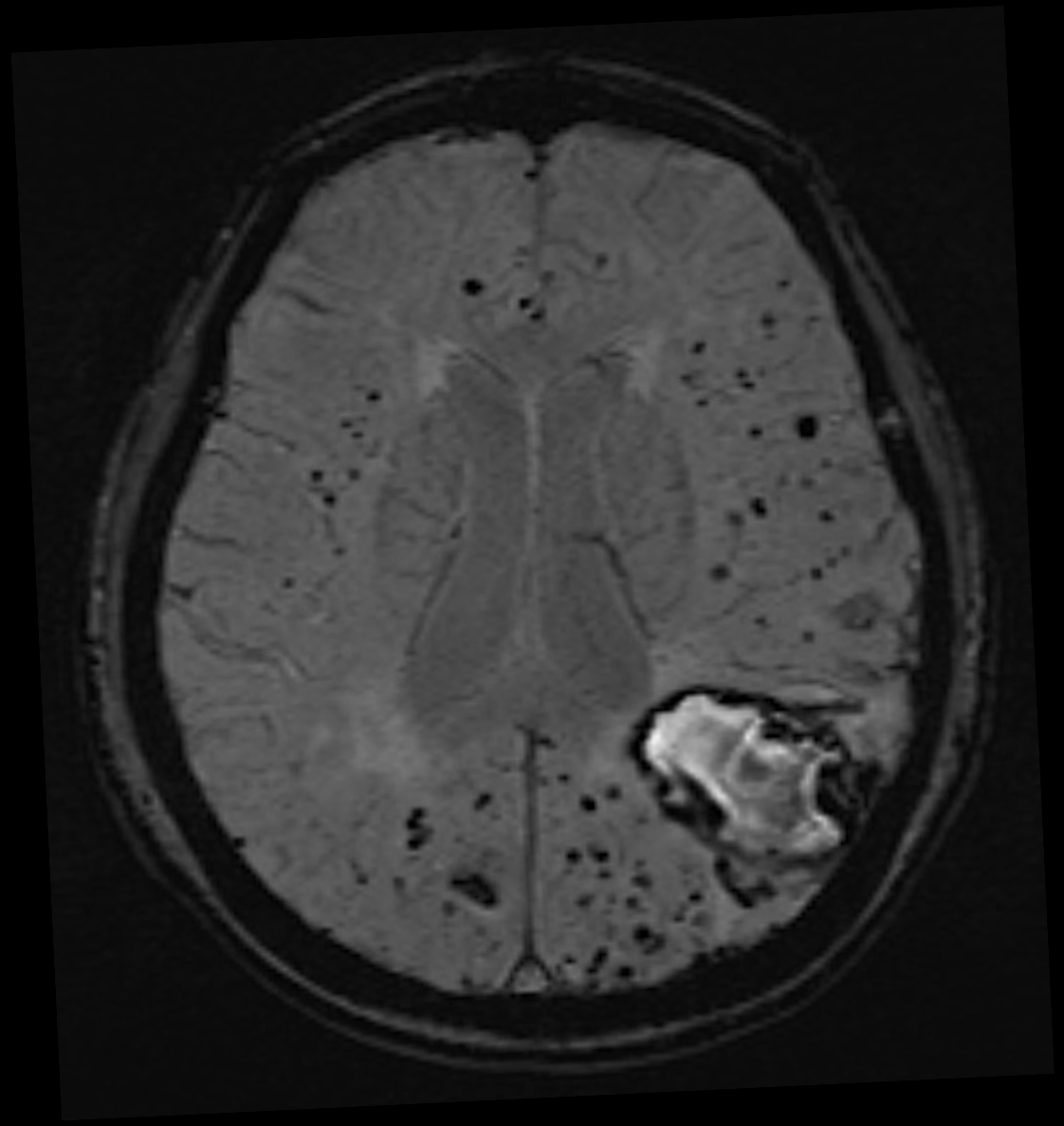
Degenerated arterioles from human brains with CAA (amyloid in red)

