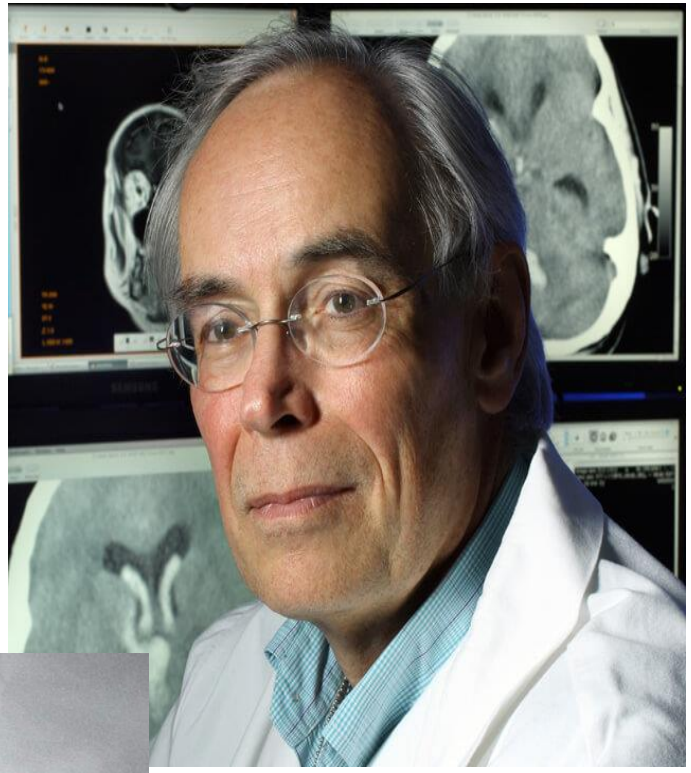
11-1-2019

Cerebral Amyloid Angiopathy and Intracerebral Hemorrhage

Mohammed Rehman

CEREBRAL AMYLOID ANGIOPATHY AND ICH – A SYSTEMATIC REVIEW

MOHAMMED F REHMAN, DO



Objectives

- Definition of CAA as a disease
- Key clinical/MRI signatures
- Implications for treatments, BP, OAC etc.
- latest developments, current trends – No RCTs to date.

Key Take Home Message

- MRI is crucial when CAA is suspected
  - For diagnosis
  - For prognosis
- Cortical superficial siderosis – driver of bleeding
- CAA is not only about hemorrhage – ischemic Lesions, encephalopathies, inflammation/angiitis.

What is CAA

Operational definitions – 3 intersecting levels:

1. Neuropathological level

2. Key clinical presentations / Boston criteria

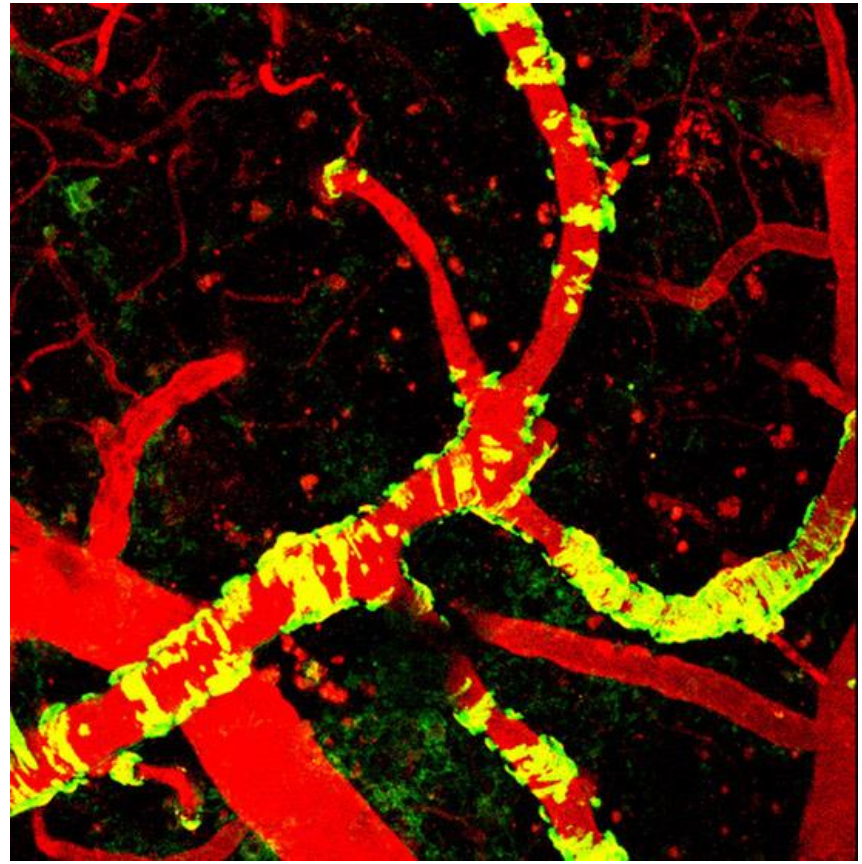
- Spontaneous lobar ICH (10-30% of all ICH)
- CAA non-ICH syndromes
  - "Amyloid spells", acute cSAH
  - dementia
  - CAA related vaculopathies

3. MRI markers and other biomarkers

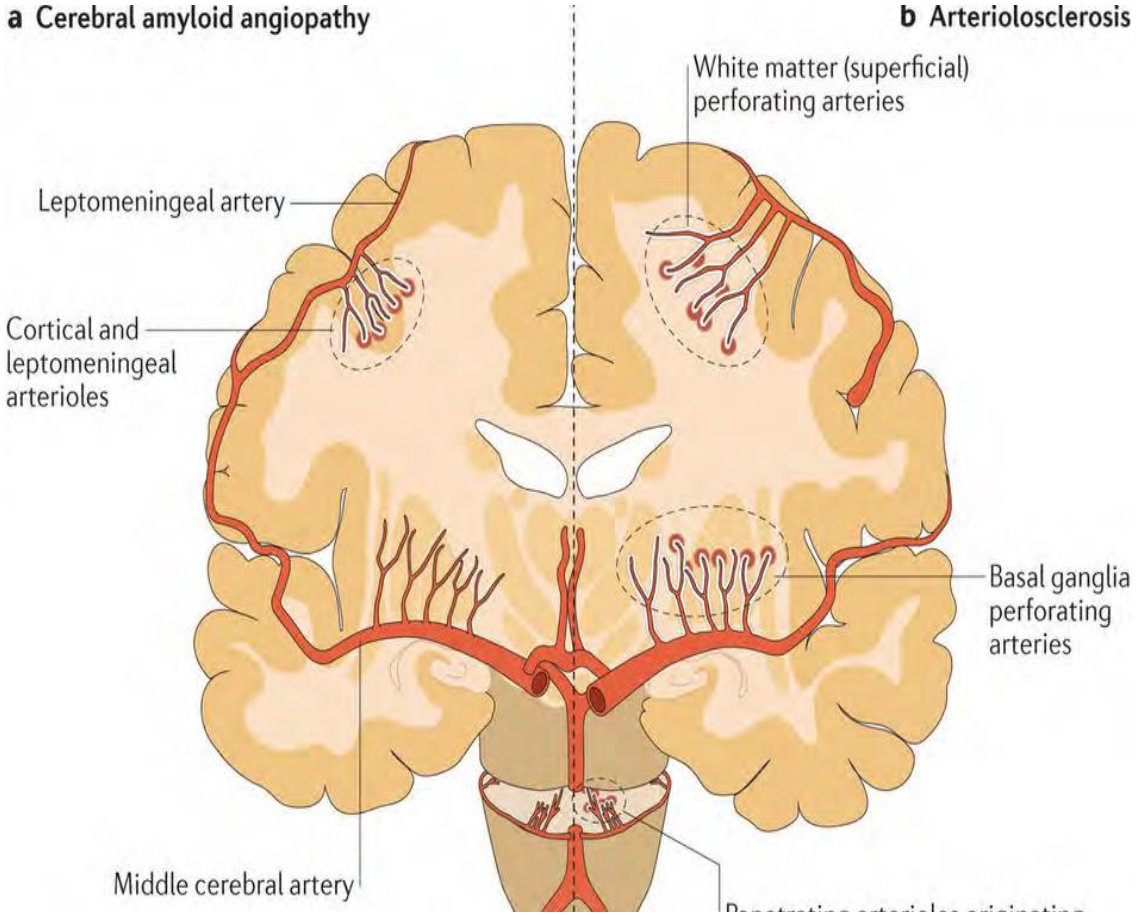
- Early diagnosis – incidental finding

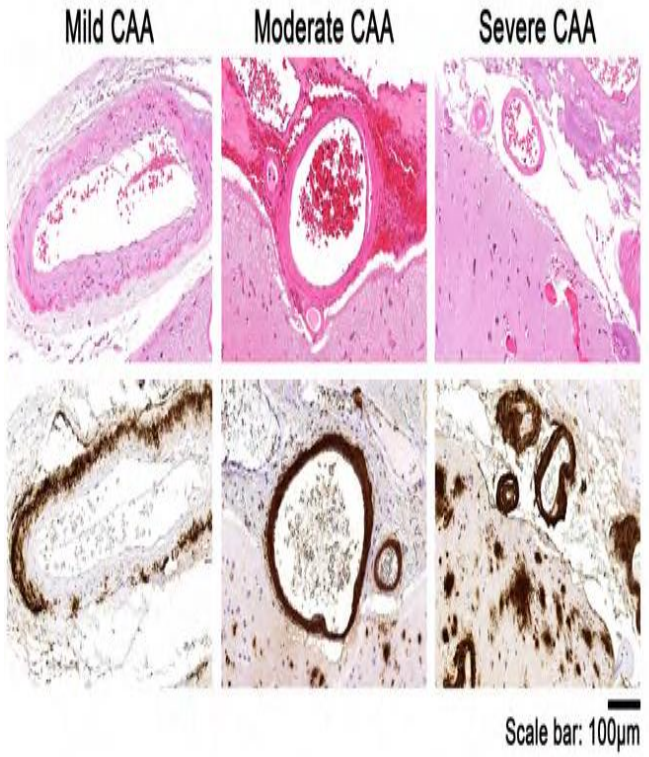
Cerebral Amyloid Angiopathy

- Disease of the elderly (~50% of ICH in >80)
- Deposition of amyloid protein in media/adventitia of small cortical arteries, arterioles and capillaries
- Cortex and cerebellum

