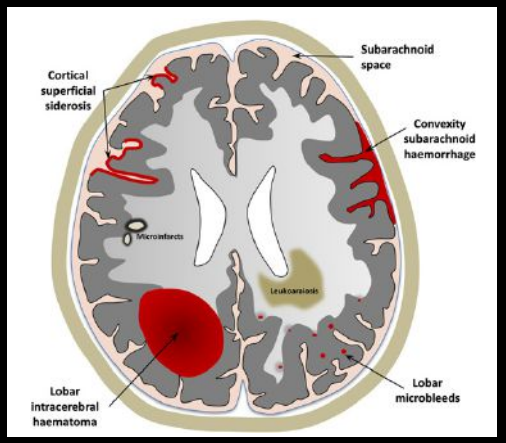
# Sporadic Cerebral Amyloid Angiopathy: A Clinical Approach

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# Disclosures

- **Consultancy:** Daiichi Sankyo Company, Bayer AG, Servier Canada Inc., Boehringer Ingelheim, BMS/Pfizer, Apopharma Inc.

- **Speaker's Bureau:** Bayer AG, Servier Canada Inc.

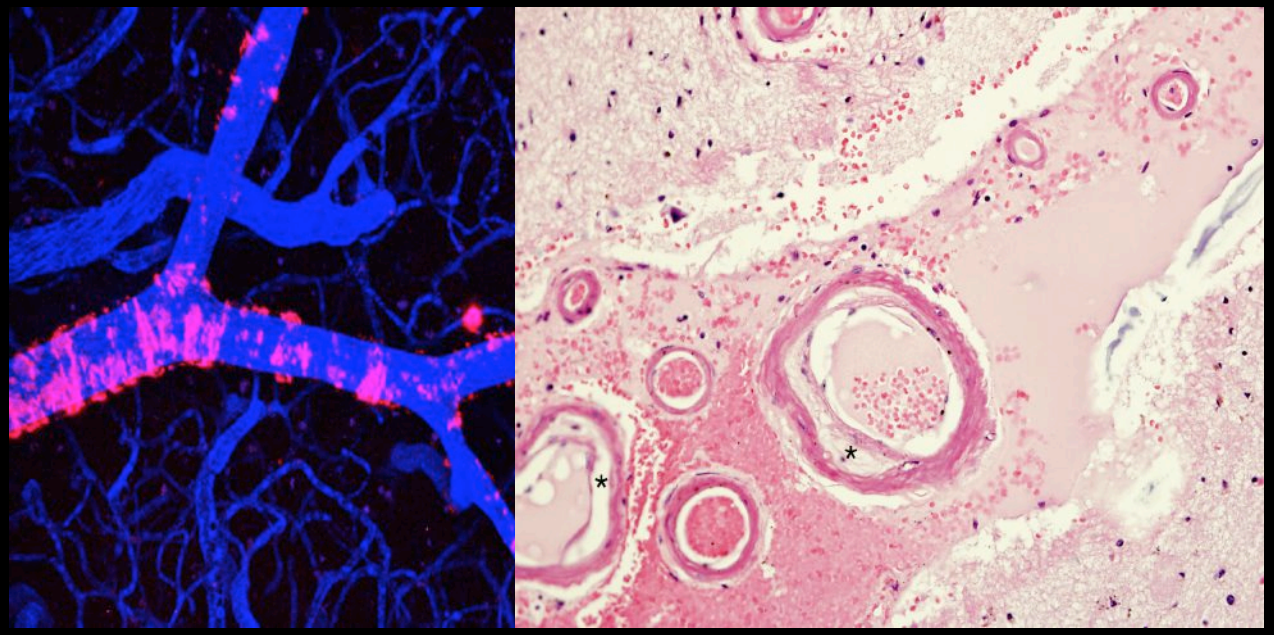
- **Research funding:** Bayer AG, Servier Canada Inc., Daiichi Sankyo Company, BMS/Pfizer, Portola, OctaPharma inc.

# Objectives

- Review the pathophysiology and epidemiology of cerebral amyloid angiopathy (CAA).
- Highlight key clinical and neuroimaging manifestations of the disease.
- Summarize optimal management of patients with CAA and ongoing clinical dilemmas

# Sporadic Cerebral Amyloid Angiopathy

- A common cerebral small vessel disease (microangiopathy) characterized by progressive beta-amyloid deposition in the vessel wall of small to medium sized arterioles (max diameter: 2 mm)



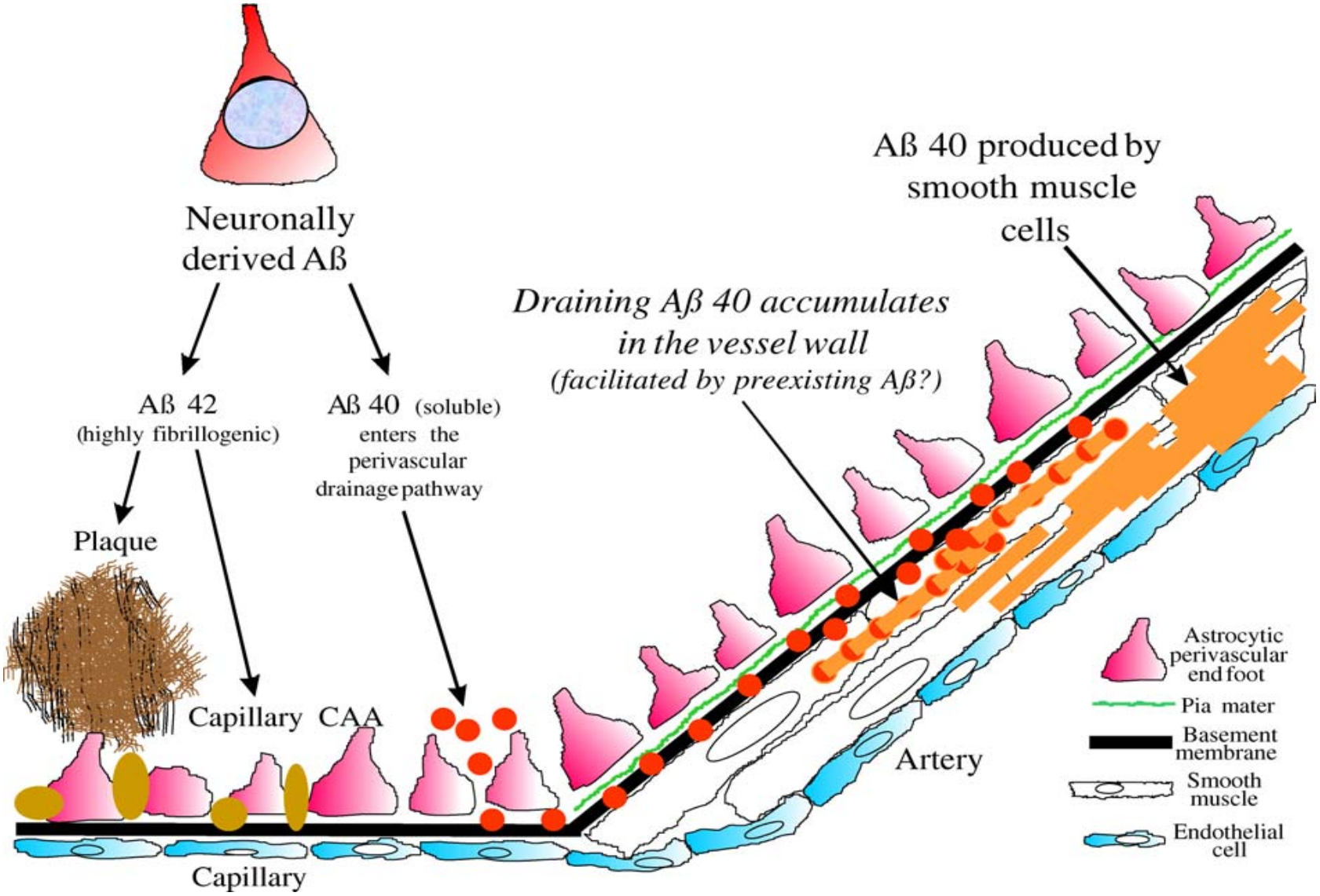
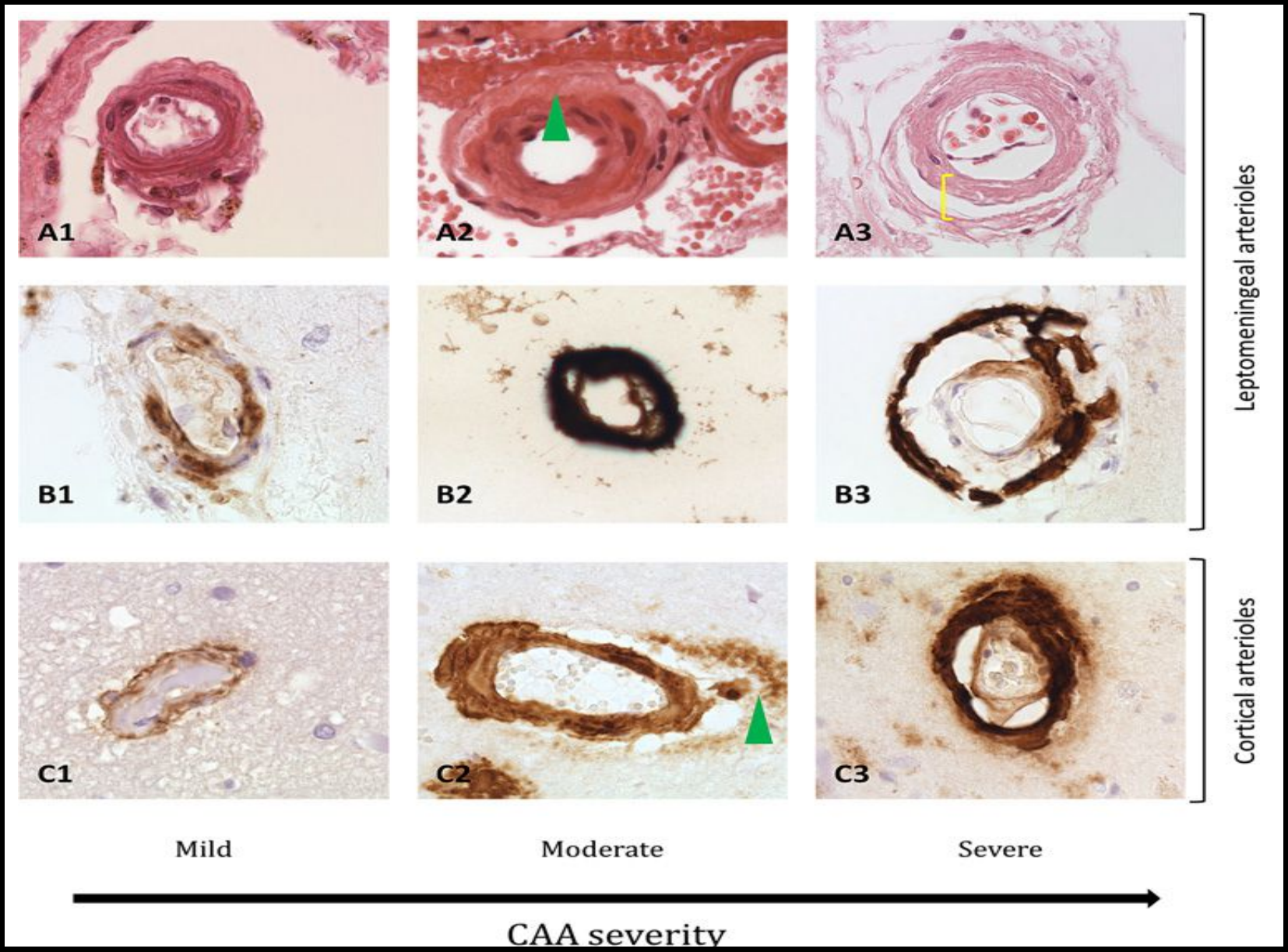
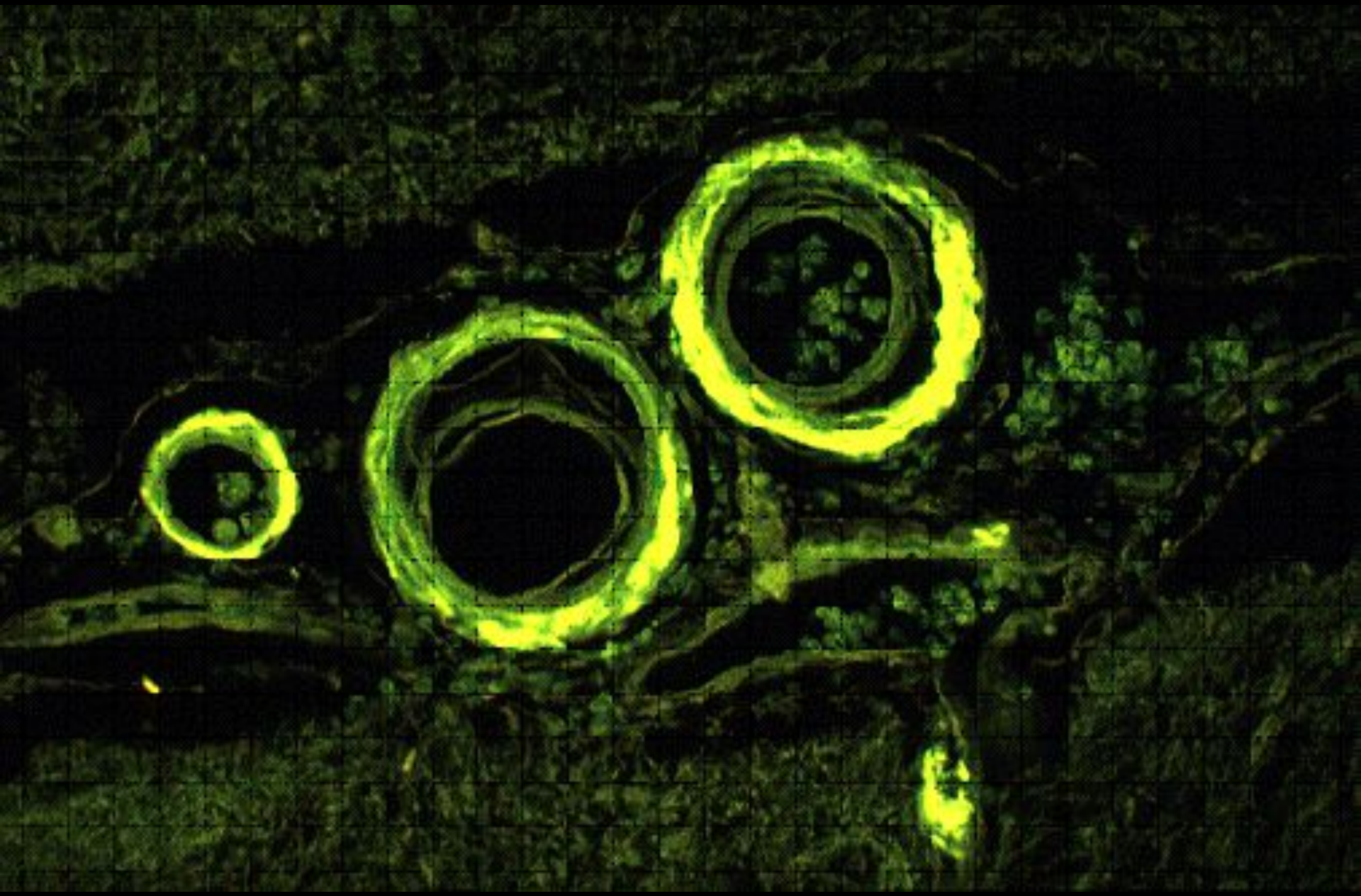