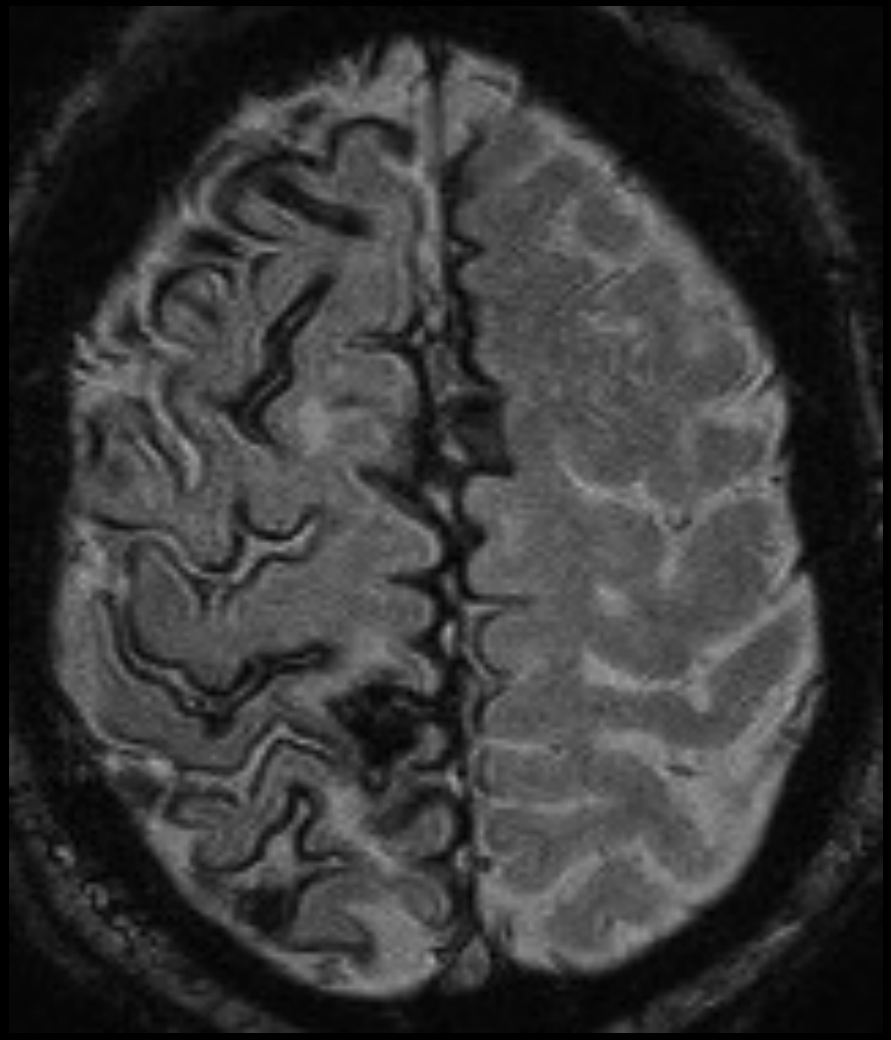




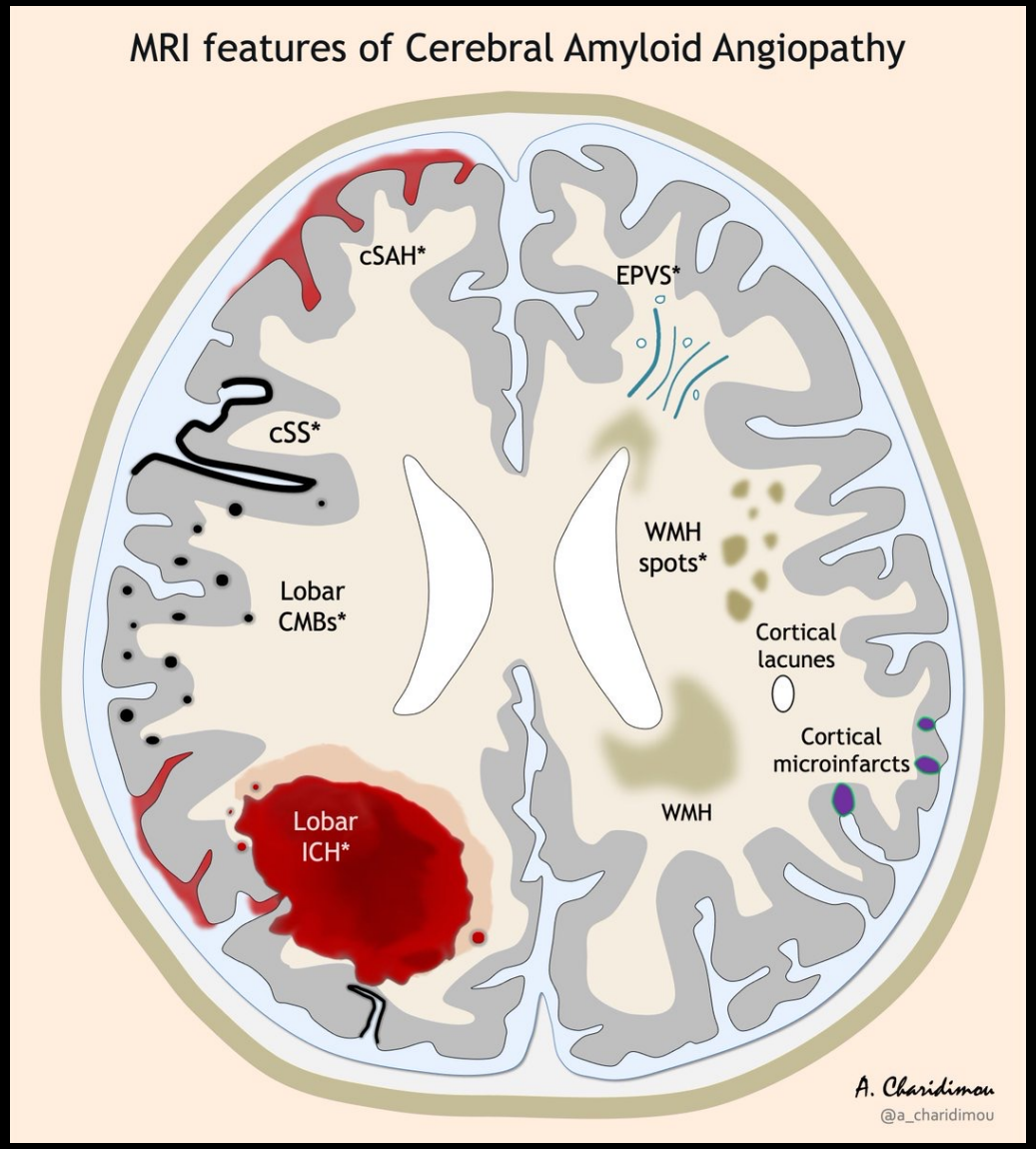
Via: SchragLab @LabSchrag

“Looks like CAA”- Powerful diagnostic tool





CAA: Radiological markers & Clinical syndromes



No symptoms
Incidental MRI finding

CAA pathology in the brain

Lobar ICH

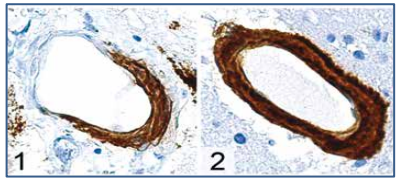
Acute cSAH
TFNEs

Hemorrhagic stroke

Cognitive Impairment
Neuropsychiatric sxs
Alzheimer's Disease

CAA-ri & ARIA

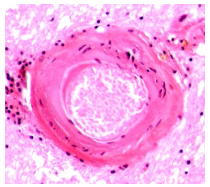
The “Yin & yang” SVD model

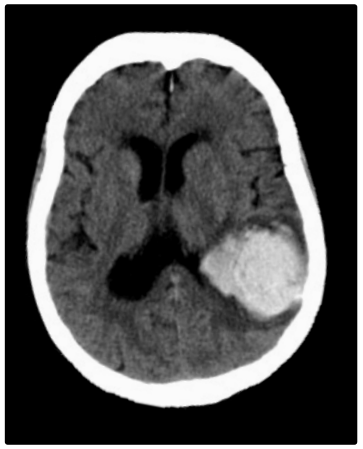


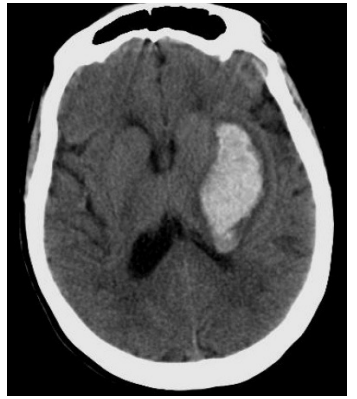
Cerebral amyloid angiopathy (CAA)