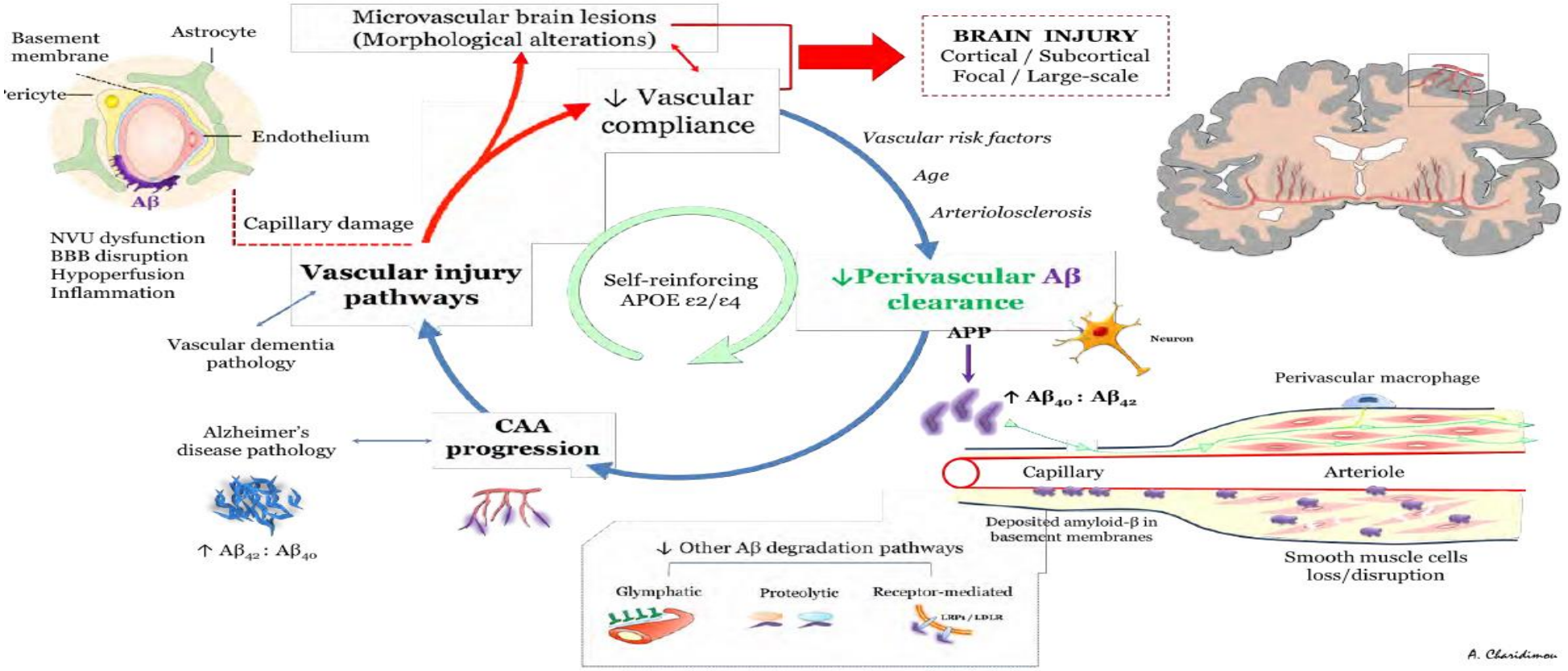


What is CAA?
Pathologically common, clinically relevant

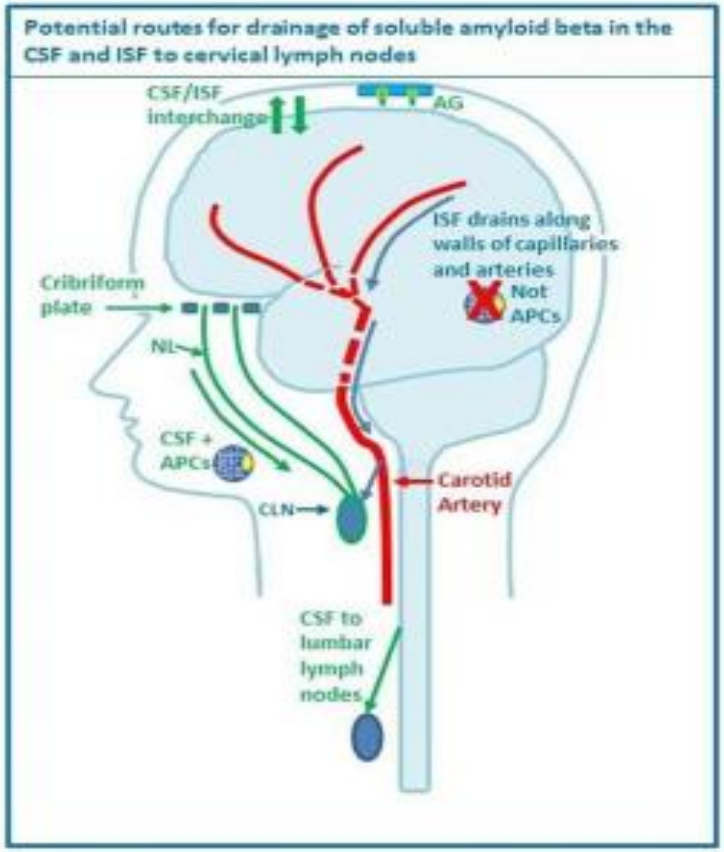




CAA pathophysiology: complex, poorly understood



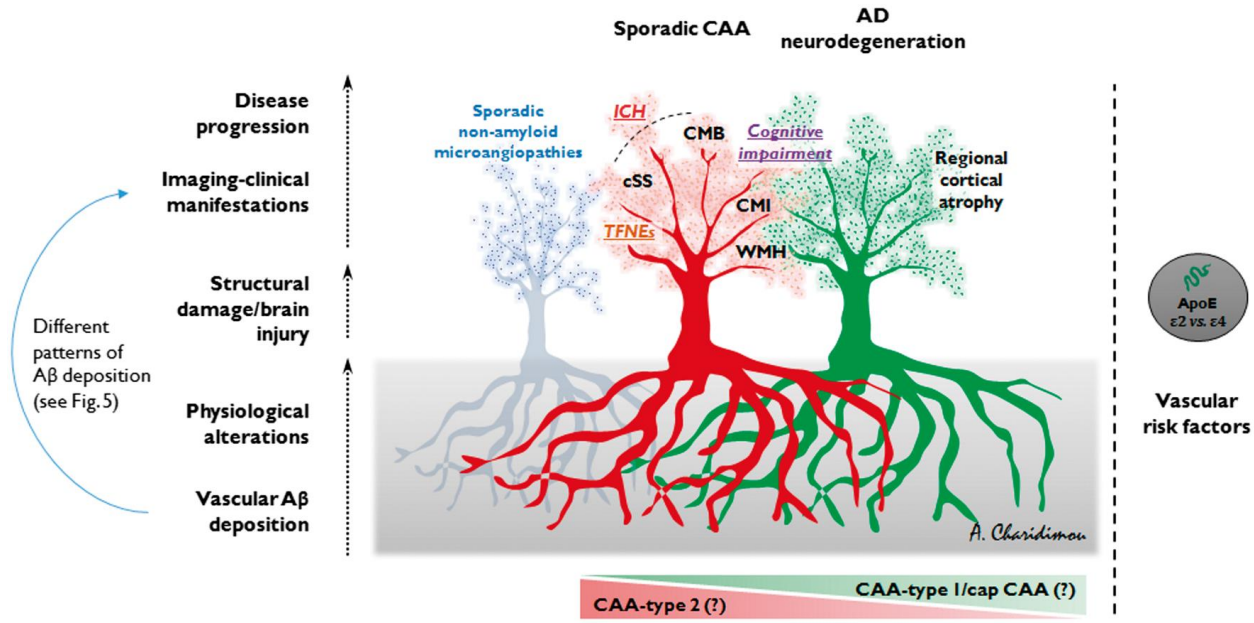
Drainage pathways for CSF and interstitial fluid (ISF) to cervical lymph nodes.



Gargi Banerjee et al. J Neurol Neurosurg Psychiatry 2017;88:982-994

JNNP

Figure 5 Suggested heuristic schematic of the possible different phenotypes of CAA and directions in the expression of ...