**Fig. 6** Hypothetical pathomechanism for CAA: Neuronally derived Aβ42 fibrillizes into plaques and is the major constituent of Aβ in capillary CAA, while Aβ40 remains soluble and enters the perivascular drainage pathway where it accumulates in blood vessel walls in the presence of Aβ40, which is produced by smooth muscle cells

# CAA: Pathology




*J Neurol Neurosurg Psychiatry* 2012;**83**:124–137



# CAA: Pathology

- Predominantly affects leptomeningeal and cortical arterioles, capillaries and rarely venules.
- Very focal, patchy and asymmetric process
- Rarely involves white matter, cerebellum.
- Almost never involves basal ganglia and brainstem.

# Cerebral Amyloid Angiopathy: Incidence and Complications in the Aging Brain
# II. The Distribution of Amyloid Vascular Changes

H.V. VINTERS, M.D., F.R.C.P.(C),* AND J.J. GILBERT, M.D., F.R.C.P.(C)

TABLE 3 *All Areas of Cerebral Cortex with Severe Involvement (3+) by CAA*

| Ages years | Cases with 3+ / Number of cases | Frontal lobes | | Temporal lobes | | Parietal lobes | | Occipital lobes | | Hippocampus | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | R | L | R | L | R | L | R | L | R | L |
| 60–69 | 1/1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 70–79 | 6/12 | 1 | 2 | 1 | 1 | 2 | 3 | 3 | 3 | 0 | 0 |
| 80–89 | 6/13 | 2 | 2 | 2 | 2 | 3 | 4 | 4 | 3 | 0 | 0 |
| 90+ | 1/4 | | | | | | 1 | 1 | 1 | | |
| Totals | 14/30 | 4 | 5 | 4 | 4 | 6 | 9 | 9 | 8 | 1 | 1 |

L = left; R = right.

# CAA: Epidemiology

- Advancing age is the strongest known demographic risk factor

**Table 2** Prevalence of vascular and parenchymal Aβ deposition according to age in the 100 brains in which 2 or more cortical blocks were examined

| Age (years) | Vascular | | Parenchymal |
|---|---|---|---|
| | Leptomeningeal | Cortical | |
| 51–60 ($n = 9$) | 0 | 0 | 2 (22%) |
| 61–70 ($n = 22$) | 4 (18%) | 2 (9%) | 9 (41%) |
| 71–80 ($n = 35$) | 8 (23%) | 7 (20%) | 19 (54%) |
| 81–90 ($n = 33$) | 13 (39%) | 9 (27%) | 21 (64%) |
| 91–100 ($n = 1$) | 0 | 0 | 1 |
| Total ($n = 100$) | 25 (25%) | 18 (18%) | 52 (52%) |

*Journal of Clinical Neuroscience* (2003) **10**(2), 186–189

# CAA: Epidemiology

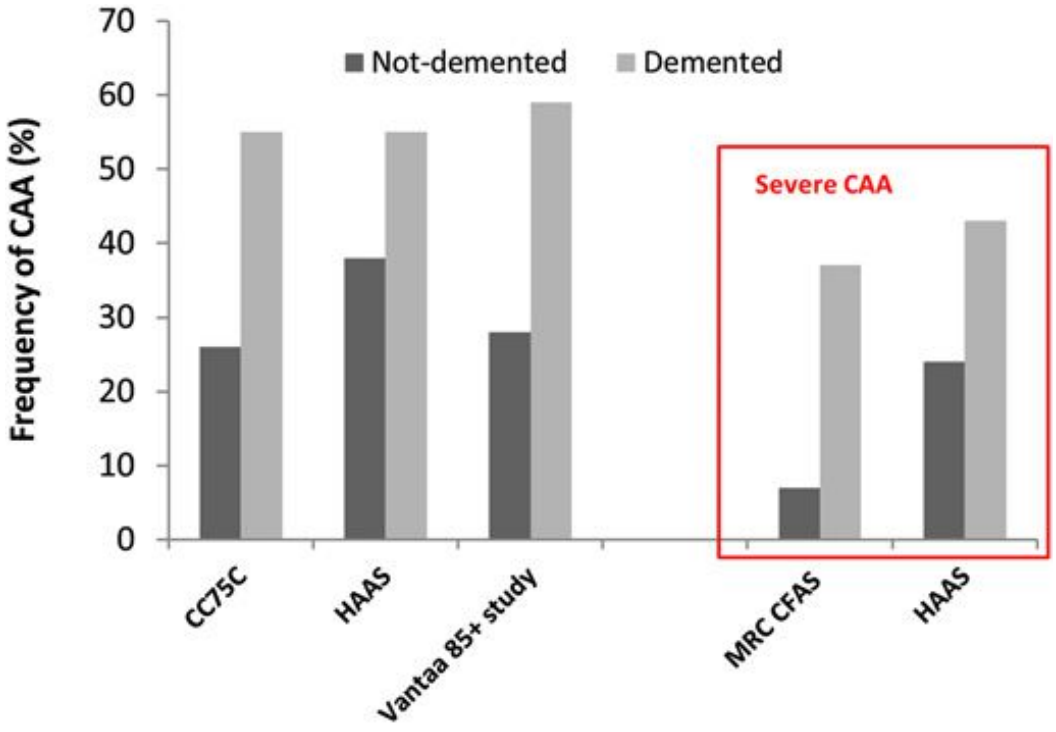



**Figure 1** The frequency of cerebral amyloid angiopathy (CAA) in demented and non-demented elderly individuals in population based clinicopathological studies. Note the increased prevalence of CAA, even if only severe pathology is taken into account. CC75C, Cambridge City over 75 Cohort[21]; HAAS, Honolulu—Asia Ageing Study[23]; Vantaa 85+ study[24]; MRC—CFAS, MRC Cognitive Function and Ageing Study.[22]

20 – 40% in non-demented elderly.

50 – 60% in demented elderly.

Alzheimer's disease: 90% have some degree of CAA (25% severe)

*J Neurol Neurosurg Psychiatry* 2012;**83**:124—137

# CAA: APOE ε2 and ε4 alleles

- Strong dose dependent effect on the risk of developing CAA and its clinical severity.

- Associated with:
  - sporadic CAA-related lobar ICH
  - younger age of first ICH
  - greater likelihood of hematoma expansion
  - poorer clinical outcome
  - a higher risk of recurrence

*J Neurol Neurosurg Psychiatry* 2012;**83**:124–137

# Association of apolipoprotein E ε2 and vasculopathy in cerebral amyloid angiopathy

S.M. Greenberg, MD, PhD; J.-P.G. Vonsattel, MD; A.Z. Segal, MD; R.I. Chiu, BA; A.E. Clatworthy, BA; A. Liao, BS; B.T. Hyman, MD, PhD; and G.W. Rebeck, PhD

NEUROLOGY 50 **April 1998**

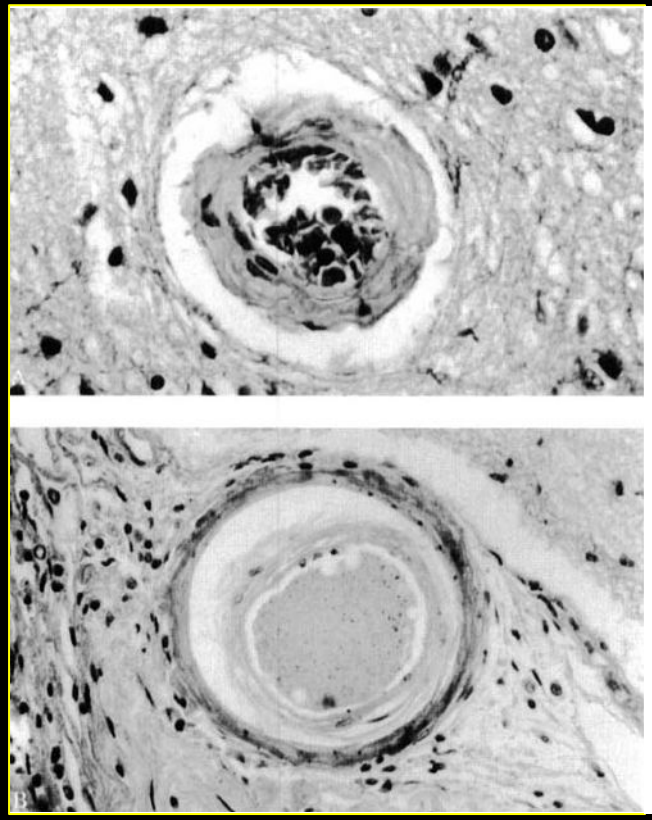
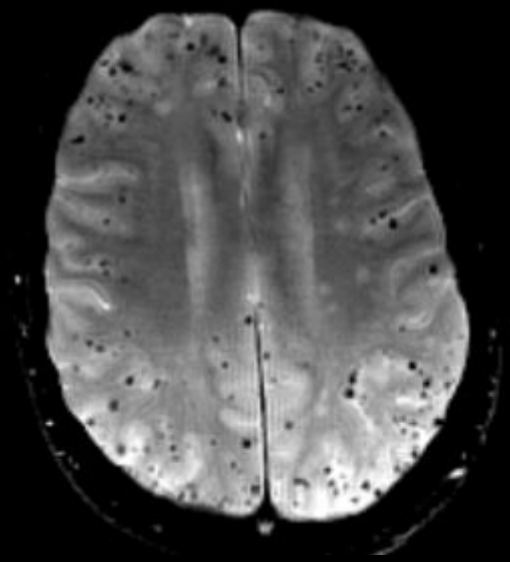


***Table 3*** *Association of apolipoprotein E ε2 with CAA-related vasculopathic changes*

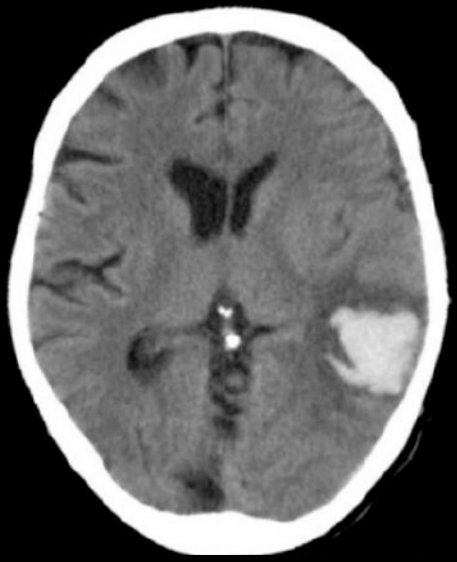
| CAA pathology | No. of brains | Allele frequency ε2 | ε3 | ε4 |
|---|---|---|---|---|
| Replacement of media with amyloid | 52 | 0.01 | 0.55 | 0.44 |
| Replacement of media with amyloid + vasculopathic changes | 23 | 0.09* | 0.45 | 0.46 |

* $p = 0.03$.