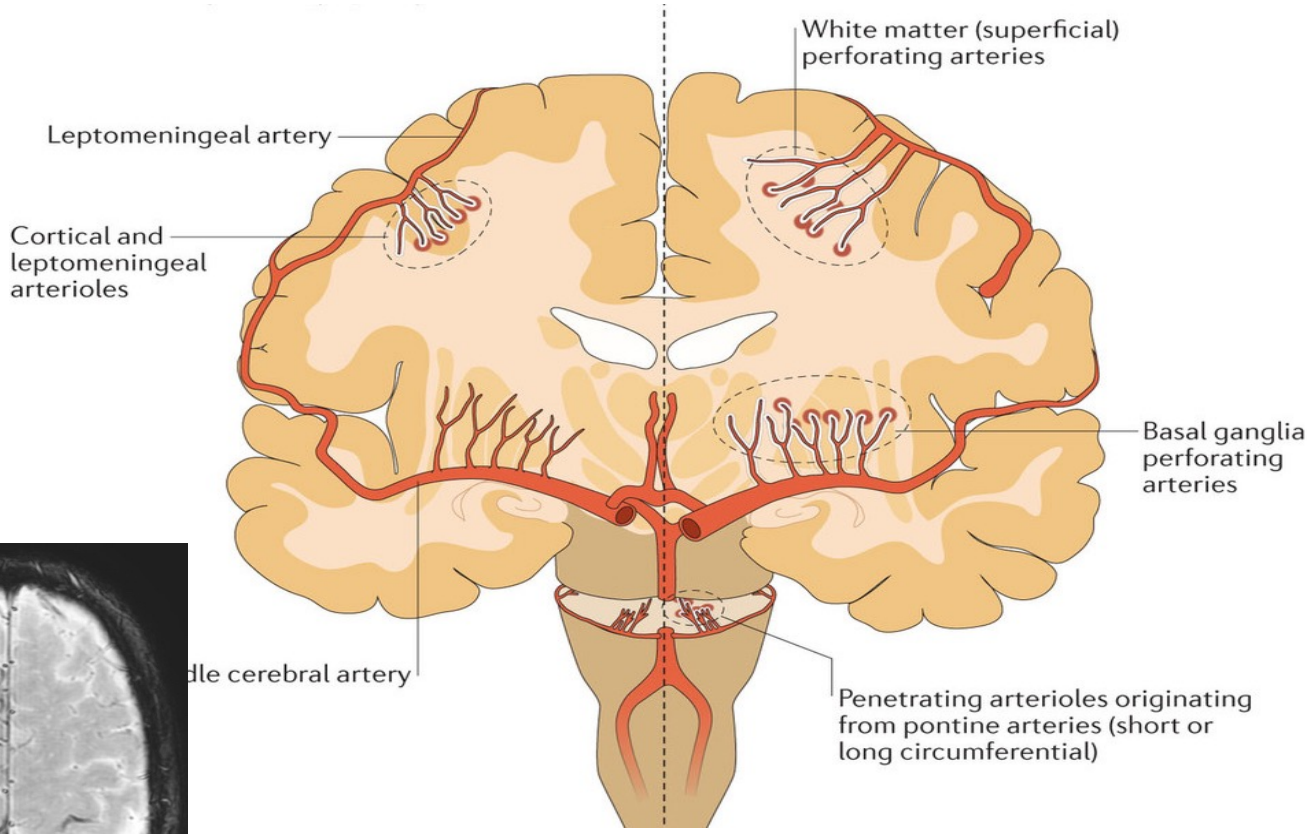
Non-amyloid SVD

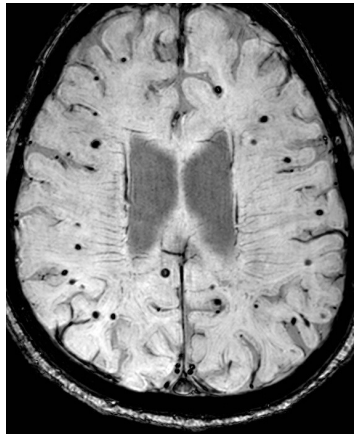
“Hypertensive/deep perforator arteriopathy”

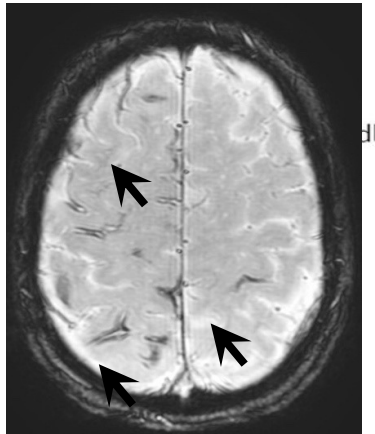


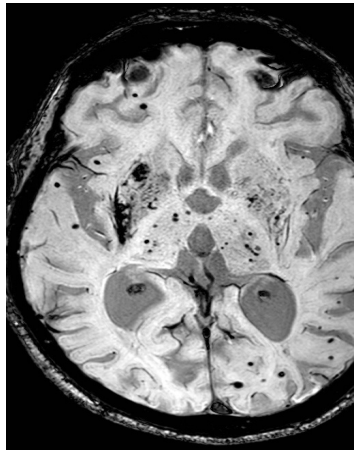












Boston Criteria v1.0 and v1.5 ("modified")

Definite CAA

Full postmortem exam with severe CAA

Probable CAA with Supporting Pathology

Evacuated specimen showing CAA

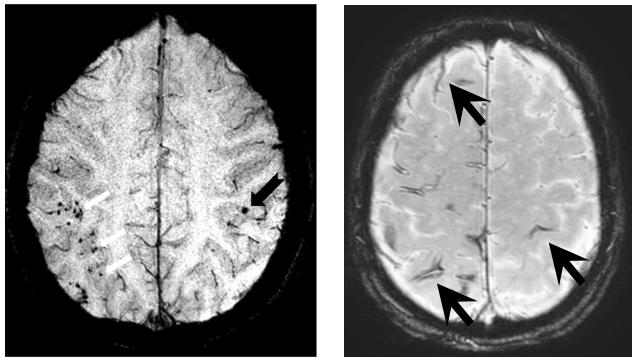
v1.5
included cortical superficial siderosis presence

Probable CAA*

- Multiple (≥2) bleeds/microbleeds
- OR Single bleed/microbleed AND any cSS (focal or disseminated)
- Strictly lobar location (no deep bleeds/microbleeds)
- No other cause

Possible CAA

Single lobar bleed, no other cause



*age ≥55 years, no other cause of hemorrhage

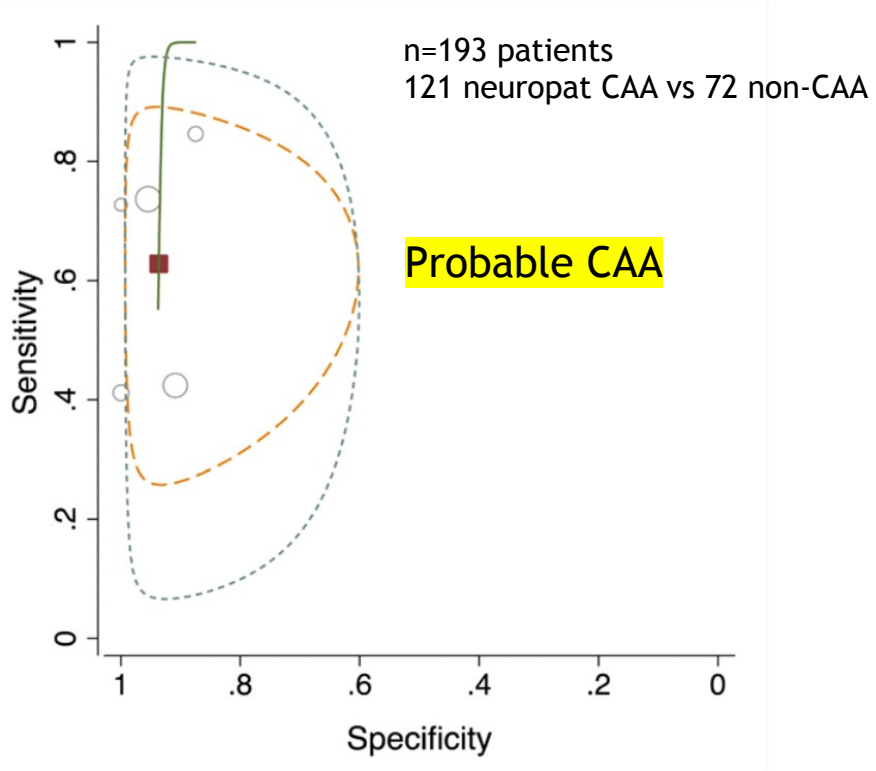
Case records of the Massachusetts General Hospital. Weekly clin
Cerebral hemorrhage in a 69-year-old woman receivin

N Engl J Med. 1996 Jul 18;335(3):189-96.