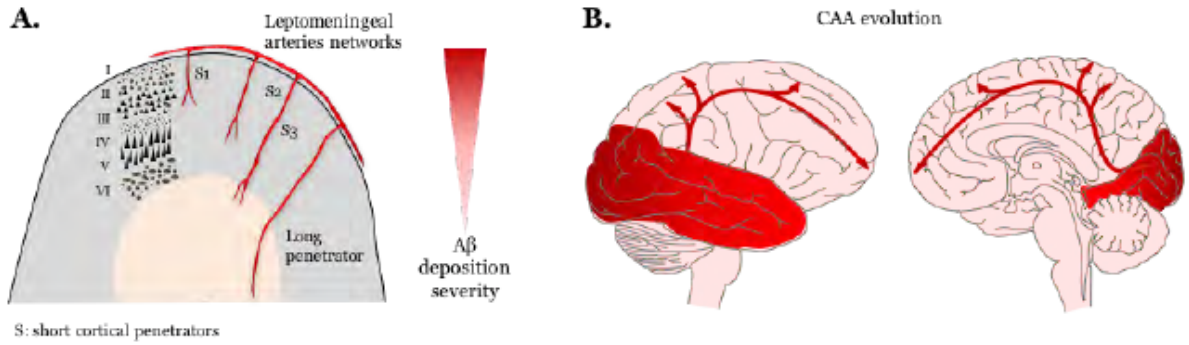
Brain, Volume 140, Issue 7, July 2017, Pages 1829–1850, https://doi.org/10.1093/brain/awx047

Pantelakis, S. : Msschr. Psychiat. Neurol. *126*, 219–256, 1954

Clinique psychiatrique universitaire, Bel-Air près Genève
(Dir.: Prof. Dr F. Morel)

Un type particulier d'angiopathie sénile du système nerveux central: l'angiopathie congophile. Topographie et fréquence

Par STEFANOS PANTELAKIS



Pathological hallmarks of CAA :

(a) preferential involvement of small arterioles and capillaries of the leptomeninges, cerebral cortex, and cerebellar cortex

(b) topographical distribution favouring posterior lobar brain regions

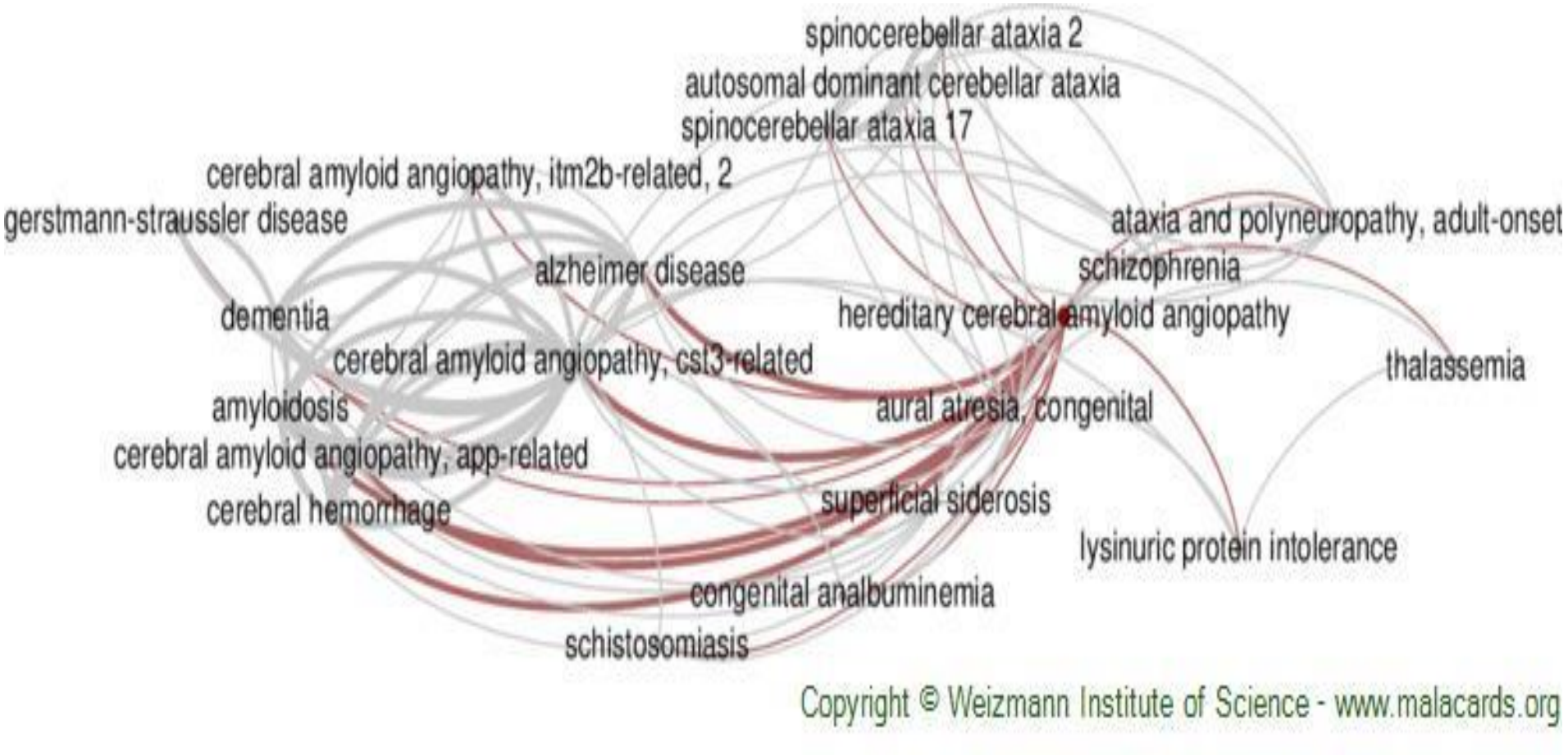
(c) the lack of involvement of white matter small vessels

(d) the association with increased age and dementia

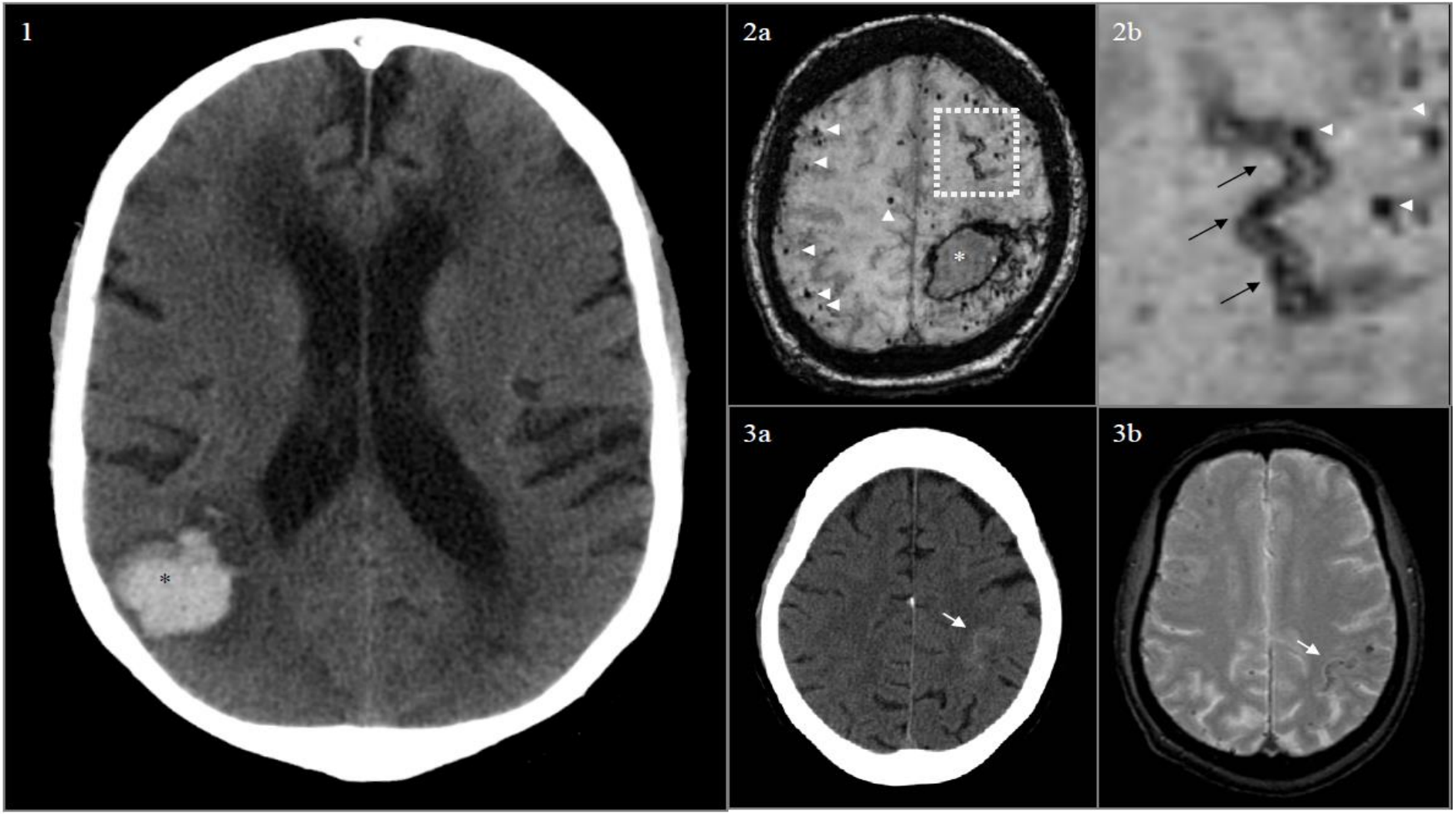
(e) the lack of association with hypertension and arteriosclerosis