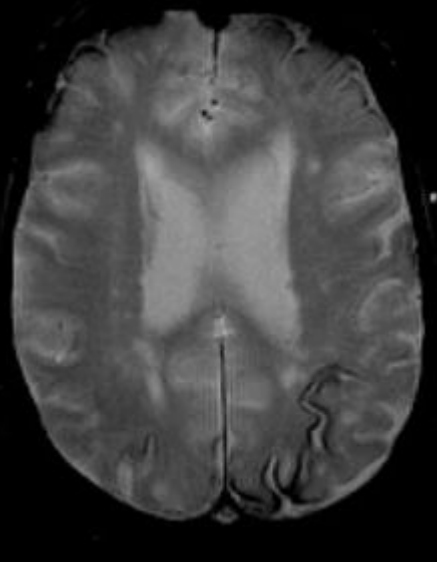
# CAA: Neuroimaging/Clinical Manifestations



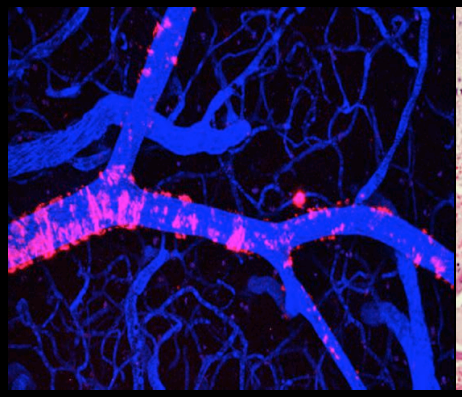
Cerebral Microbleeds

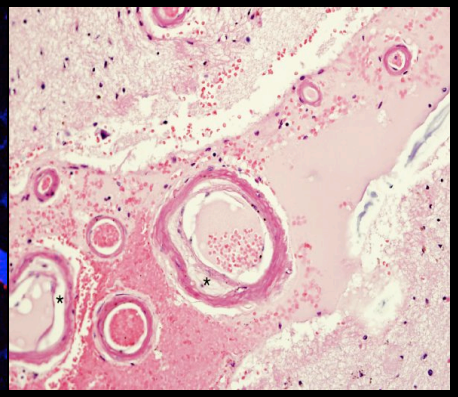


Intracerebral Hemorrhage



Cortical Superficial Siderosis





# Hemorrhagic Manifestations of CAA

J Neurosci 2007;27:1973-80.
Stroke 2008;39:3083-85
Neurology 2012;79:2335-41

# CAA: ICH

- CAA most often recognized in life by the incidence of symptomatic, spontaneous, lobar ICH.
- CAA accounts for 5-30% of all ICH

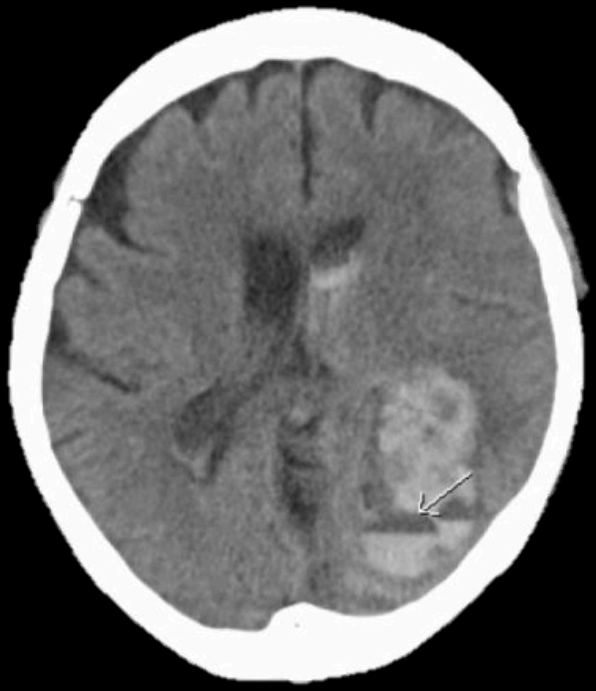
# Cerebral amyloid angiopathy: a significant cause of cerebellar as well as lobar cerebral hemorrhage in the elderly

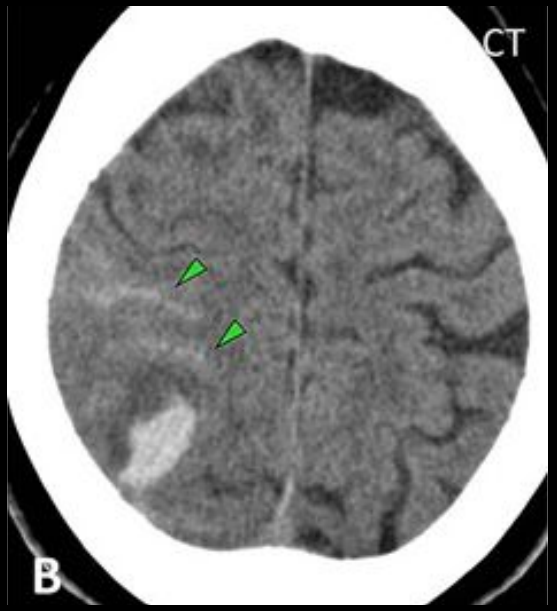
Yoshinori Itoh [a], Masahito Yamada [c], Michio Hayakawa [b], Eiichi Otomo [a] and Tadashi Miyatake [c]

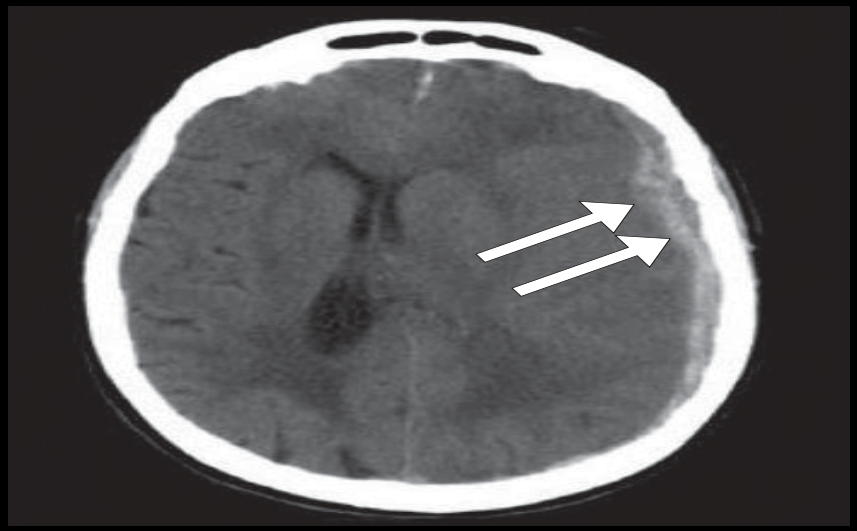
Journal of neurological sciences. 1993

CAUSES OF LOBAR, CEREBELLAR AND BRAINSTEM HEMORRHAGES

| Site | Cause | No. of cases (rate, %) |
|---|---|---|
| Lobar type | Hypertension | 14 (48.3) |
| | CAA | 9 (31.0) |
| | Trauma | 5 (17.2) |
| | Unknown | 1 (3.4) |
| Cerebellum | Hypertension | 11 (78.6) |
| | CAA | 2 (14.3) |
| | Unknown | 1 (7.1) |
| Brainstem | Hypertension | 5 (100) |




CT
B



# The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study

*Lancet Neurol* 2018; 17: 232–40

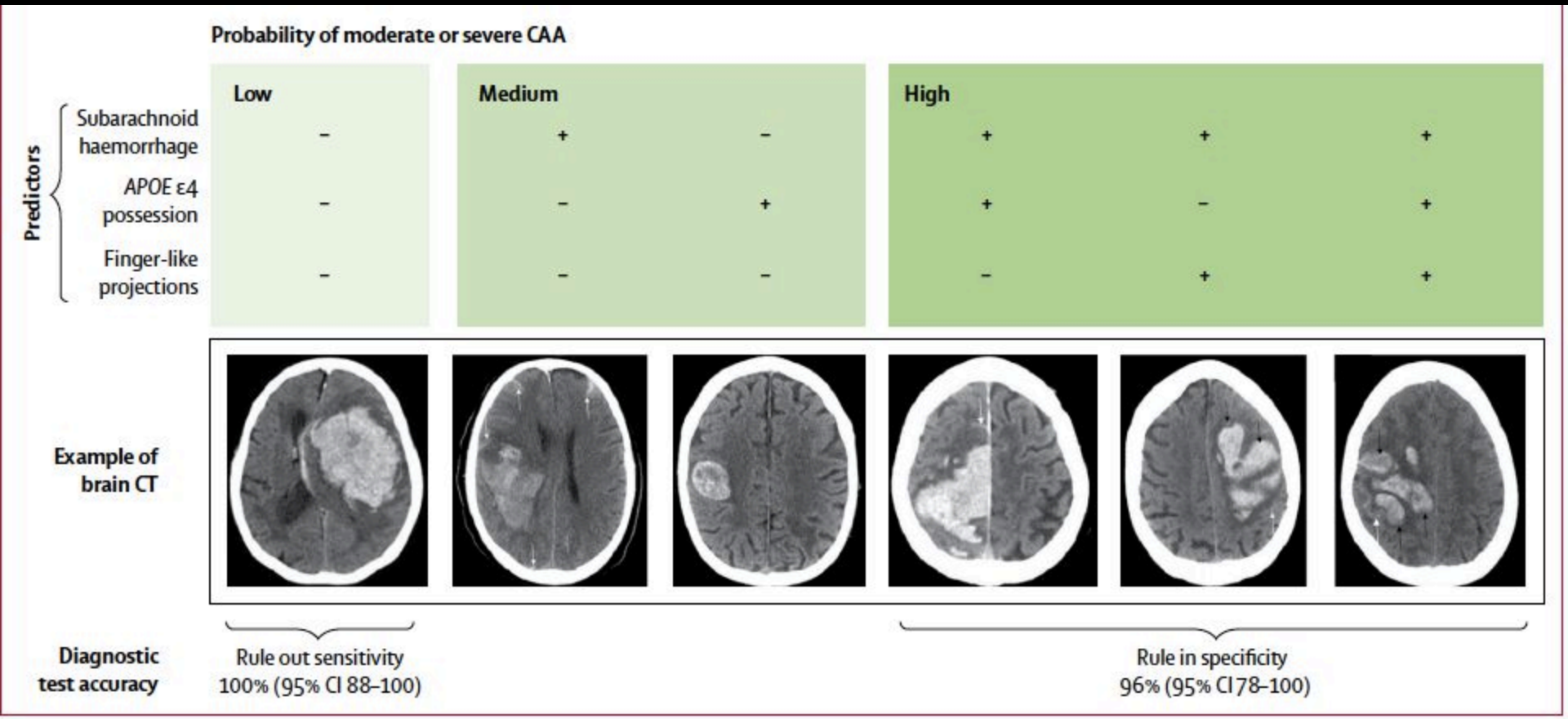



***Figure 3:*** **Categorisation of probability of lobar intracerebral haemorrhage associated with moderate or severe cerebral amyloid angiopathy according to the three predictor variables, with example CT images**

CAA=cerebral amyloid angiopathy. Adapted from Salman and Rodrigues (Creative Commons 4.0).[23]

# Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage

Renee D. Bailey, MD; Robert G. Hart, MD; Oscar Benavente, MD; and Lesly A. Pearce, MS

Neruology 2001

***Table 3*** *Site of initial bleed versus recurrent ICH*

| Location | Participants, n | Total follow-up, y | Recurrent ICH, n (% per patient–year) |
|---|---|---|---|
| Lobar ICH | | | |
| South Korea[6] | 77 | 235 | 10 (4.3) |
| Portugal[8] | 60 | 109 | 4 (3.7) |
| Siena, Italy[9] | 42 | 294 | 16 (5.4) |
| Jackson, MS, USA[11] | 13 | 31 | 0 (0.0) |
| Boston, MA, USA[12] | 71 | 141 | 19 (13.5) |
| Aggregate | 263 | 810 | 49* |

5.5% recurrence rate

Vs.