Knudsen Neurology 2001;56:537

Linn *Neurology* 2010;74:1346

Pathologic validation of Boston Criteria v1/1.5: Limited



Setting	CAA Pathology+Subjects (ICH+/ICH–)	CAA Pathology–Subjects (ICH+/ICH–)
MRI-neuropathology studies		
Hospital-based[15]	11 (11/0)	4 (4/0)
Hospital-based[10]	38 (27/11)	22 (22/0)
Hospital-based[16]	14 (9/5)	10 (10/0)
Hospital-based[17]	33 (0/33)	22 (0/22)
Population-based[17]	22 (0/22)	25 (0/25)

with ICH

without ICH

Charidimou & Boulouis *Stroke* 2022
Charidimou et al. *Int J Stroke*. 2019;14(9):956-971
Greenberg & Charidimou *Stroke* 2018;49:491

- Probable CAA: widely adopted for research/clinical use
- ⏫⏫ specificity, but limited ⏬ sensitivity
- Not widely validated (small cohorts, single center, mostly ICH), new CAA MRI markers

➢ Updating and **larger scale validation**
➢ Emerging MRI markers to ⏫ sensitivity (without compromising specificity)
➢ Build a robust probable CAA, a more inclusive possible CAA, ICH and non-ICH presentations

Methods for Boston Criteria v2.0

Inclusion criteria

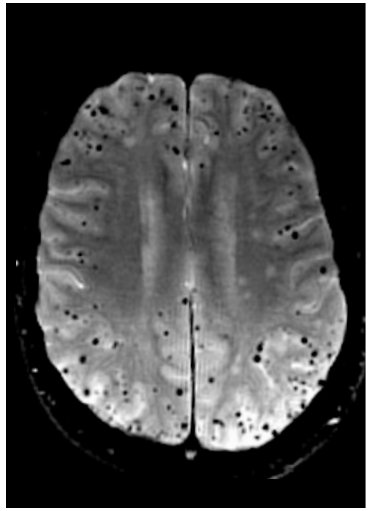
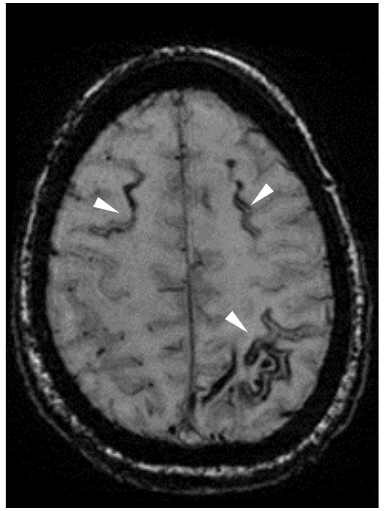
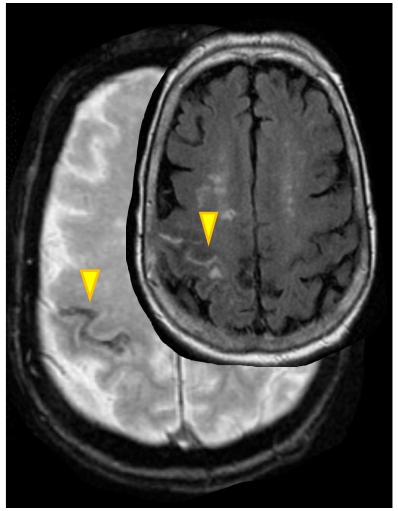
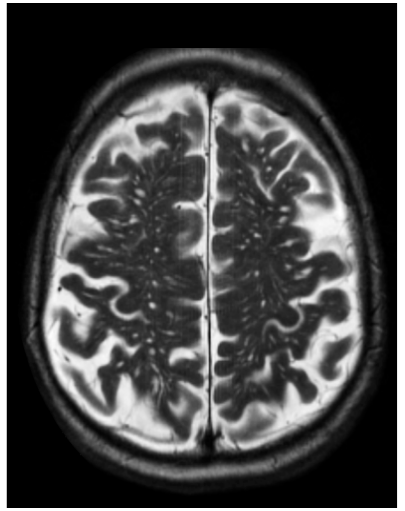
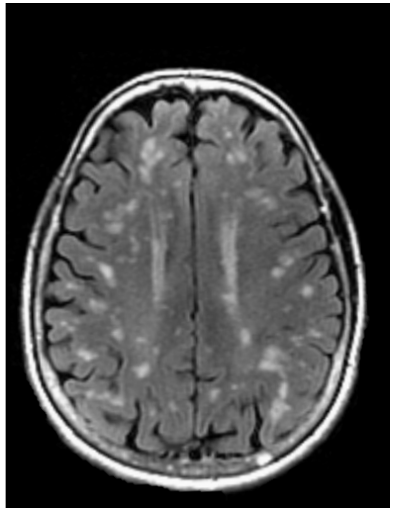
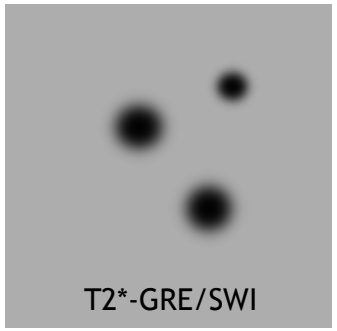
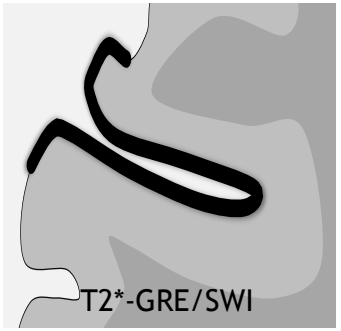
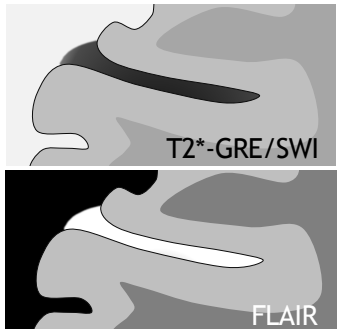
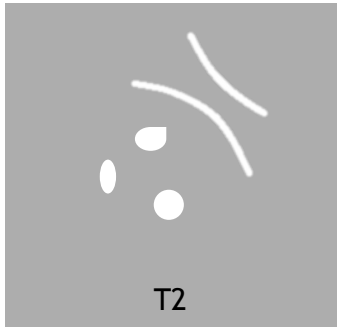
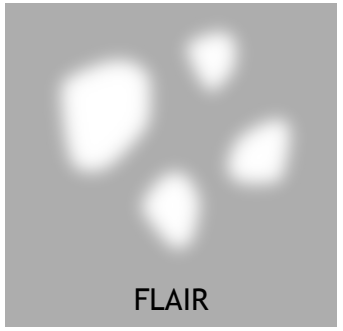
🏥 Potential CAA clinical presentation:
- ICH, TFNE, cognitive decline

🧠 Path assessment for CAA (diagnostic gold standard):
- autopsy, cortical biopsy, hematoma evacuation

⚡ Clinical MRI available
- including T2*-GRE/SWI, T2-weighted, FLAIR sequences

- Validated new criteria in independent (non-Boston) samples
  - **Derivation:** MGH Boston 1994-2012 (n=159)
  - **Temporal validation**: MGH Boston 2012-2018 (n=59)
  - **Geographical validation**: non-MGH 2004-2013 (n=123)