(f) the lack of any link with amyloidosis of other organs

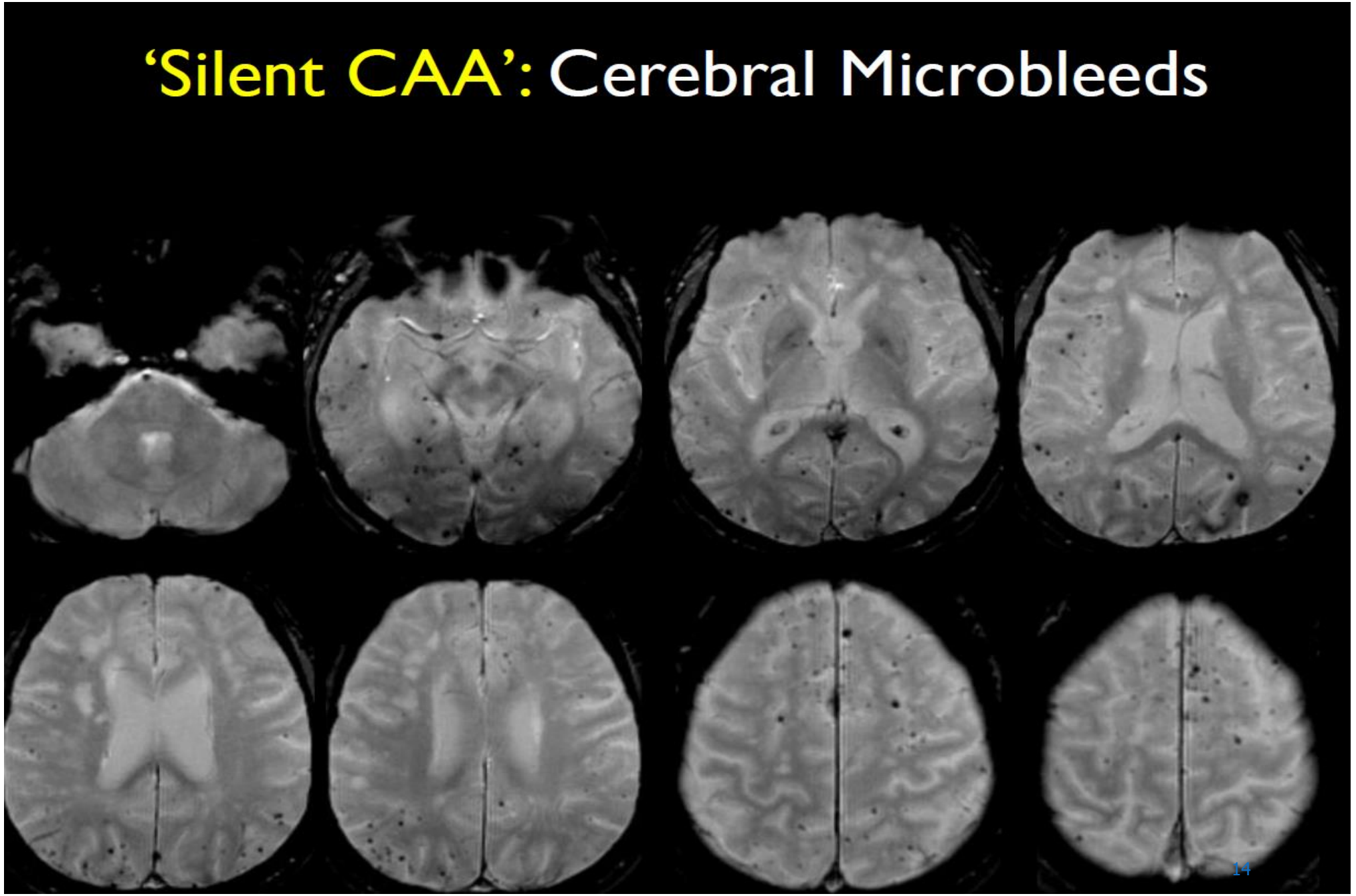
Heriditary CAA Spectrum



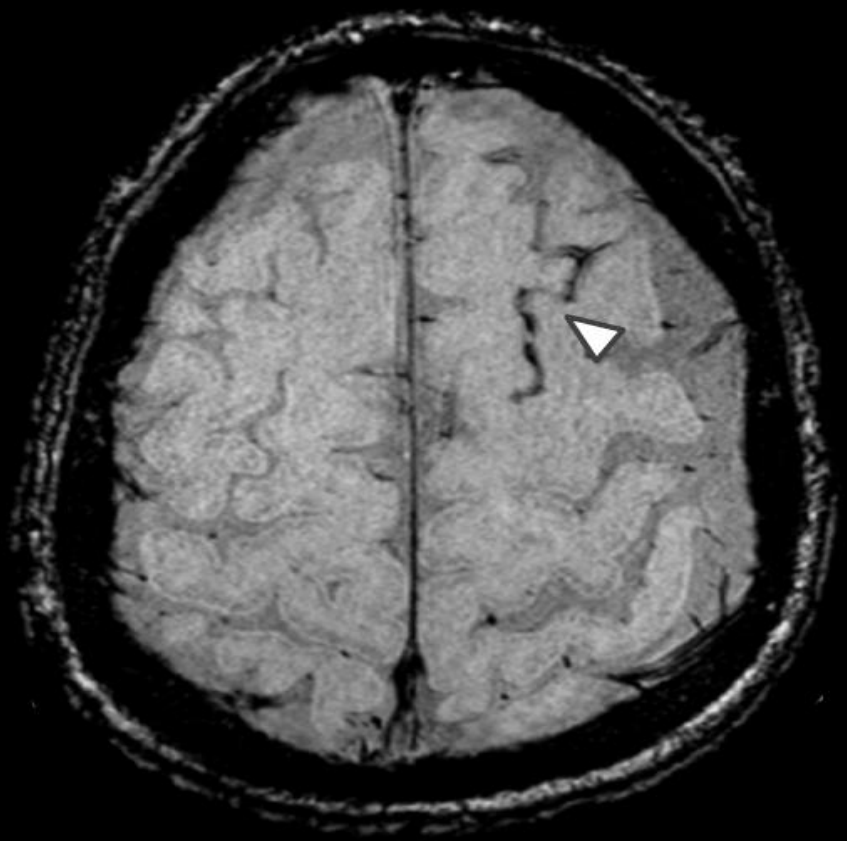
Haemorrhagic manifestations of CAA



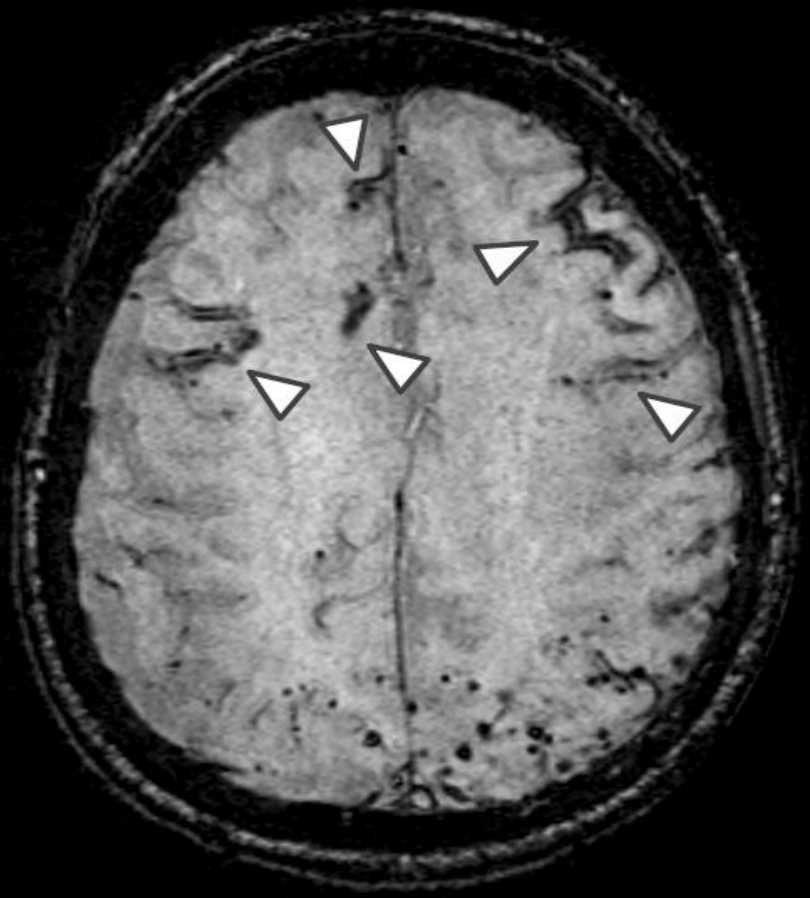
‘Silent CAA’: Cerebral Microbleeds



High Prevalence of cSS in CAA (40-70%)



Focal cSS



Disseminated cSS

CAA diagnosis – Boston Criteria

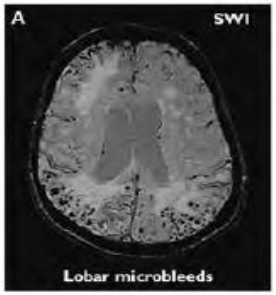
Boston criteria for CAA-related hemorrhage

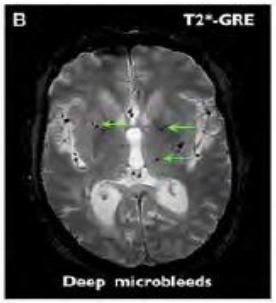
	Classic Boston criteria
Definite CAA	**Full postmortem examination demonstrating:**
	Lobar, cortical, or corticosubcortical hemorrhage
	Severe CAA with vasculopathy
	Absence of other diagnostic lesion
Probable CAA with supporting pathology	**Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:**
	Lobar, cortical, or corticosubcortical hemorrhage
	Some degree of CAA in specimen
	Absence of other diagnostic lesion
Probable CAA	**Clinical data and MRI or CT demonstrating:**
	Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
	Age ≥55 y
	Absence of other cause of hemorrhage
Possible CAA	**Clinical data and MRI or CT demonstrating:**
	Single lobar, cortical, or corticosubcortical hemorrhage
	Age ≥55 y
	Absence of other cause of hemorrhage

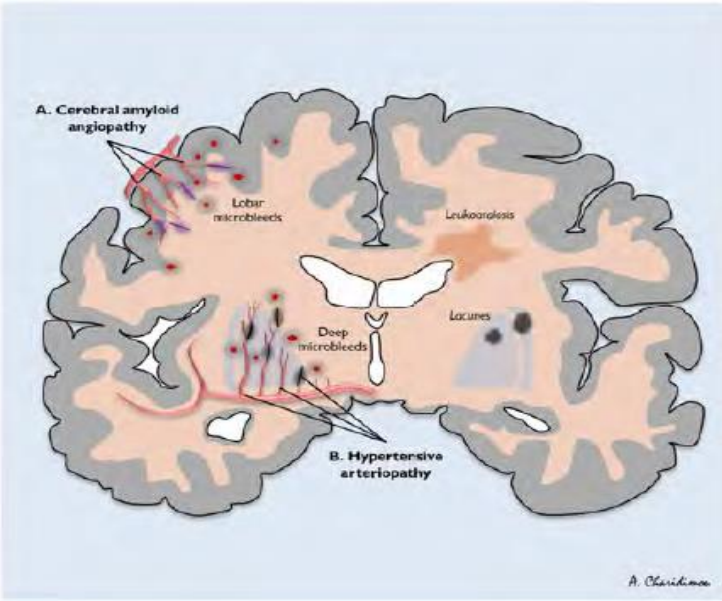
CAA Diagnosis: 'Modified' Boston criteria

	Modified Boston criteria
Definite CAA	No modification[a]
Probable CAA with supporting pathology	No modification[a]
Probable CAA	Clinical data and MRI or CT demonstrating: • Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or • Single lobar, cortical, or corticosubcortical hemorrhage and focal[b] or disseminated[c] superficial siderosis • Age ≥55 y • Absence of other cause of hemorrhage or superficial siderosis
Possible CAA	Clinical data and MRI or CT demonstrating: • Single lobar, cortical, or corticosubcortical hemorrhage or • Focal[b] or disseminated[c] superficial siderosis • Age ≥55 y • Absence of other cause of hemorrhage or superficial siderosis

- Cases: 60 ICH patients with MRI-GRE
- Reference standard: 19 autopsy, 23 ICH evacuation, 18 cortical biopsy







'Modified' Boston criteria:
Sensitivity 95% (95% CI 83–99)
Specificity 82% (95% CI 61–93)

Linn et al. Neurology 2010;74:1346-50

1. Cardinal criteria:

-Lobar ICH (symptomatic and asymptomatic)

-Lobar CMBs

-cSS (focal vs. disseminated and multifocality)

2. Supporting criteria:

-CSO-PVS (different cut-offs)

-Posterior (occipital predominance and ratio) WMH

-WMH Fazekas

-DWI lesions/microinfarcts?