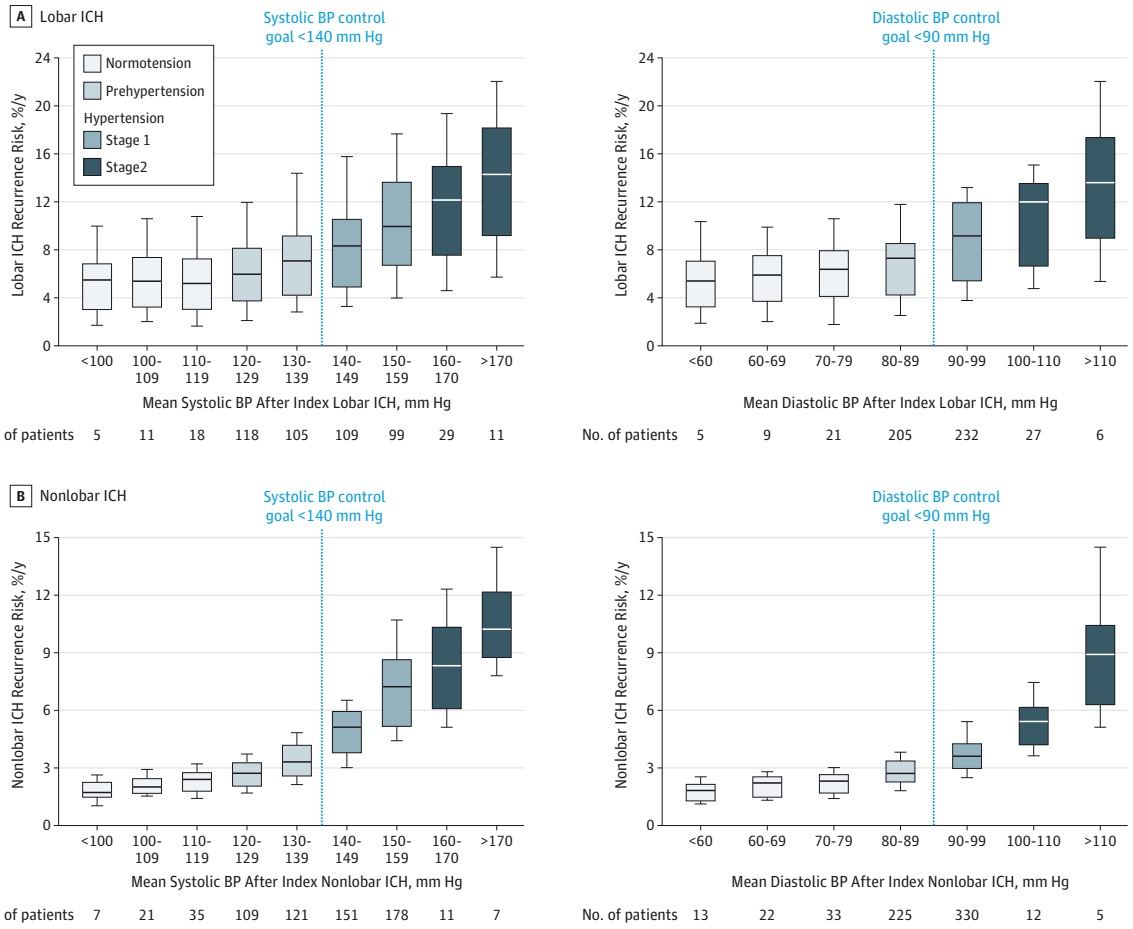
2% following deep ICH

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=1145

# Risk Factors for Primary ICH

N= 3059 first ever ICH from 32 countries

| Risk Factor | PAR |
|---|---|
| History of hypertension or BP≥140/90 | 56% |
| Lack of regular physical activity | 35% |
| Unhealthy diet | 25% |
| Psychosocial stress | 25% |
| Elevated waist-to-hip ratio | 13% |
| Current alcohol intake | 10% |
| Current smoking | 4% |
| Total: | 87% |

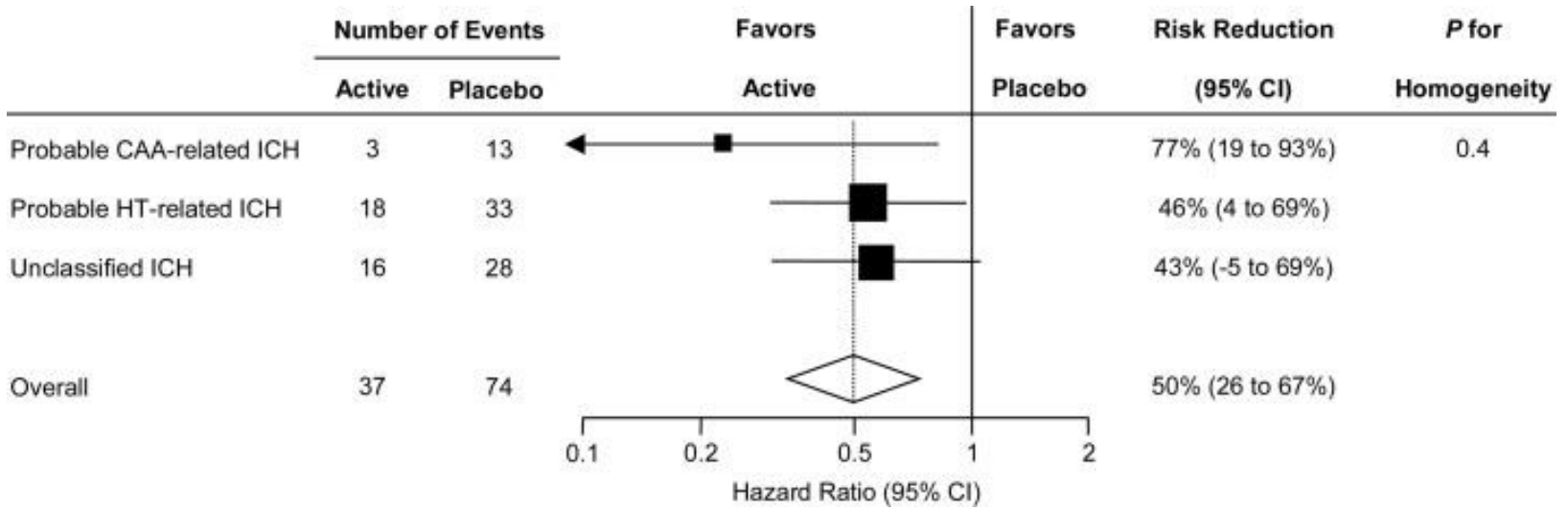
Lancet 2016; 388: 761–75

# 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.)

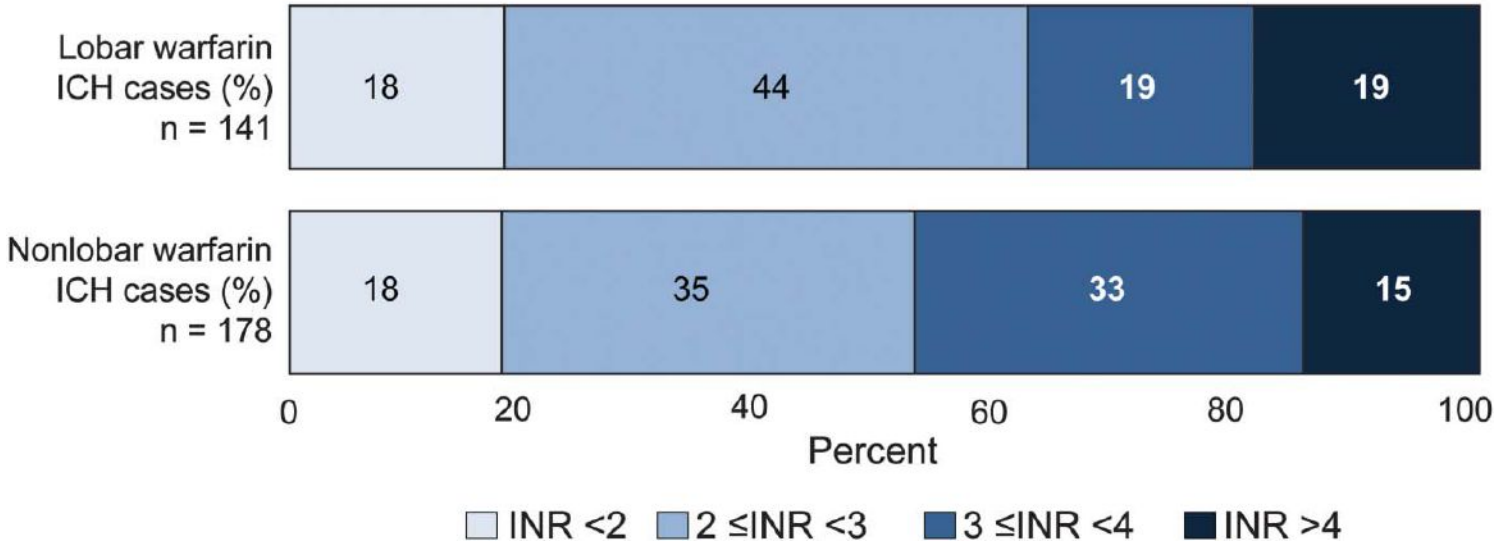



Mean BP levels were lower in CAA-related ICH 137/81 vs. 157/88 mmHG

Mean reduction of 9/4 mm Hg

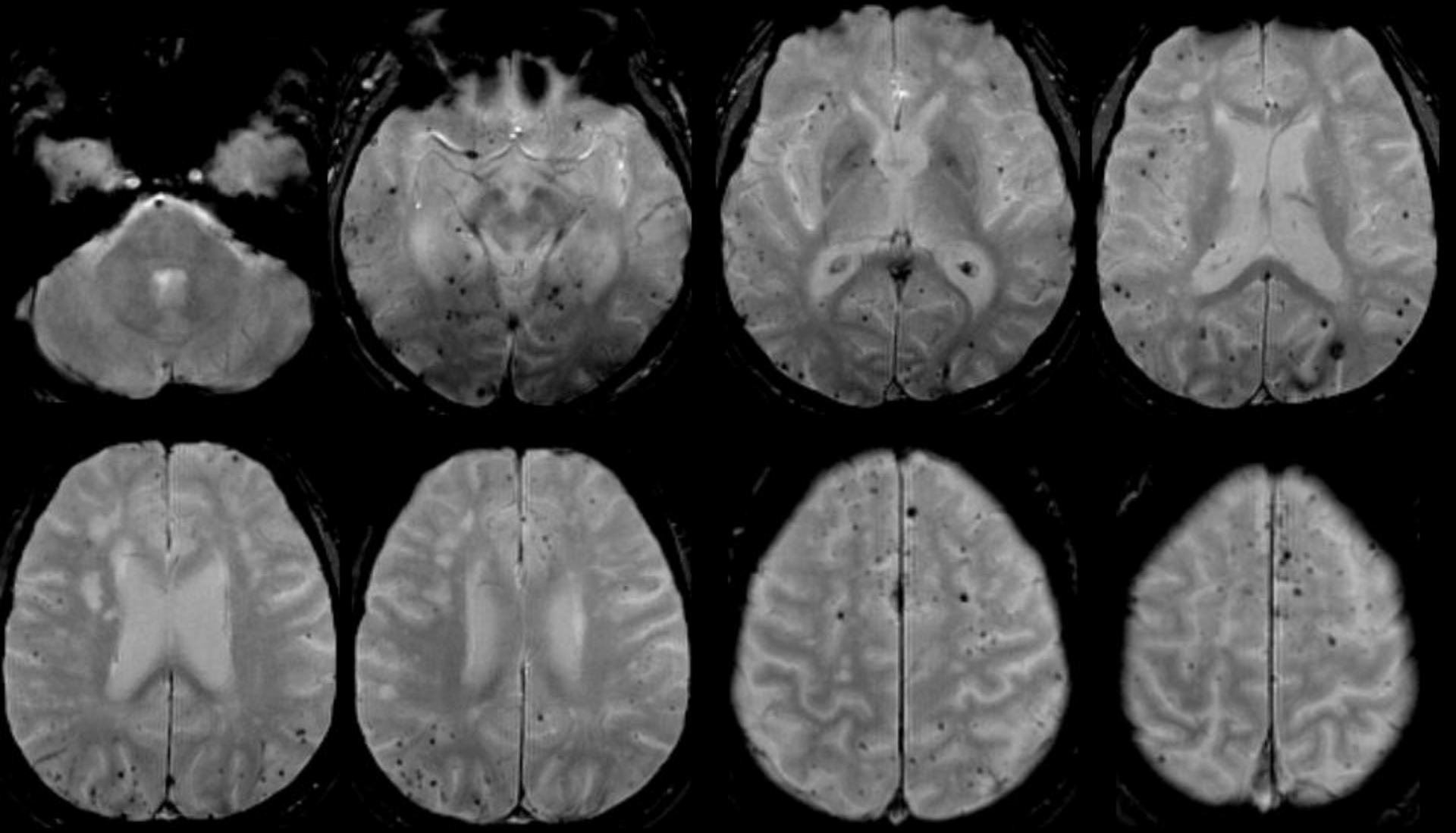
# *APOE* ε variants increase risk of warfarin-related intracerebral hemorrhage