Key MRI markers of CAA (in Boston criteria v2.0)

	Lobar cerebral microbleeds	Cortical superficial siderosis	Convexity subarachnoid hemorrhage	Severe (>20/hemisphere) perivascular spaces in centrum semiovale	Multiple (>10) subcortical spot WMH pattern
Typical MRI examples					
Typical MRI signal					

A. Charidimou

Hemorrhagic MRI markers

Non-Hemorrhagic MRI markers

Boston Criteria v2.0 for CAA Diagnosis

(1) ⚡🏥 Presentation with:

🩸 spontaneous ICH 😵‍💫 TFNEs 👤 CI/Dementia

(2) Age ≥50 y

(3) MRI features

A. 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)

B. Possible CAA

- 1 strictly lobar hemorrhagic lesion: ICH, CMB, cSS/cSAH foci

OR

- 1 WM feature (Severe CSO-PVS or multispot WMH pattern)

👤 In patients w CI/Dementia, fulfillment of criteria does not imply CAA as cause/contributor

⛔ Absence of any deep hemorrhagic lesions (cerebellar lesions not counted)

⛔ Absence of other causes of hemorrhagic lesions

Boston Criteria v2.0: Best performance

- Total n=401
- All autopsies (n=150): the absolute gold standard
- ICH vs non-ICH
- Probable vs non-probable CAA

	All autopsies (n=150)	**ICH (n=75)**	**Non-ICH (n=75)**
Sensitivity	74.5% (65.4-82.4)	90.2% (79.8-96.3)	55.1% (40.2-69.3)
Specificity	95% (83.1-99.4)	92.9% (66.1-99.8)	96.2% (80.4-99.9)
AUC	0.848 (0.794-0.901)	0.915 (0.836-0.995)*	0.756 (0.676-0.836)**

	Prior Criteria (Modified v1.5)
Sensitivity	64.5% (54.9%-73.4%)
Specificity	95% (83.1%-99.4%)
AUC	0.798 (0.741-0.854)

*v2.0 superior to v1.5 p=0.0005 *p=0.0047 **p=0.04*

Charidimou A, et al. Lancet Neurol 2022;21:714-725.

Panel: Notable changes in Boston Criteria v2.0 vs v1.5 and their consequences

1. Age cut-off lowered to **50 years and older** (from 55)

2. Potential **CAA-related clinical presentation** is a prerequisite to apply the criteria:
   - Spontaneous ICH, TFNEs/cSAH, Cognitive impairment or dementia

3. Presence and **multiplicity of cortical superficial siderosis** (and cSAH) foci have a more central role
   - Probable CAA can now be diagnosed in patients presenting with cortical superficial siderosis only

4. **Non haemorrhagic features** are now included in the criteria (severe perivascular spaces in the centrum semiovale or white matter hyperintensities in a multispot pattern)
   - Hence, CAA can be diagnosed in the absence of haemorrhagic markers

5. INR>3 (and any OAC use) is no longer an exclusion criterion

Boston criteria performance in a population-based settings

Boston criteria v2.0	Rush cohort
Sensitivity	38.8%
Specificity	83.5%

Boston criteria v1.0	Rush cohort	Framingham cohort
Sensitivity	26.5%	4.5%
Specificity	90.2%	88%%

- Diagnostic accuracy is rather poor
- Do we really need to diagnose CAA in asymptomatic people?
- **Risk of unsubstantiated therapeutic nihilism and withholding beneficial Rx**

Maria Clara Zanon Zotin, In preparation

Martinez-Ramirez et al. (2015). Alzheimer's & dementia, 11(12), 1480-1488

Decision making for stroke prevention in CAA & AF

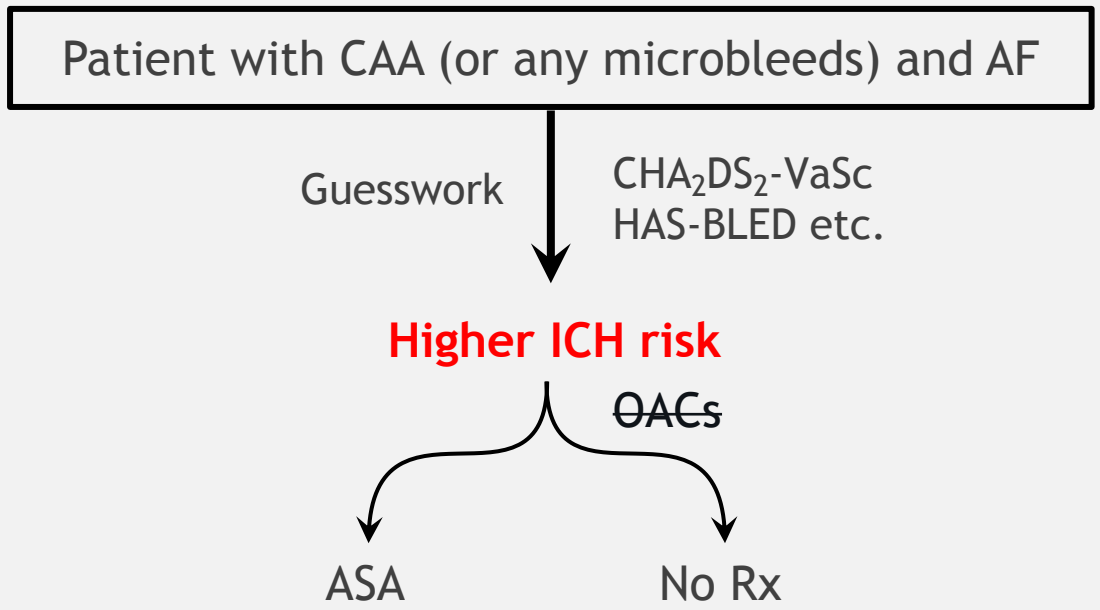
-Clinical framework for decision making in CAA & AF