3. Other features with possible significance:

-Clinical syndrome/presentation

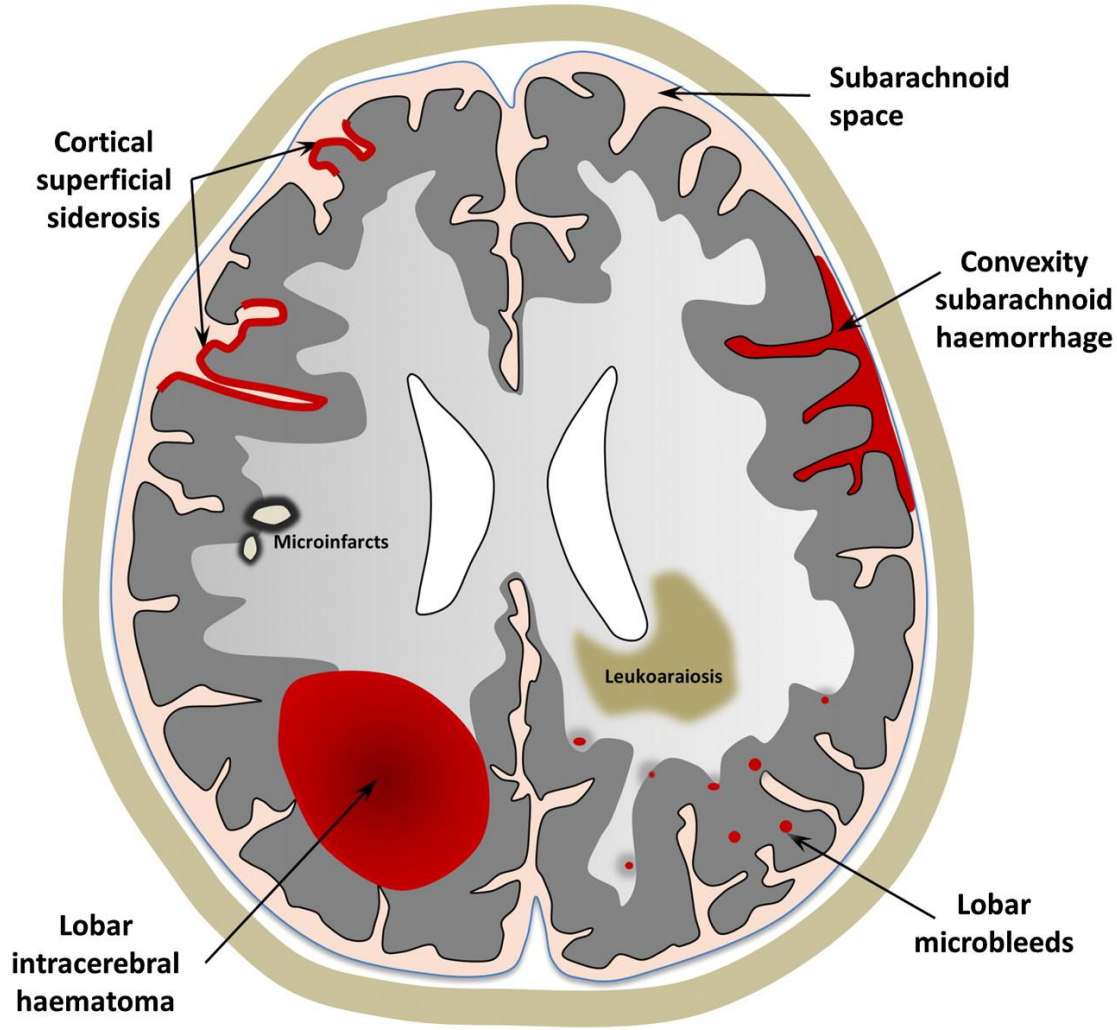
-APOE genotype

-White matter spots (>10 spots)

-Atrophy

-Amyloid PET, CSF? Other biomarkers?

A schematic representation of the spectrum of haemorrhagic and ischaemic manifestations of sporadic cerebral amyloid angiopathy, visible on MRI.



Andreas Charidimou et al. J Neurol Neurosurg Psychiatry 2012;83:124-137

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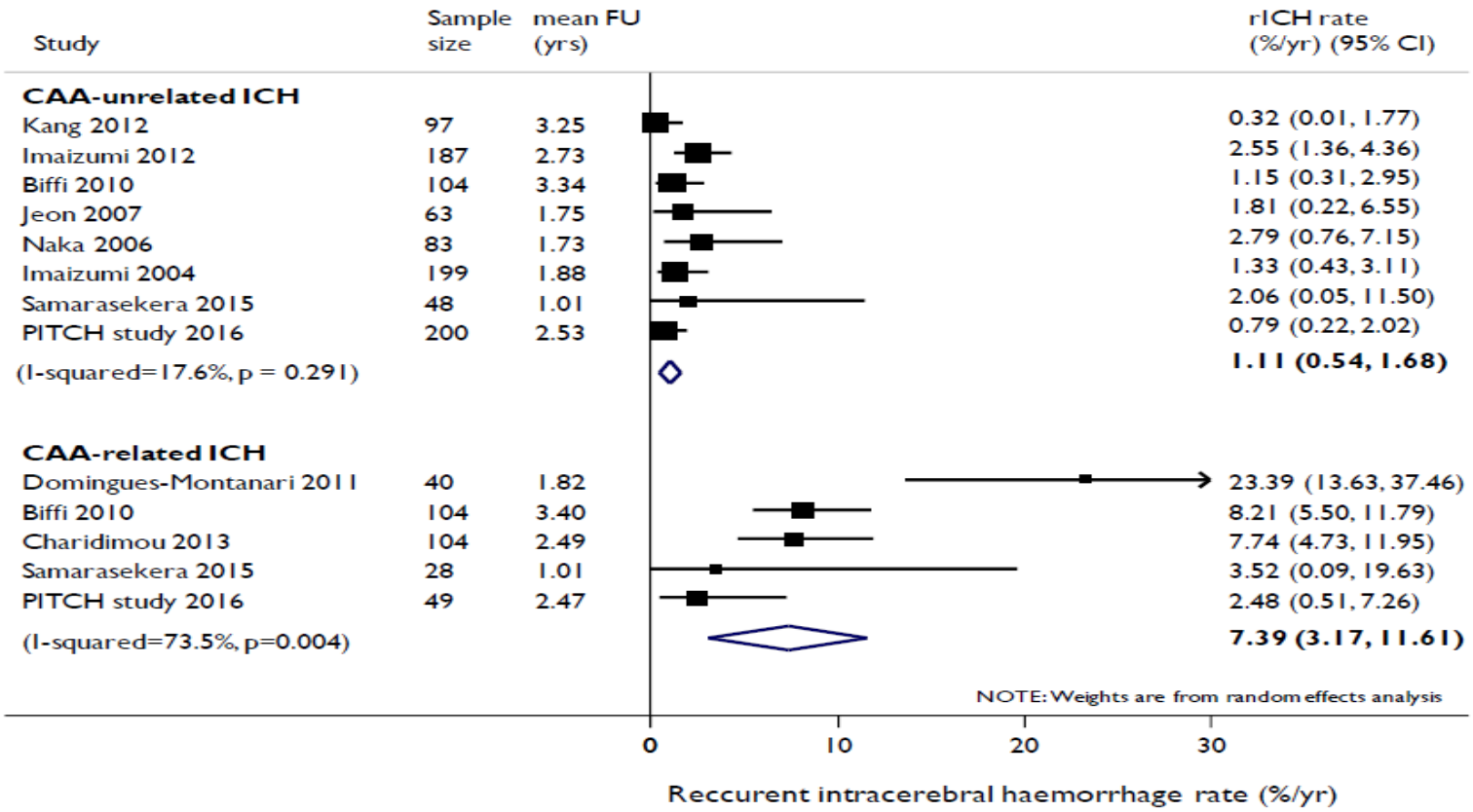
Why is CAA clinically relevant?