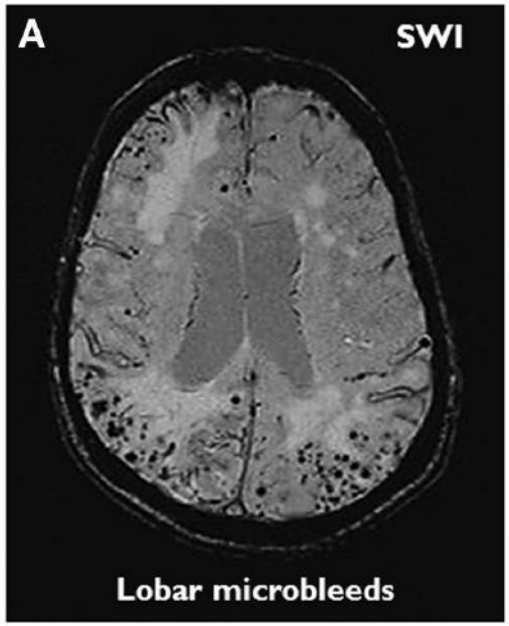
2014;83:1139-1146

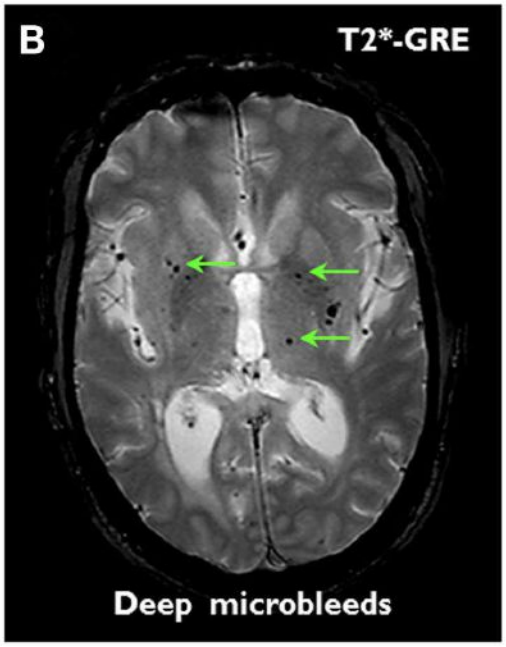


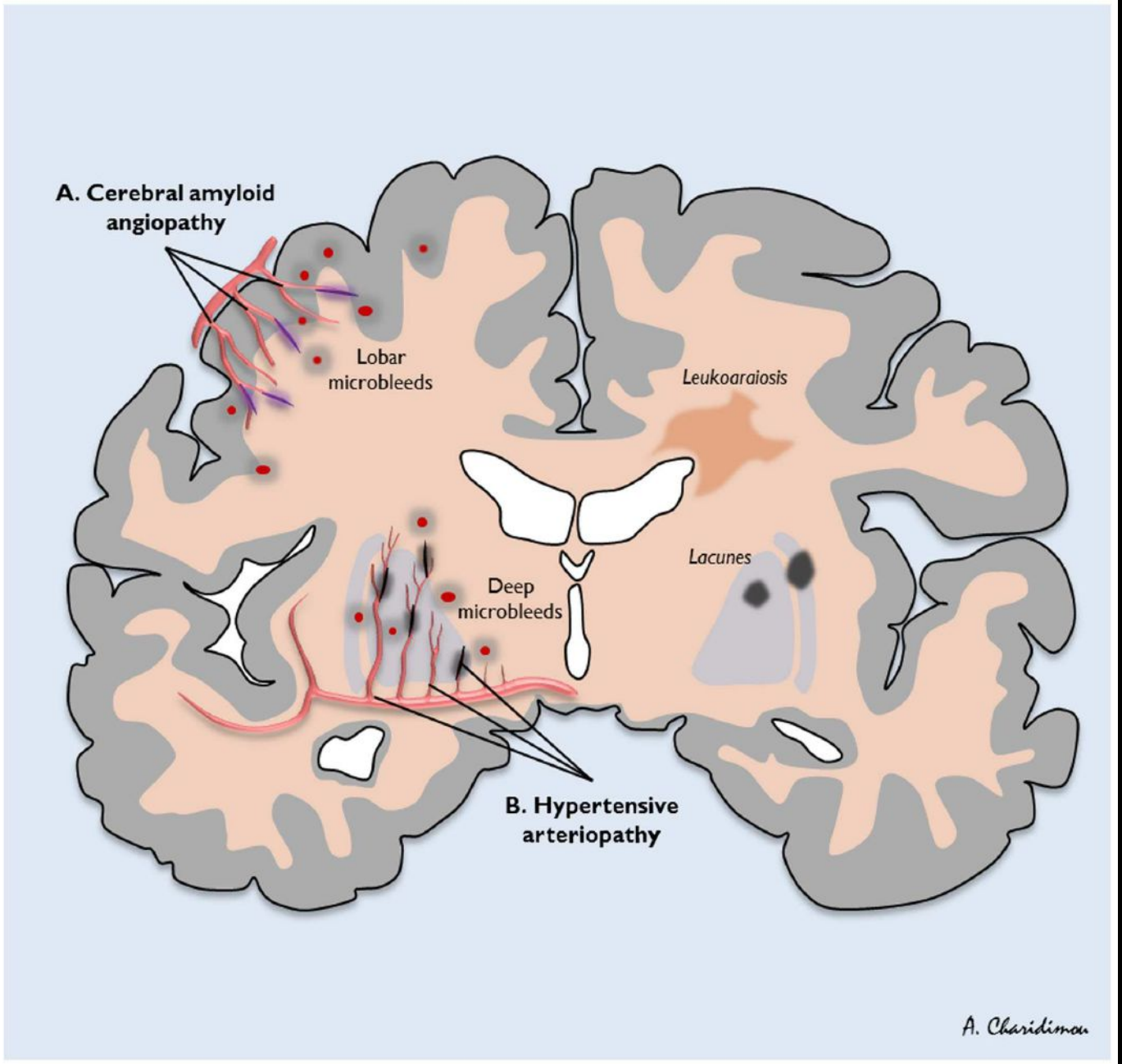

ICH = intracerebral hemorrhage; INR = international normalized ratio.

# CAA: Cerebral Microbleeds




A
SWI
Lobar microbleeds


B
T2*-GRE
Deep microbleeds


A. Cerebral amyloid angiopathy
Lobar microbleeds
Leukoaraiosis
Lacunes
Deep microbleeds
B. Hypertensive arteriopathy
A. Charidimou

# Clinical diagnosis of cerebral amyloid angiopathy: Validation of the Boston Criteria

Katherine A. Knudsen, BA; Jonathan Rosand, MD; Diane Karluk, MD; and Steven M. Greenberg, MD, PhD

## Appendix

**Boston Criteria for Diagnosis of CAA-Related Hemorrhage***

1. Definite CAA
   Full postmortem examination demonstrating:
   - Lobar, cortical, or corticosubcortical hemorrhage
   - Severe CAA with vasculopathy†
   - Absence of other diagnostic lesion
2. 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
3. Probable CAA
   Clinical data and MRI or CT demonstrating:
   - Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)
   - Age ≥55 years
   - Absence of other cause of hemorrhage‡
4. Possible CAA
   Clinical data and MRI or CT demonstrating:
   - Single lobar, cortical, or corticosubcortical hemorrhage
   - Age ≥55 years
   - Absence of other cause of hemorrhage‡

Featured Article

# Diagnostic value of lobar microbleeds in individuals without intracerebral hemorrhage

Sergi Martinez-Ramirez[a,b,*,1], Jose-Rafael Romero[c,d,1], Ashkan Shoamanesh[a,d], Ann C. McKee[c,d,e,f], Ellis Van Etten[a], Octavio Pontes-Neto[a], Eric A. Macklin[g], Alison Ayres[a], Eitan Auriel[a], Jayandra J. Himali[d,h], Alexa S. Beiser[c,d,h], Charles DeCarli[i], Thor D. Stein[e,f], Victor E. Alvarez[c,j], Matthew P. Frosch[k], Jonathan Rosand[l], Steven M. Greenberg[a], M. Edip Gurol[a], Sudha Seshadri[c,d], Anand Viswanathan[a]

| Cohort | Sensitivity | Specificity | NPV | PPV |
|---|---|---|---|---|
| **MGH (N=124)** | | | | |
| Probable CAA (>1 lesion) | 51% | 95% | 51% | 88% |
| | | | | |
| **Framingham Heart Study (N=47)** | | | | |
| Probable CAA (>1 lesion) | 4.5% | 88% | 51% | 25% |

Featured Article

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Sergi Martinez-Ramirez[a,b,*,1], Jose-Rafael Romero[c,d,1], Ashkan Shoamanesh[a,d], Ann C. McKee[c,d,e,f], Ellis Van Etten[a], Octavio Pontes-Neto[a], Eric A. Macklin[g], Alison Ayres[a], Eitan Auriel[a], Jayandra J. Himali[d,h], Alexa S. Beiser[c,d,h], Charles DeCarli[i], Thor D. Stein[e,f], Victor E. Alvarez[c,j], Matthew P. Frosch[k], Jonathan Rosand[l], Steven M. Greenberg[a], M. Edip Gurol[a], Sudha Seshadri[c,d], Anand Viswanathan[a]

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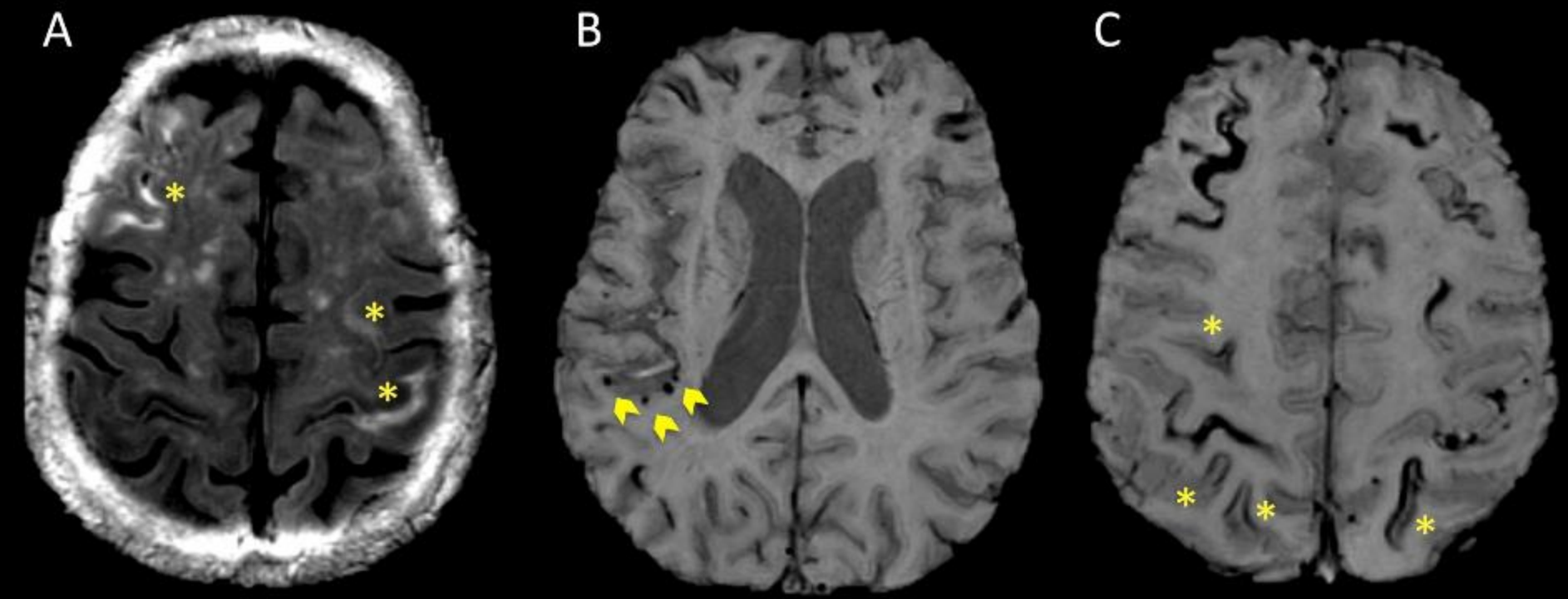
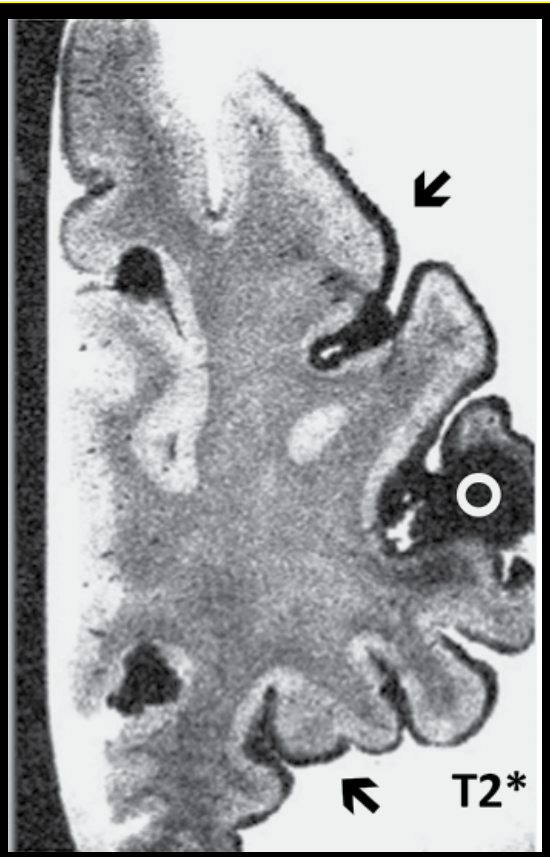
# CAA: Cortical Superficial Siderosis (cSS)