** When recruitment to a RCT is not available **

-MRI phenotyping in CAA

-Observational data – high risk of bias

How it has been



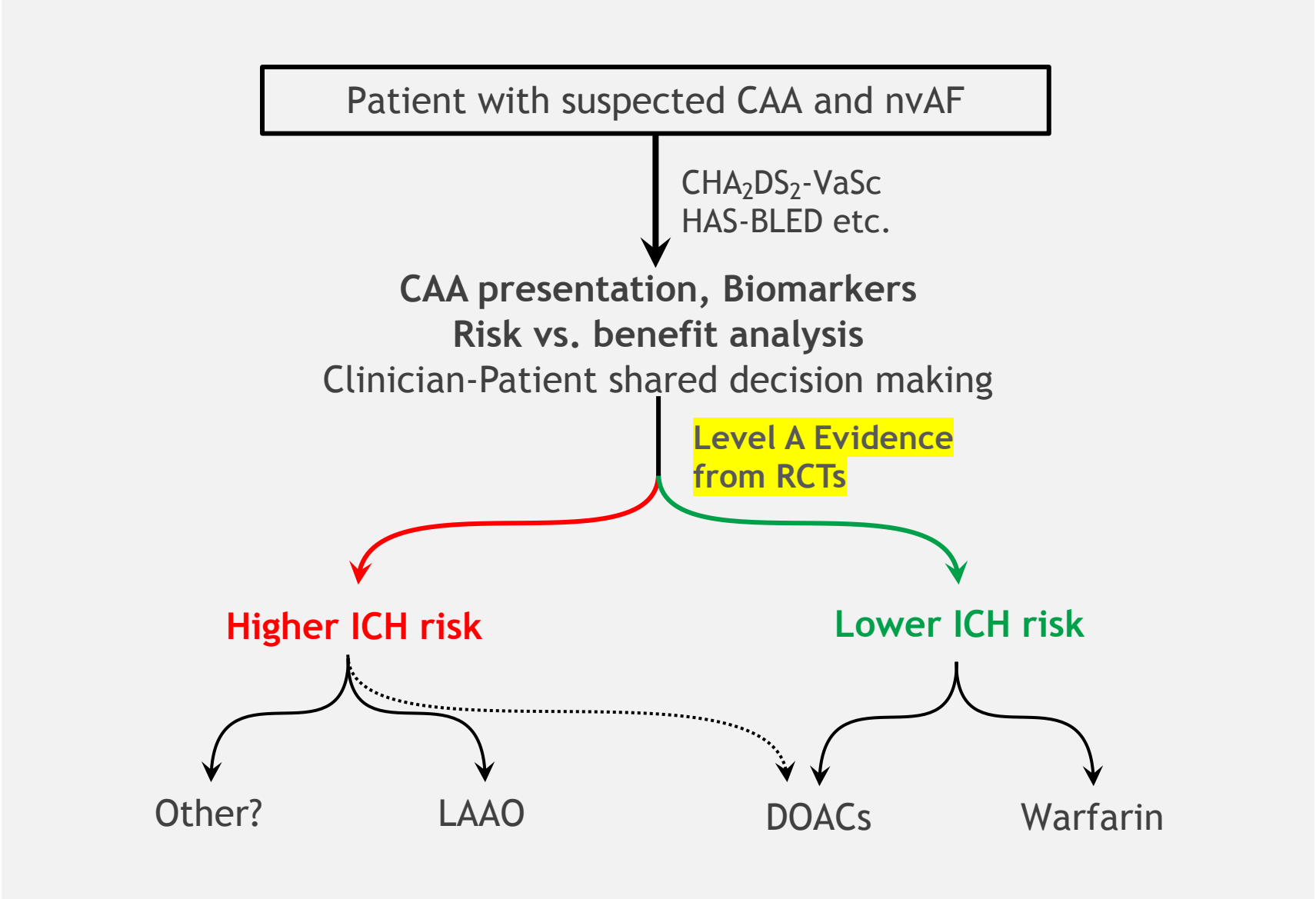
Common myths:

(a) CAA causes ICH

(b) OAC should be avoided in CAA (extremely high ICH risk >> benefit)

(c) Cerebral microbleeds=CAA=ICH

How it should be…TBC



How to get there
(until RCT Level A evidence is available)

1. Estimate baseline ICH risk in CAA (no OAC)
2. Expected increase in ICH risk with OAC

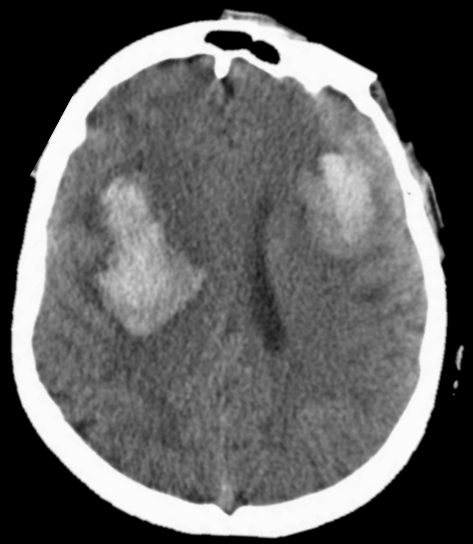
Risk

3. Estimate IS risk without OAC
4. Expected reduction in IS risk with OAC

Benefit

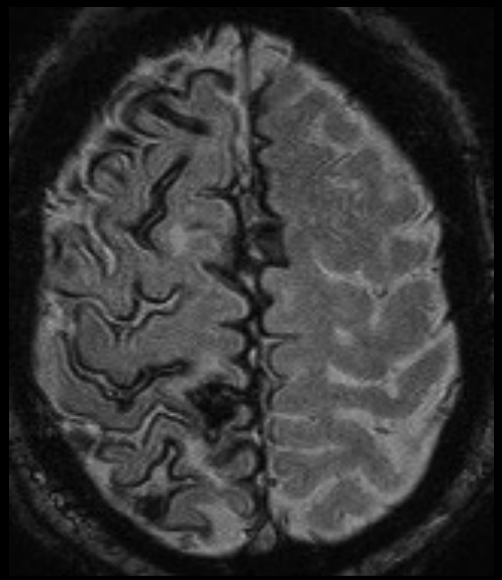
---->Individualized Risk-Benefit analysis

1. Baseline ICH risk depends on CAA phenotype: syndrome, cSS



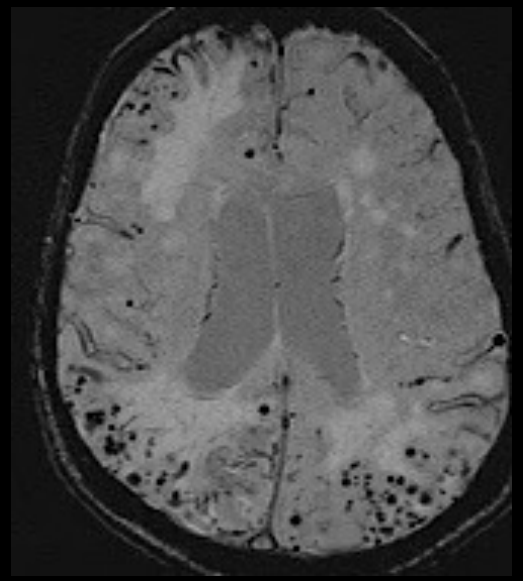
Lobar ICH

~10% per year



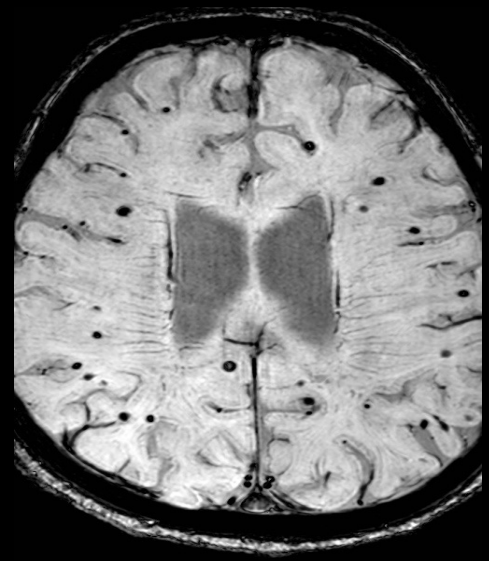
CAA-related TFNE
CAA-related cSAH

~10-20% per year



VCID-CAA

~3% per year



Asymptomatic CAA
(Lobar CMBs general population or IS/TIA)