- **High risk of ICH recurrence (~7-8% per year)**
- Long-term management centred on recurrent CAA-ICH prevention
- Implications for anticoagulation decisions



Lobar CMBs and rICH risk in CAA-ICH: meta-analysis

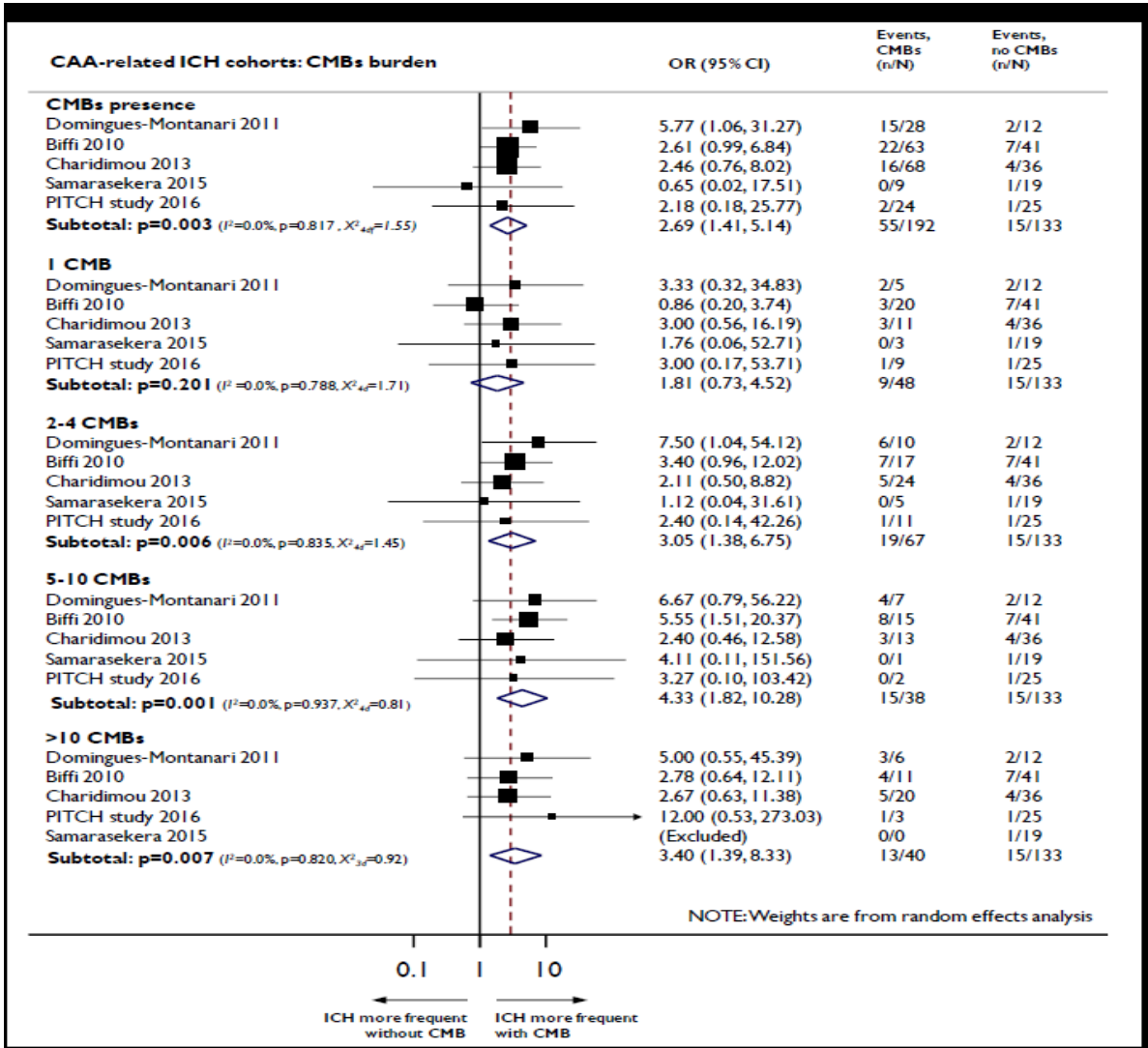
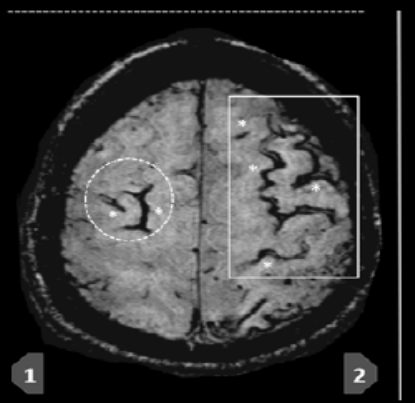


Table 2 Multivariate analysis of predictors of recurrent lobar ICH in patients with CAA

Variable	HR	95% CI	p Value
Previous lobar hemorrhage (other than index event)	4.80	1.4–15.6	0.005
Microbleeds			
1	1.88	0.5–7.6	>0.2
2–4	2.93	1.3–4.0	0.041
≥5	4.12	1.6–9.3	0.001
CT-WMH present (posterior)	4.72	1.44–15.47	0.010
Antiplatelet exposure after index event	3.95	1.6–8.3	0.021

Biffi et al. Neurology 2010

cSS not rated in these studies



‘Silent’ CAA in ischaemic stroke/TIA patients

Meta-analysis of 15 cohorts

Risk of ICH and ischeamic stroke in patients with ischaemic stroke/TIA patients

Table 1 Pooled relative risk for recurrent ischemic stroke and intracerebral hemorrhage for different cerebral microbleed (CMB) burden and distribution (all risk ratios are compared to the reference category of no CMBs)

	Ischemic stroke					Intracerebral hemorrhage				
CMB distribution, n	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI	Pooled absolute event rates, n/N (%)	Pooled absolute risk increase, %	Pooled RR	Lower 95% CI	Upper 95% CI
CMB presence	115/1,284 (9)	3.4	1.8	1.4	2.5	49/1,142 (4.3)	3.8	6.3	3.5	11.4
1 CMB	31/433 (7.2)	1.8	1.8	1.0	3.1	8/354 (2.3)	1.7	4.6	1.9	10.7
2-4 CMBs	44/433 (10.2)	4.8	2.4	1.3	4.4	9/383 (2.3)	1.8	5.6	2.4	13.3
≥5 CMBs	34/342 (10.5)	5.1	2.7	1.5	4.9	24/274 (8.8)	8.2	14.1	6.9	29.0
Strictly lobar	31/332 (9.3)	3.9	2.0	1.4	2.9	12/332 (3.6)	3.2	10.5	4.5	24.3
Strictly deep	29/437 (6.6)	1.2	1.6	1.0	2.7	6/437 (1.4)	1	3.3	1.3	8.5
Mixed	44/411 (10.7)	5.3	2.6	1.5	4.3	25/411 (6.1)	5.7	11.1	5.5	22.6

Neurology. 2016;87(14):1501-1510

-It is reasonable to provide anticoagulation to patients with silent lobar CMBs when there is an indication (eg, AF).

-When anticoagulation is needed, a novel oral anticoagulant might be preferred.

AHA/ASA Scientific Statement

Prevention of Stroke in Patients With Silent Cerebrovascular Disease

A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

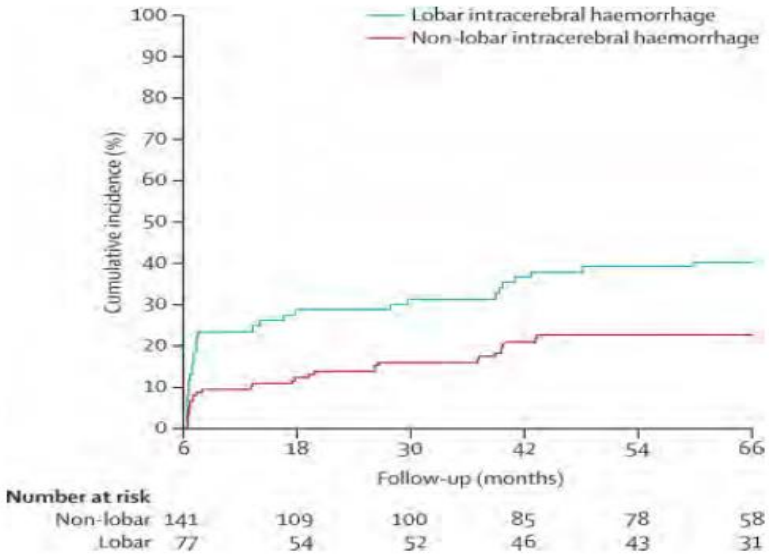
Stroke. 2017;48:e44-e71.

Why CAA as disease target

Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study

Solène Moulin, Julien Labreuche, Stéphanie Bombois, Costanza Rossi, Gregoire Boulouis, Hilde Hénon, Alain Duhamel, Didier Leys, Charlotte Cordonnier

Lancet Neurol 2016



	Subhazard ratio	95% CI	p value
Disseminated superficial siderosis	7·45	4·27-12·99	<0·0001
Cortical atrophy score per 1-point increase	2·61	1·70-4·01	<0·0001
>5 cerebral microbleeds	2·33	1·38-3·94	<0·0001
Older age per 10-year increase	1·34	1·00-1·79	0·03

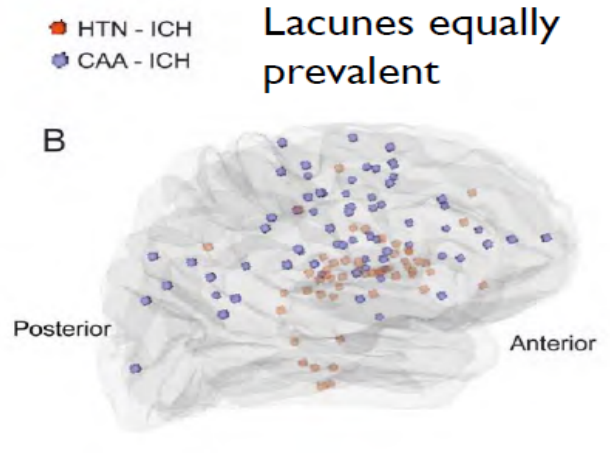
Table 6: Independent prognostic factors of new-onset dementia with MRI lesions after the 6-month landmark as determined by backward stepwise multivariable analysis (in the overall population with MRI data available)

Cumulative rates of new-onset dementia

Summary that far…

- CAA is a common, well-defined SVD
- CAA presentations associated with future lobar ICH and dementia
  - potential opportunity to prevent both
- MRI markers key for risk stratification
- Vascular disease/comorbidities common in CAA patients

Comorbidities in CAA-ICH	~% prevalence
Hypertension	50-80
AF (most with CHA_2DS_2-VaSc⩾2)	10-30
Previous lobar ICH history	10-20
Diabetes mellitus	20
Hyperlipedaemia	25-30
Cardiovascular disease	10-20
Ischaemic stroke/TIA	10-15