# Superficial Siderosis of the Central Nervous System: A Post-Mortem 7.0-Tesla Magnetic Resonance Imaging Study with Neuropathological Correlates

J. De Reuck[a] V. Deramecourt[a, b, c, h] C. Cordonnier[a, d] F. Auger[a, e]
N. Durieux[a, e] F. Pasquier[a, b] R. Bordet[a, f] L. Defebvre[a, g]
D. Caparros-Lefebvre[i] C.A. Maurage[a, c, h] D. Leys[a, d]

Cerebrovasc Dis 2013;36:412–417



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

Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy

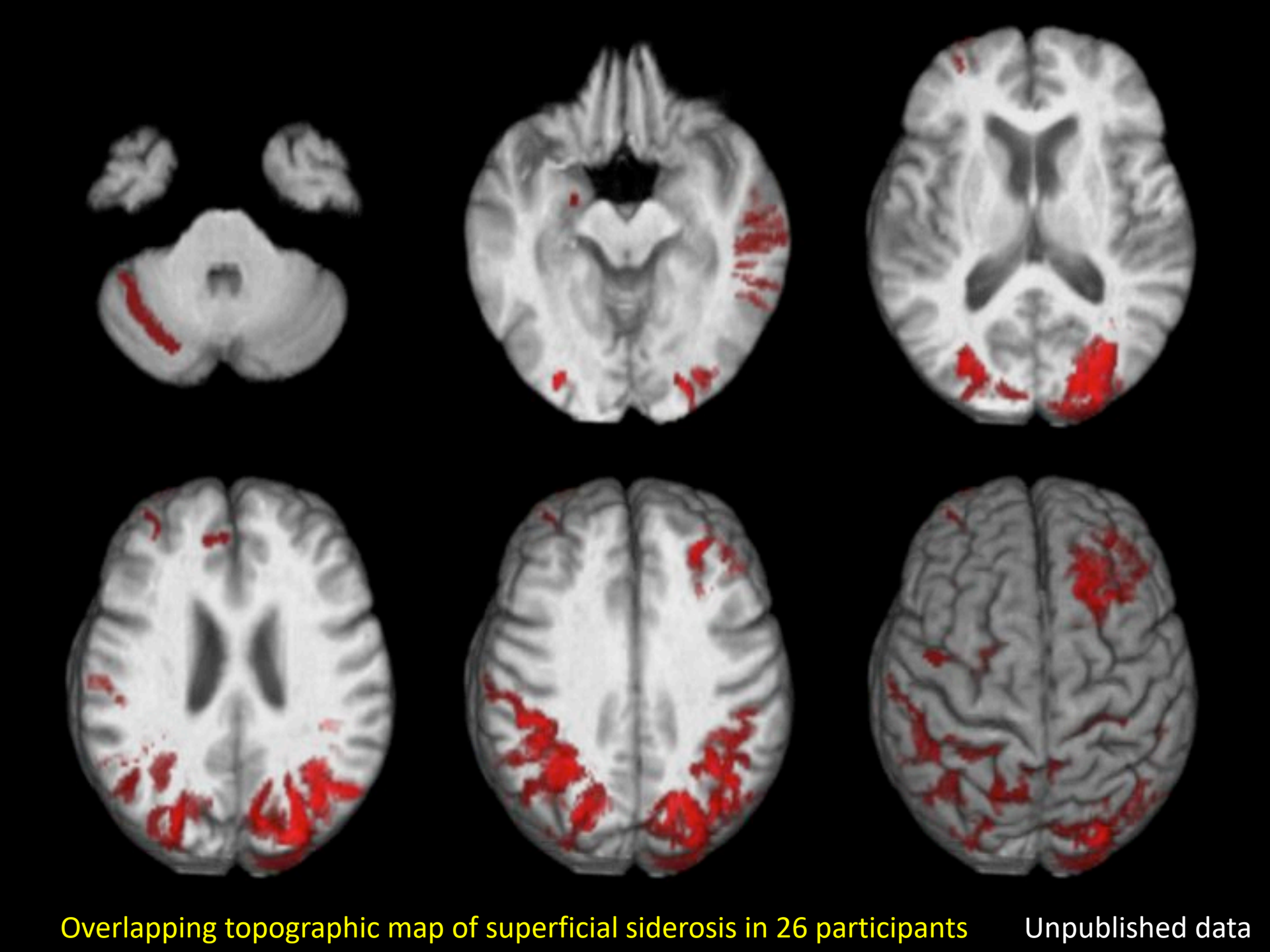
*Neurology*® 2010;74:1346-1350

Prevalence and mechanisms of cortical superficial siderosis in cerebral amyloid angiopathy

*Neurology*® 2013;81:626-632

**Superficial Siderosis of the Central Nervous System: A Post-Mortem 7.0-Tesla Magnetic Resonance Imaging Study with Neuropathological Correlates**

Cerebrovasc Dis 2013;36:412–417



Overlapping topographic map of superficial siderosis in 26 participants

Unpublished data

# Superficial Siderosis: Predictor of Future Symptomatic ICH

Cortical superficial siderosis and intracerebral hemorrhage risk in cerebral amyloid angiopathy

*Neurology*® 2013;81:1666-1673

Risk of ICH at 4 years (n=118): 25% without SS, 30% with focal and 74% with disseminated SS. HR (disseminated SS): 3.2 (95% CI 1.4 – 7.4, p = 0.008)

# Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy

J. Linn, MD
A. Halpin, MD
P. Demaerel, PhD
J. Ruhland
A.D. Giese, PhD
M. Dichgans, PhD
M.A. van Buchem, PhD
H. Bruckmann, PhD
S.M. Greenberg, PhD

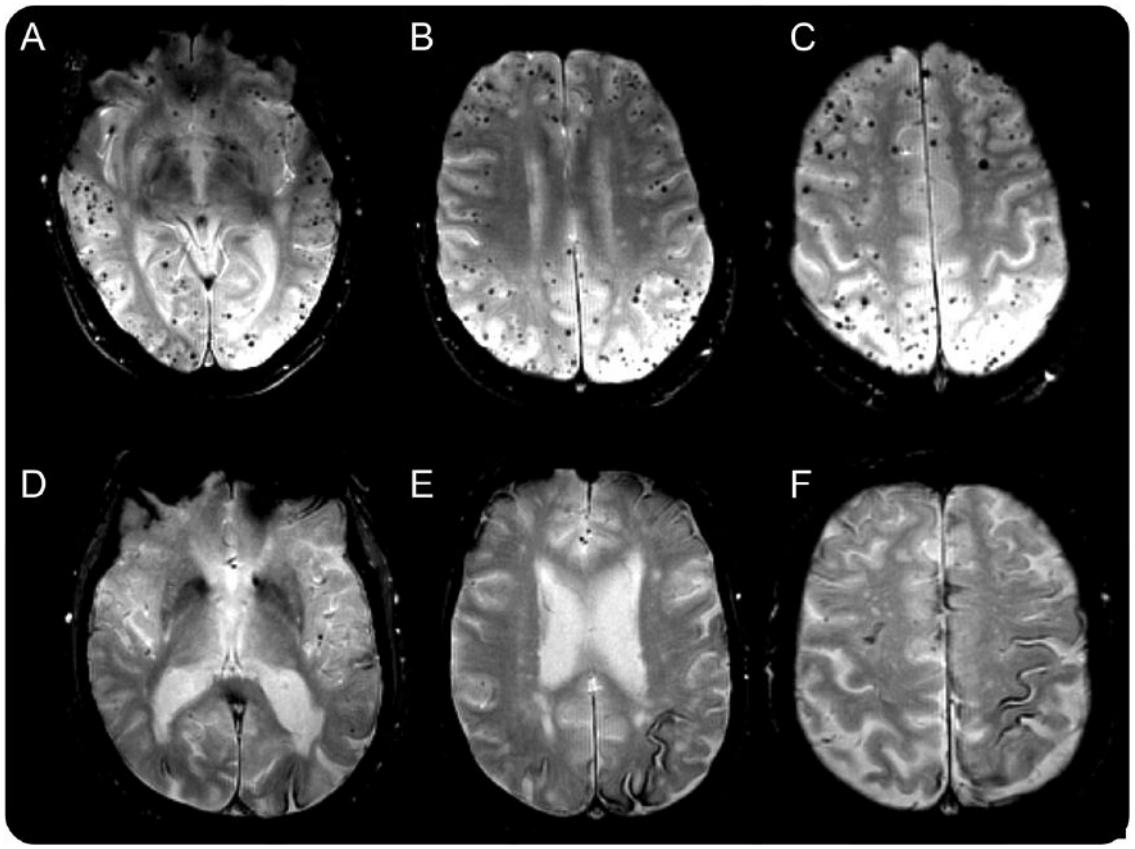
*Neurology*® 2010;74:1346–1350

Including superficial siderosis in the Boston Criteria improves its sensitivity by 5% (modified Boston Criteria).

# Interrelationship of superficial siderosis and microbleeds in cerebral amyloid angiopathy

Ashkan Shoamanesh, MD
Sergi Martinez-Ramirez, MD
Jamary Oliveira-Filho, MD, PhD et al.

**Figure** Representative cases of cerebral microbleed and cortical superficial siderosis predominant cerebral amyloid angiopathy phenotypes




APOE 4

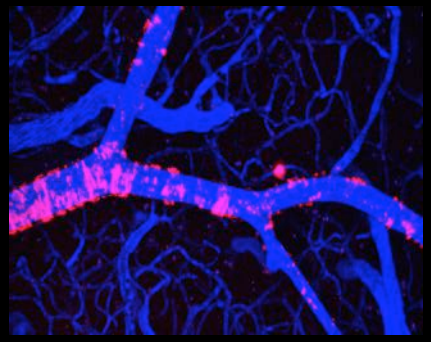
APOE 2

# Pathological steps leading to CAA-related hemorrhage

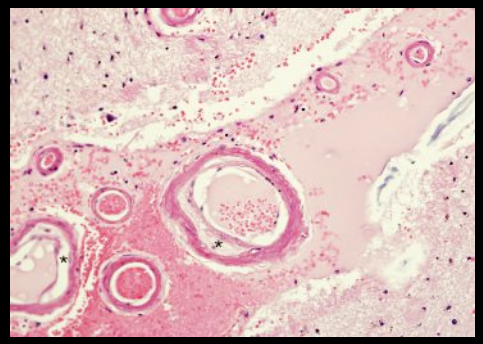
Age

APOE ε2

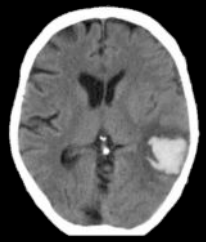
Antithrombotics
Statins?
Hypertension
Minor head injury



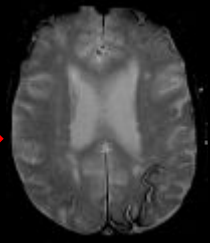
Cortical and leptomeningeal vessel amyloid deposition



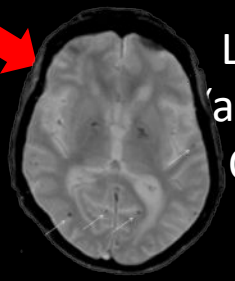
Vasculopathic changes



ICH

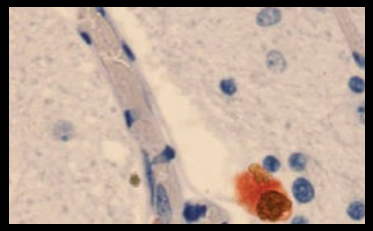


SS



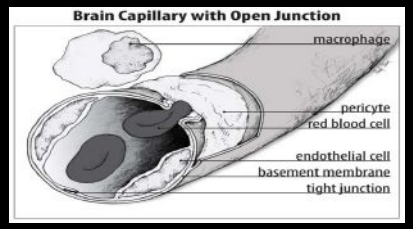
Lower ƒ 'arteriolar CMBs"

APOE ε4



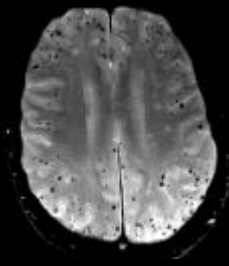
CAA 1: Propensity for capillaries

Inflammation?