IS/TIA: ~1% per year
Gen pop: 0.3% per year

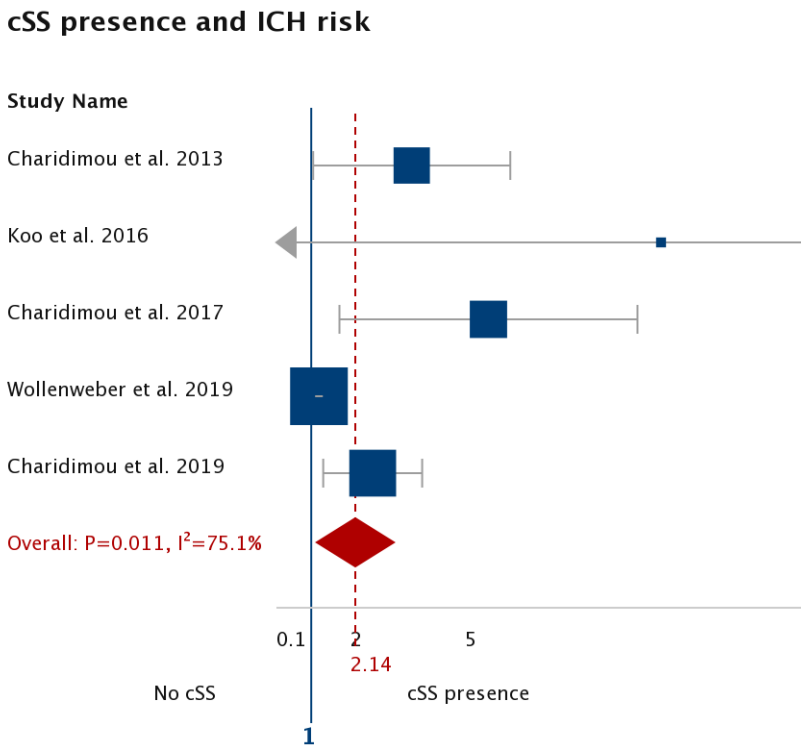
ARTICLE CLASS OF EVIDENCE

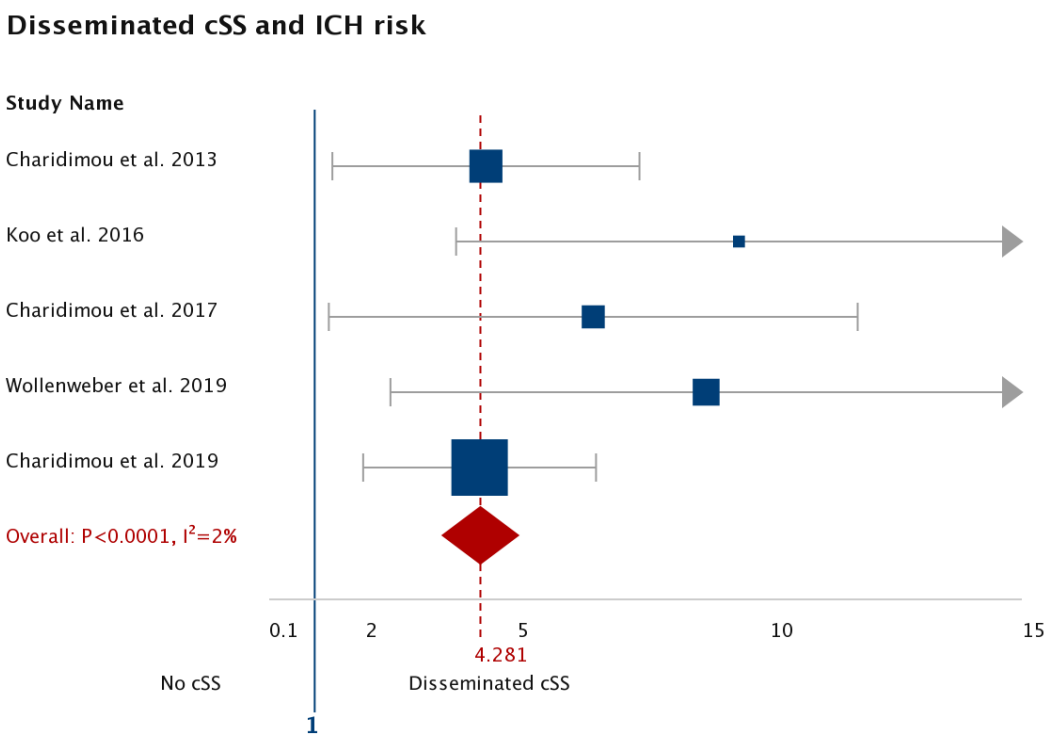
Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy

A meta-analysis

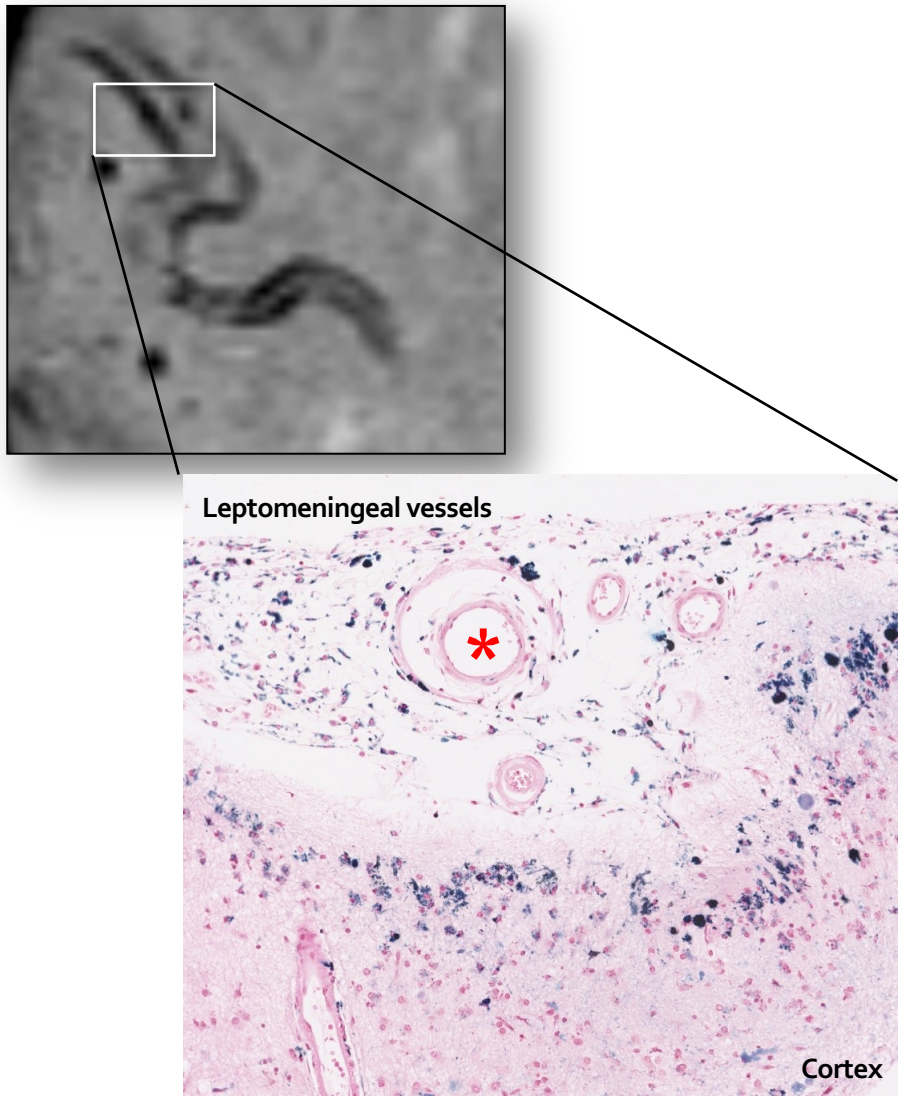
Neurology® 2019;93:e1-e11.