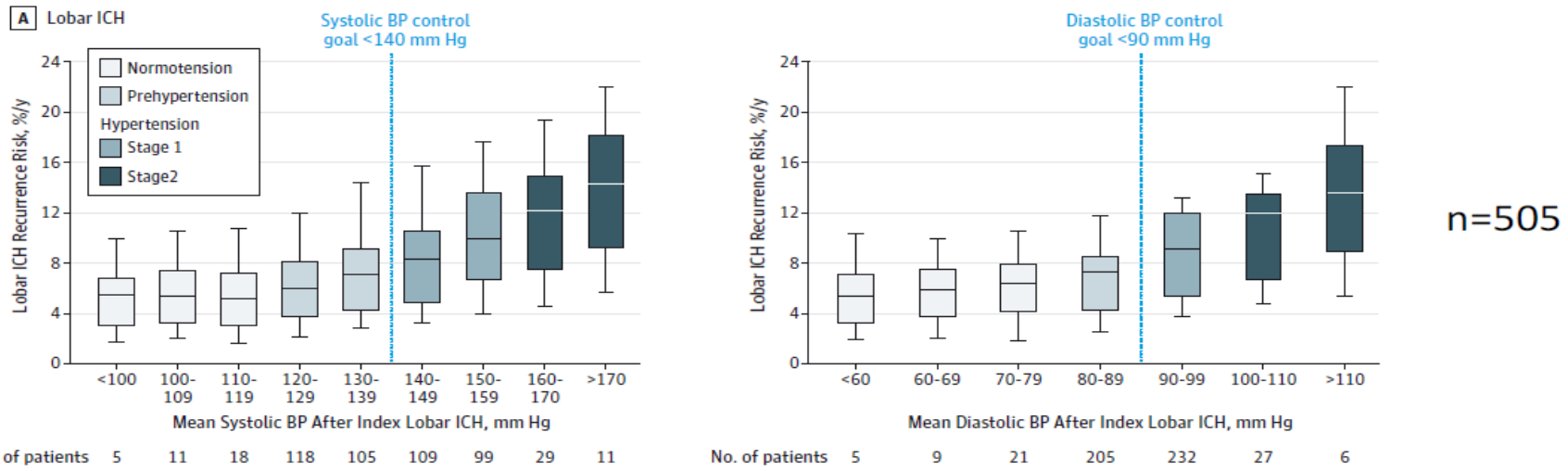
Pasi M et al. Neurology. 2017

Original Investigation

Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage

Alessandro Biffi, MD; Christopher D. Anderson, MD, MMSc; Thomas W. K. Battey, BS; Alison M. Ayres, BA; Steven M. Greenberg, MD, PhD; Anand Viswanathan, MD, PhD; Jonathan Rosand, MD, MSc

Figure 2. Estimated Yearly Risk of Recurrent ICH Based on Mean Blood Pressure Measurements During Follow-up



n=505

-Inadequate BP control during follow-up associated with higher lobar ICH recurrence risk
-RCTs needed to address the benefits and risks of stricter BP control in ICH survivors

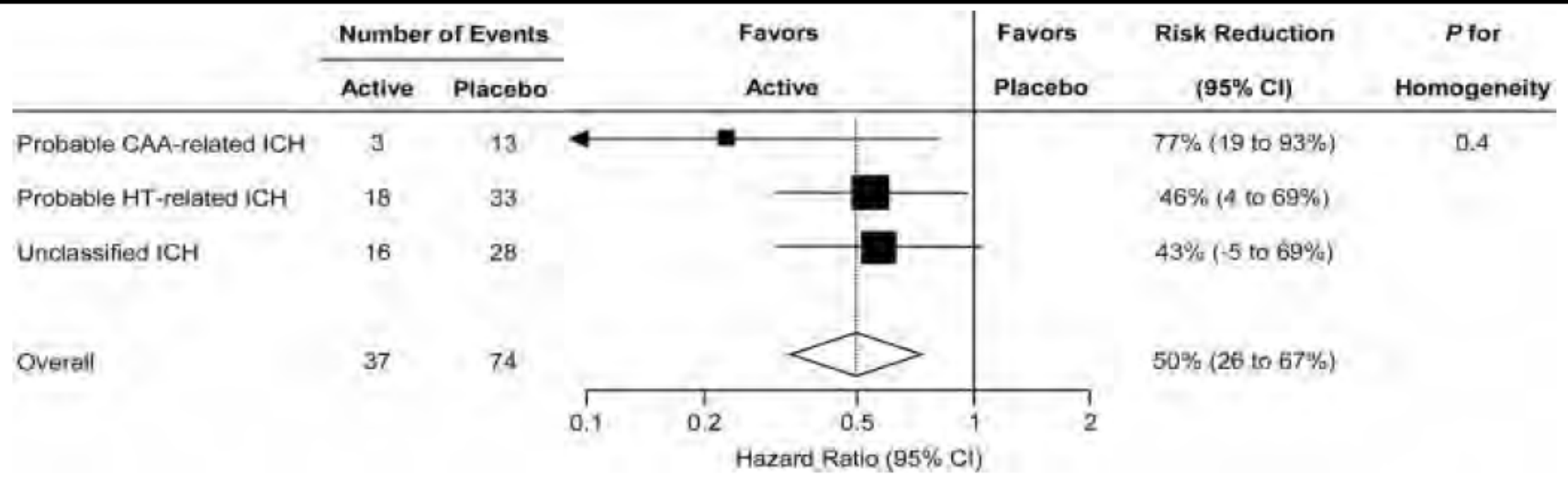
JAMA. 2015;314(9):904-912. doi:10.1001/jama.2015.10082

Effects of Perindopril-Based Lowering of Blood Pressure on Intracerebral Hemorrhage Related to Amyloid Angiopathy

The PROGRESS Trial

Hisatomi Arima, MD; Christophe Tzourio, MD; Craig Anderson, MD; Mark Woodward, PhD; Marie-Germaine Bousser, MD; Stephen MacMahon, PhD; Bruce Neal, MD; John Chalmers, MD; for the PROGRESS Collaborative Group

(*Stroke*. 2010;41:394-396.)



Mean BP levels were lower in CAA-related ICH 137/81 vs. 157/88 mmHg

Mean reduction of 9/4 mm Hg

AF after CAA-ICH: A hot dilemma

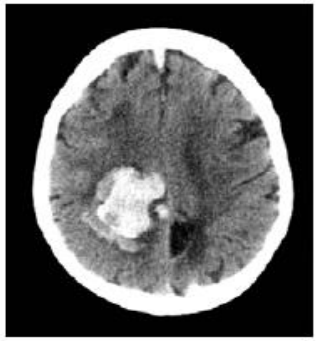
- Start oral anticoagulation (OAC)?
  - warfarin vs. DOACs?
  - vs. no antithrombotic
  - vs. antiplatelet
  - vs. left atrial appendage occlusion

- Stratification according to CAA MRI signatures?
  - cSS/CMBs

- Stratification according to CHA_2DS_2-VaSc score?

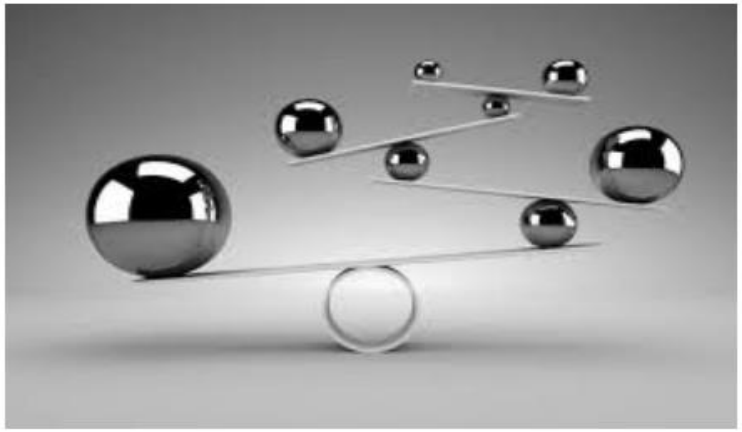
- <u>No data from RCTs of OAC after ICH</u>

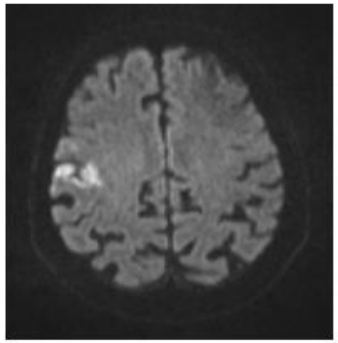
Antithrombotic decisions in CAA
Balancing risks



Risk of Ischemic Event

Without antithrombotic With antithrombotic





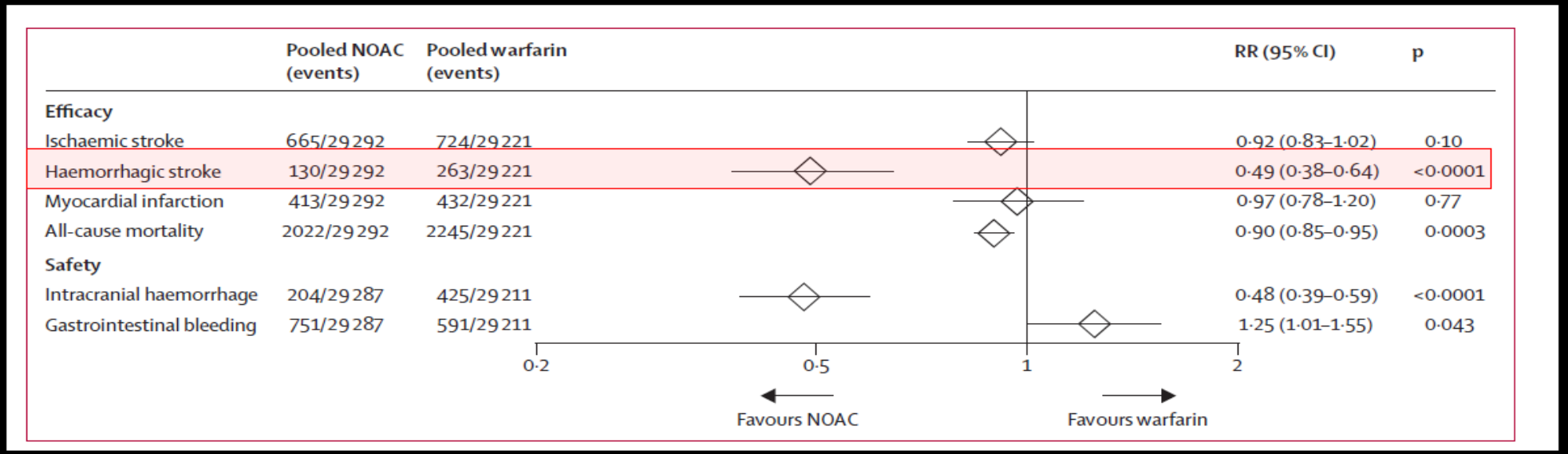
Without antithrombotic With antithrombotic