Opening of tight junctions

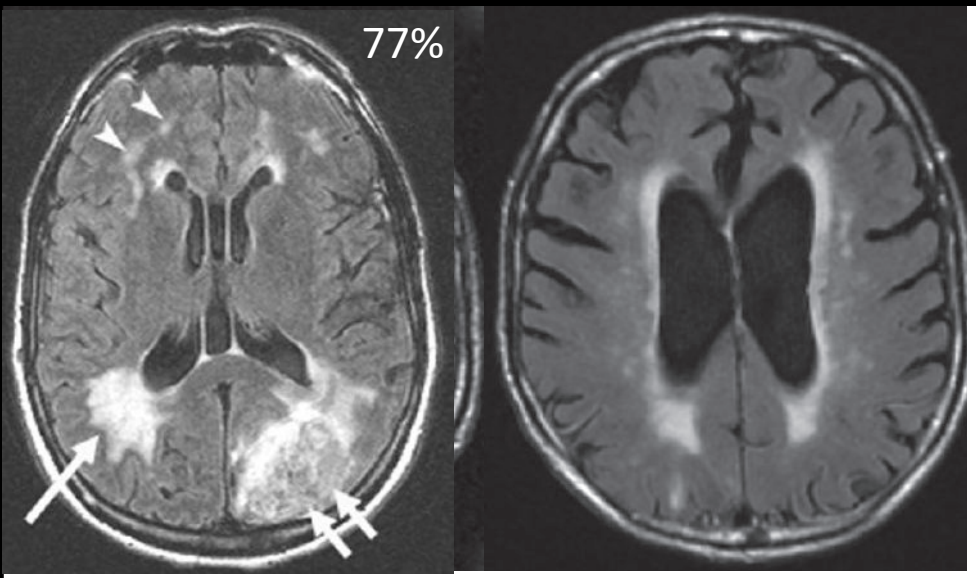
?

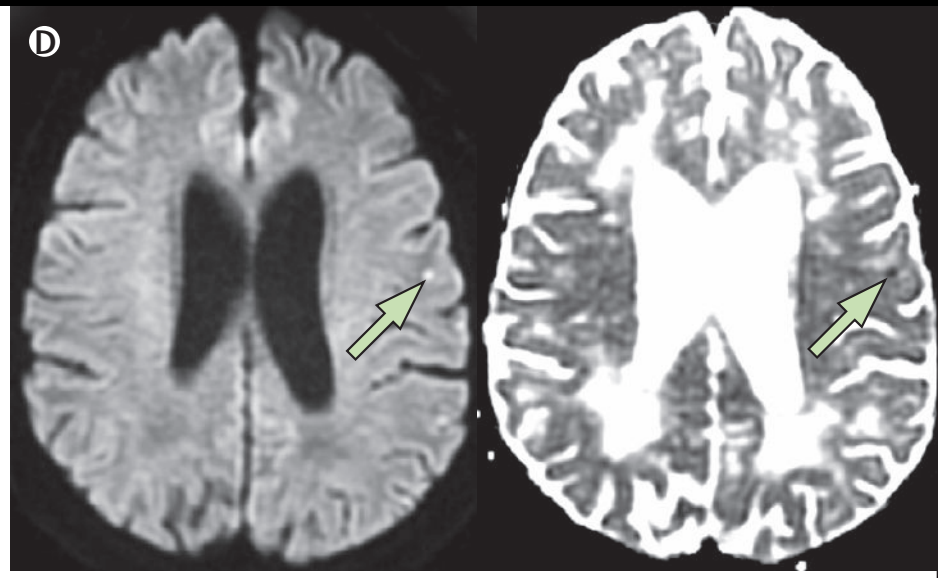


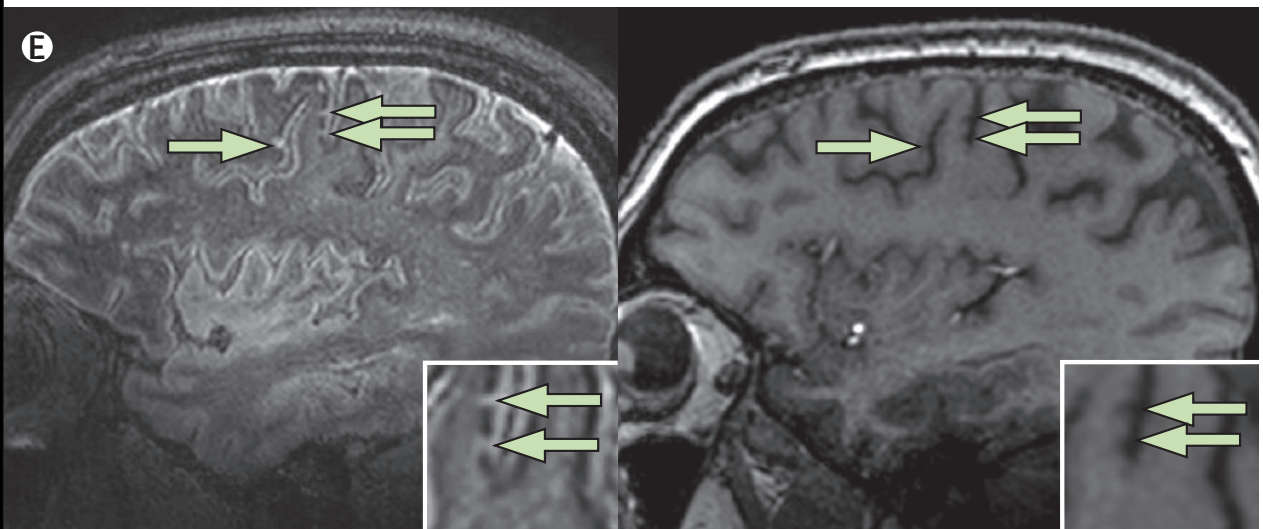
Higher ƒ "capillary CMBs"

# CAA: Ischemic Markers

13% beyond 2 weeks post ICH
Average of 8/year



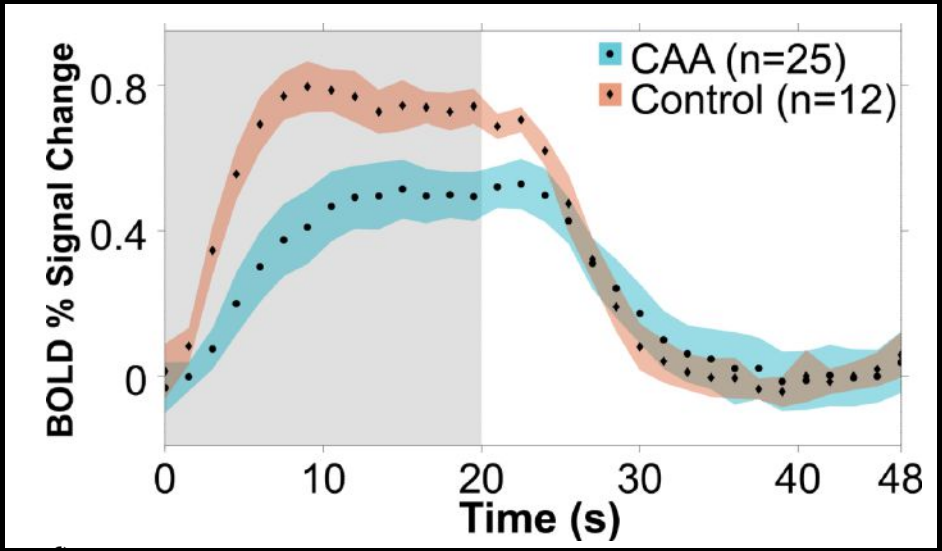



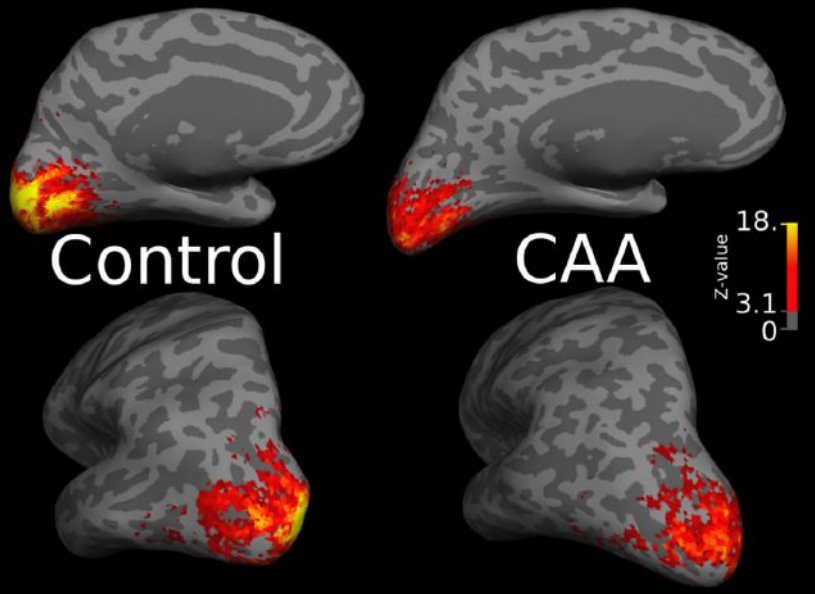




*Lancet Neurol* 2014; 13: 419–28

# Functional MRI Detection of Vascular Reactivity in Cerebral Amyloid Angiopathy

**Andrew Dumas, MA**[1], **Gregory A Dierksen, M.Eng**[1], **M Edip Gurol, MD**[1], **Amy Halpin, BA**[1], **Sergi Martinez-Ramirez, MD**[1], **Kristin Schwab, BA**[1], **Jonathan Rosand, MD, Msc**[1], **Anand Viswanathan, MD, PhD**[1], **David H Salat, PhD**[2,3], **Jonathan R Polimeni, PhD**[3], and **Steven M Greenberg, MD, PhD**[1]