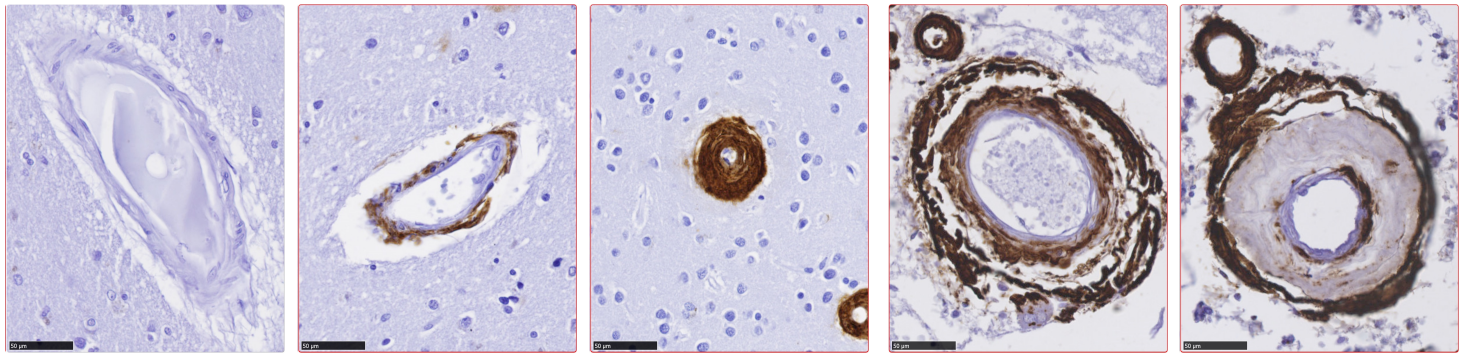
- CAA patients: T2*-MRI at baseline and follow-up for future ICH
- Data from 6 eligible studies (n = 1,239)
- Mean follow-up: 3.1 years (range 1–4 years)
- 162/1239 patients had a lobar ICH - 6.9% per yr (95% CI: 3.9%–9.8%)
- Pooled HR adjusted for CMBs, WMH, Age, ICH history: CMBs no longer a predictor





CAA: Breaking Bad





Amyloid-β deposition

CAA-related vasculopathies

⇧ Bleeding Risk

Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies

Lancet Neurol 2019; 18: 653–65

Asymptomatic CAA in ischaemic stroke/TIA patients

	Symptomatic intracranial haemorrhage (n=16 447 for multivariable model)			Symptomatic ischaemic stroke (n=16 464 for multivariable model)		
	Rate, per 1000 patient-years	Absolute rate increase, per 1000 patient-years	Adjusted hazard ratio	Rate, per 1000 patient-years	Absolute rate increase, per 1000 patient-years	Adjusted hazard ratio
None	4 (3–5)	..	1 (ref)	30 (28–33)	..	1 (ref)
Any	12 (10–14)	8 (7–9)	2·45 (1·82–3·29)	46 (42–51)	16 (14–18)	1·23 (1·08–1·40)
One	8 (5–12)	4 (2–7)	1·87 (1·23–2·84)	37 (31–44)	7 (3–11)	1·14 (0·94–1·37)
Number						
Two to four	9 (6–14)	5 (3–9)	1·89 (1·22–2·93)	48 (40–56)	18 (12–23)	1·17 (0·97–1·42)
Five or more†	23 (16–31)	19 (13–26)	4·55 (3·08–6·72)	64 (53–77)	34 (25–43)	1·47 (1·19–1·80)
Ten or more†	27 (17–41)	23 (14–36)	5·52 (3·36–9·05)	64 (48–84)	34 (20–51)	1·43 (1·07–1·91)
20 or more†	39 (21–67)	35 (18–62)	8·61 (4·69–15·81)	73 (46–108)	43 (18–75)	1·86 (1·23–2·82)
Anatomical distribution						
Mixed	20 (14–28)	16 (11–23)	2·38 (1·55–3·65)	60 (49–73)	30 (21–40)	1·12 (0·88–1·41)
Deep	17 (13–22)	13 (10–17)	2·57 (1·78–3·70)	57 (49–66)	27 (21–33)	1·14 (0·96–1·36)
Lobar	13 (9–16)	9 (6–9)	1·87 (1·29–2·71)	48 (42–56)	18 (14–23)	1·17 (0·99–1·40)
Probable cerebral amyloid angiopathy	9 (4–18)	5 (1–13)	1·29 (0·60–2·77)	48 (34–66)	18 (6–33)	1·31 (0·94–1·83)

ICH risk according to baseline CMBs in patients treated with OAC (n=7737)

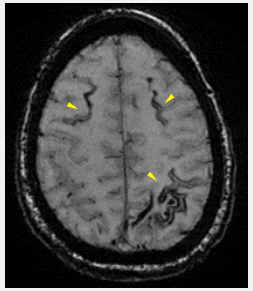
Patient with suspected CAA and nvAF

SVD/CAA clinic
Neurocardiology

CHA_2DS_2-VaSc

Assess CAA phenotype, base ICH/IS risk

- Prior lobar ICH → RTC of DOAC/LAAO if available
- Review brain MRI w SWI
  (or T2*-GRE if SWI not available)
- Apply Boston criteria



cSS presence/severity

→ Asymptomatic CAA/CMBs
-Best evidence AF Rx

Higher ICH risk
-Multifocal cSS
-2nd lobar ICH

Medium ICH risk
-Focal cSS
?

Lower ICH risk
-No cSS
(<5 lobar CMBs?)

Reassess risk: uncontrolled HTN, focal cSS (f/up MRI)

LAAO
(Other Rx: ASA?)

DOACs (e.g. Apixaban)
(~8 w post ICH)

(Target BP consistently <130/80)

A. Charidimou

Summary: Approach in CAA-related syndromes

1. Patients (≥50 years) with suspected CAA (lobar ICH, TFNEs, cognitive impairment) should have MRI with **T2*-GRE or SWI (preferably) for application of the Boston Criteria v2.0**
   - *The Boston criteria are not meant to be a rigid box!*
   - *But a conceptual framework to approach CAA diagnosis using available MRI markers/tools*
   - Needs familiarity with component CAA MRI markers

2. Potential **CAA-related clinical presentation** is a meaningful prerequisite to apply the criteria

3. Presence and **multiplicity of cortical superficial siderosis** are strongly suggestive of CAA
   - could allow for a "provisional CAA" diagnosis in patients with mixed bleeds (data needed)

5. Risk-benefit analysis re stroke prevention and anticoagulation decisions, incorporating CAA phenotype, MRI markers (cSS) and a multidisciplinary approach. Randomise!!!

Thank you

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