Risk of CAA-related ICH

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

Lancet 2014; 383: 955–62



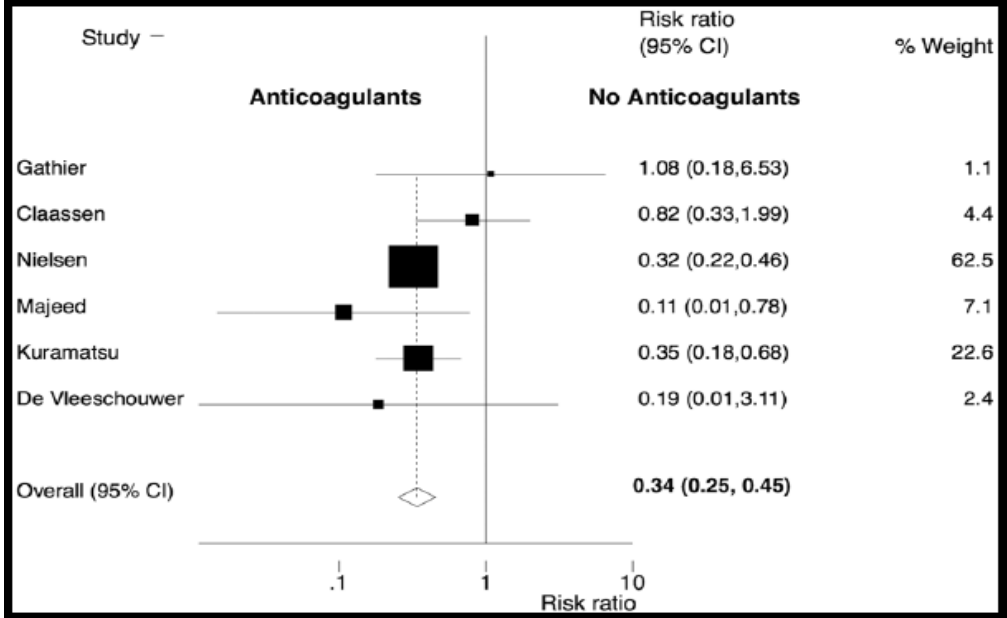
51% reduction in hemorrhagic stroke

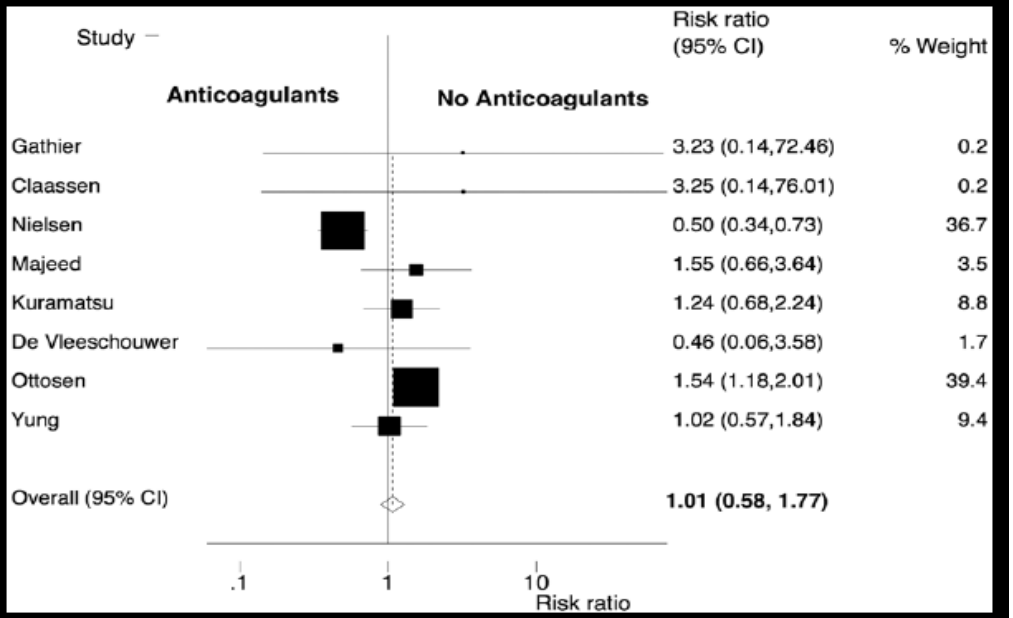
Restarting Anticoagulant Therapy After Intracranial Hemorrhage

A Systematic Review and Meta-Analysis

Santosh B. Murthy, MD, MPH; Ajay Gupta, MD; Alexander E. Merkler, MD; Babak B. Navi, MD, MS; Pitchaiah Mandava, MD, PhD, MSEE; Costantino Iadecola, MD; Kevin N. Sheth, MD; Daniel F. Hanley, MD; Wendy C. Ziai, MD, MPH; Hooman Kamel, MD

OAC: warfarin





Stroke . 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.016327

Antithrombotic decisions in CAA
Some basic principles – Avoid fuzzy logic

- CAA/CMBs literature over-emphasises ICH risk
- Data on CAA come from observational studies vs. RCTs for OAC
- Don't mistake statistical certainty for size of effect

- Absolute risks (%/year) for future ICH and ischaemic stroke instead
- Conflating overall risk (ischemic stroke vs. ICH) with risk reductions
  - Instead assess risk reduction for cardiac/cerebrovascular events with antithrombotics vs. ICH risk increase

- Future ICH risk is not uniform - Clinical context:
  - CAA-related syndrome, CAA-ICH vs. non-ICH CAA, silent CAA
- Haemorrhagic CAA signatures: cSS

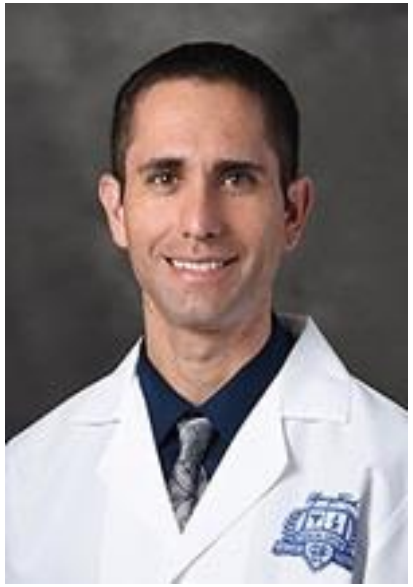
- Consider the severity of the consequences
  - ICH has higher mortality than ischemic stroke

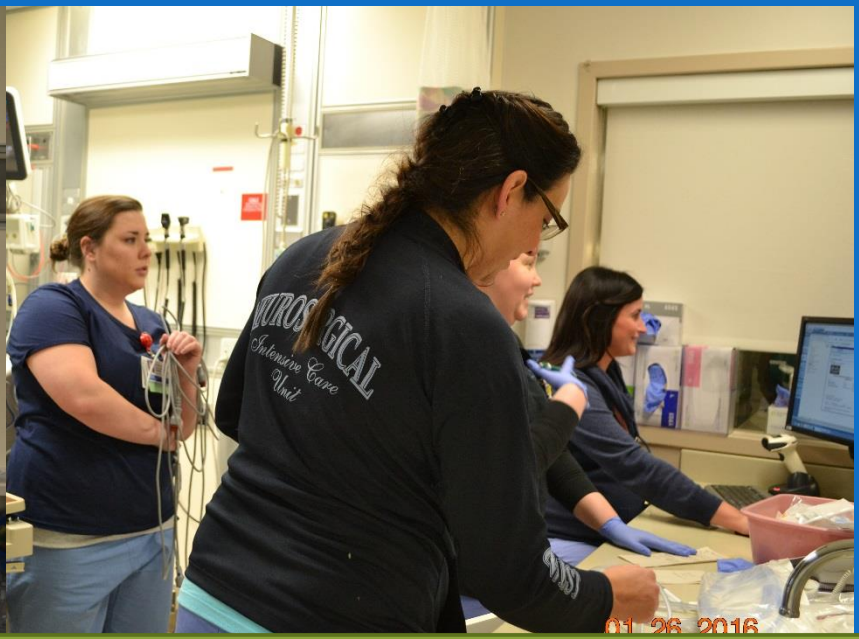
Current advice in CAA management

- MRI key for risk stratification - cSS one of the most promising markers
- Clinical spectrum: CAA-ICH, CAA non-ICH, silent CAA presentations
- Vascular disease prevention in CAA-ICH patients
  - Blood pressure control (target SBP < 130 mmHg)
  - Avoidance of antithrombotic therapies unless clear indication
  - NOACs?? Probably safer but no direct data available
  - RANDOMISE PATIENTS IN ONGOING/FUTURE TRIALS
  - Statins: Use with caution/reserve for compelling indications
- Incidental CMBs/cSS and no ICH history
  - current evidence is insufficient to recommend avoiding anticoagulation if there is a strong indication
- Cognitive dysfunction
  - Screen and follow-up for cognitive decline
  - High risk of dementia following lobar ICH

Our Team

Neurointensivists





Neuro ICU (C-6West)

Henry Ford
HEALTH SYSTEM

all for you