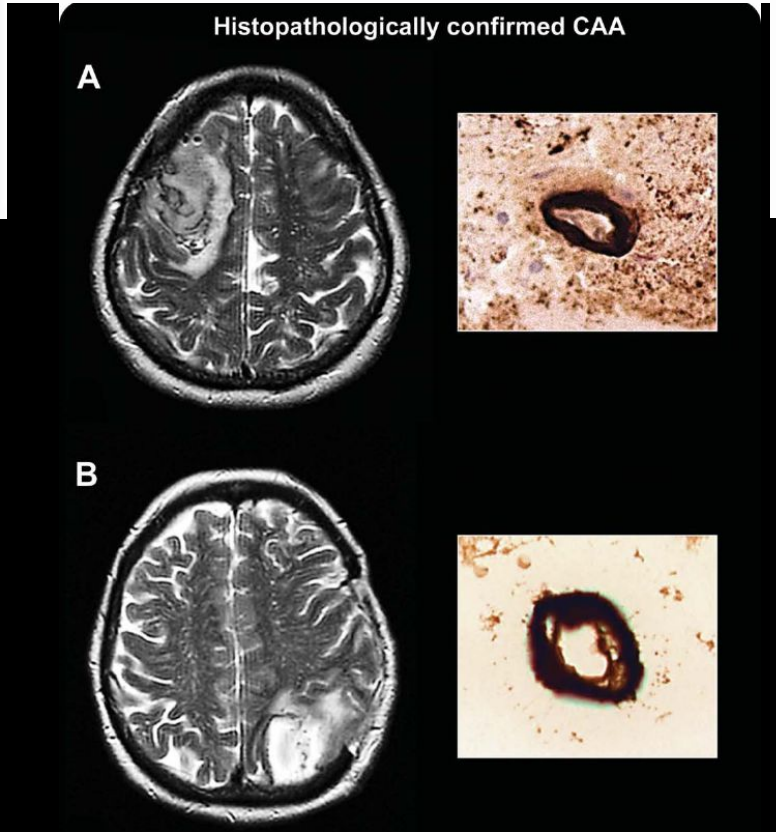



# CAA: Additional Markers

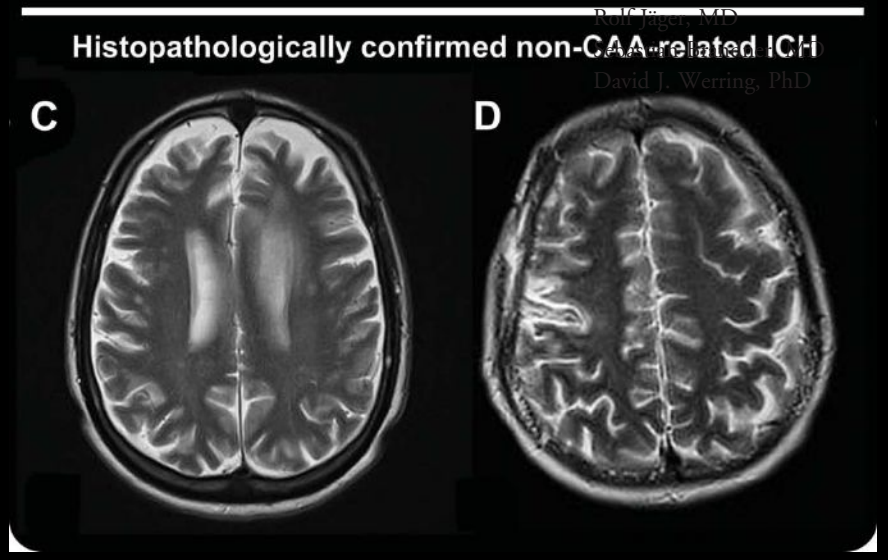
## White matter perivascular spaces

### An MRI marker in pathology-proven cerebral amyloid angiopathy?

Andreas Charidimou, MD, MSc
Zane Jaunmuktane, MD
Jean-Claude Baron, PhD
Matthew Burnell, PhD
Pascale Varlet, PhD
Andre Peeters, MD
John Xuereb, FRCPath
Rolf Jäger, MD
David J. Werring, PhD




60% high burden



# CAA: Pittsburgh compound B PET imaging

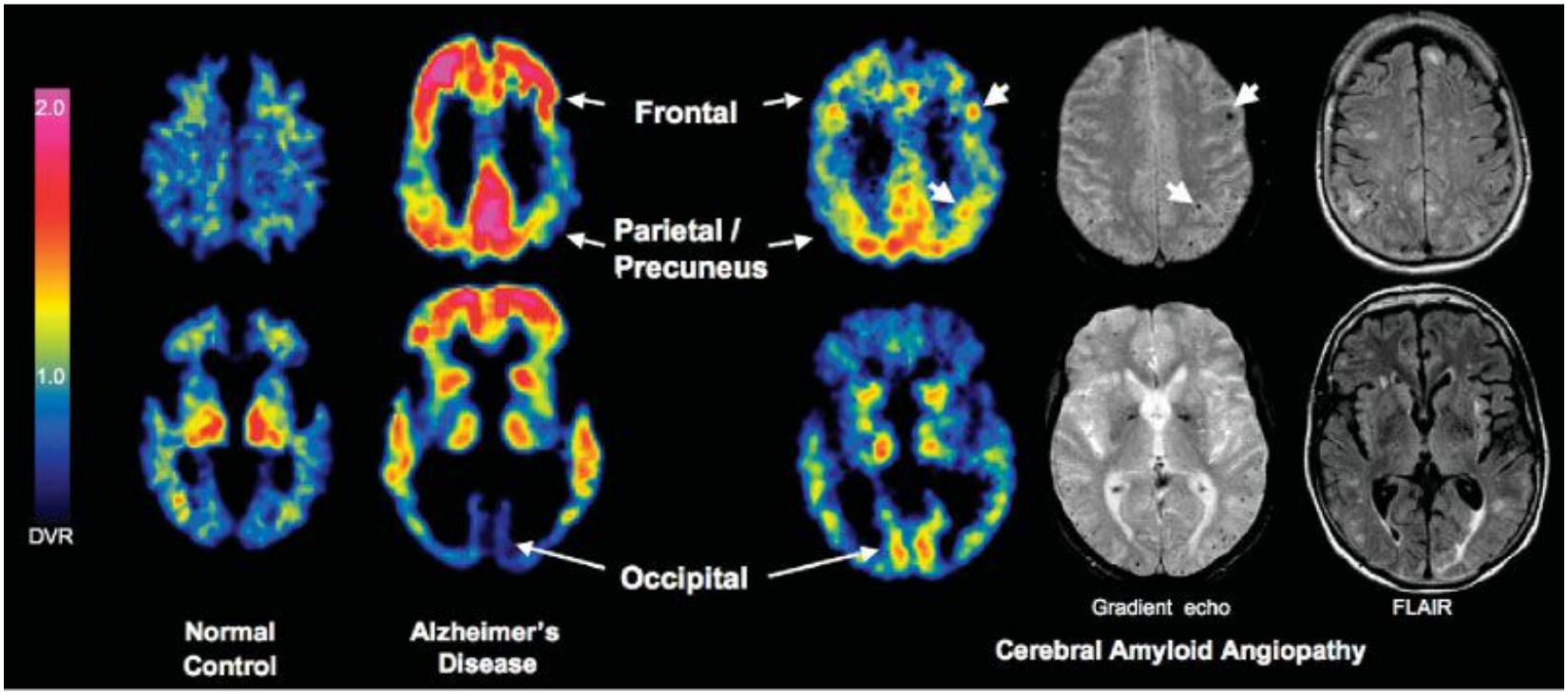


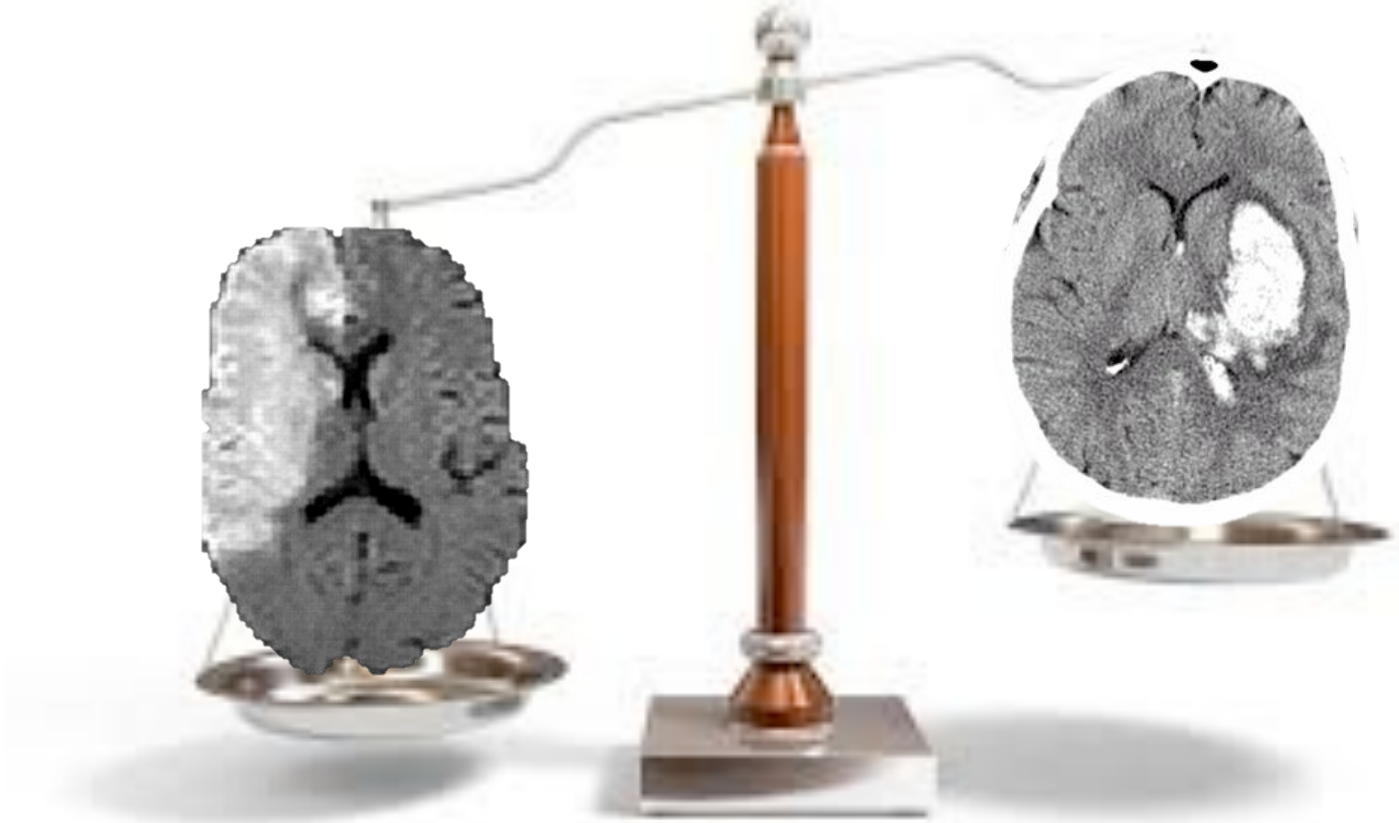

*Fig 1. Representative Pittsburgh Compound B (PiB)-positron emission tomographic (PET) images at two transaxial levels from normal control (NC) (PiB-negative), Alzheimer's disease (AD), and cerebral amyloid angiopathy (CAA; Subject 4; see Table 2) subjects. Compared with AD and NC, CAA subjects had an intermediate level of global PiB retention (shown quantitatively in Fig 2), but compared with AD, had relatively increased occipital retention (see Fig 3). Microbleeds seen in this patient, shown in coregistered gradient echo magnetic resonance images, at times appear proximal to foci of amyloid deposition* (small arrows).

Ann Neurol 2007;62:229–234

# CAA: Management

- Secondary CAA-related ICH prevention
  - Blood pressure control (target SBP < 130 mmHg)
  - Lifestyle modification (exercise, smoking, alcohol, stress management)
- Cognitive dysfunction
  - Screen and follow for cognitive decline and depression
  - Treatment with cognitive enhancing rx (donepezil, galantamine or memantine) and antidepressants as indicated.

Concomitant indications for antithrombotic and statin therapy?



# Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial

*Rustam Al-Shahi Salman, David P Minks, Dipayan Mitra, Mark A Rodrigues, Priya Bhatnagar, Johann C du Plessis, Yogish Joshi, Martin S Dennis, Gordon D Murray, David E Newby, Peter A G Sandercock, Nikola Sprigg, Jacqueline Stephen, Cathie L M Sudlow, David J Werring, William N Whiteley, Joanna M Wardlaw, Philip M White, on behalf of the RESTART Collaboration**

| | Start antiplatelet therapy (n=268) | Avoid antiplatelet therapy (n=268) | Log-rank test p value | Unadjusted analysis | | Adjusted analysis | |
|---|---|---|---|---|---|---|---|
| | | | | HR (95% CI) | p value | HR (95% CI) | p value |
| **Primary outcome** | | | | | | | |
| Recurrent symptomatic spontaneous intracerebral haemorrhage | 12 4% | 23 9% | 0·057 | 0·51 (0·26–1·03) | 0·062 | 0·51 (0·25–1·03) | 0·060 |
| **Sensitivity analyses of the primary outcome** | | | | | | | |
| Recurrent symptomatic spontaneous intracerebral haemorrhage or symptomatic stroke of uncertain subtype | 12 | 24 | 0·041 | 0·49 (0·25–0·99) | 0·046 | 0·49 (0·24–0·98) | 0·044 |
| Recurrent symptomatic spontaneous intracerebral haemorrhage or death of undetermined cause | 13 | 25 | 0·047 | 0·51 (0·26–1·00) | 0·051 | 0·51 (0·26–0·99) | 0·048 |
| **Secondary outcomes** | | | | | | | |
| All major haemorrhagic events (all types of symptomatic spontaneous or traumatic intracranial haemorrhage, or symptomatic major extracranial haemorrhage) | 18 | 25 | 0·27 | 0·71 (0·39–1·30) | 0·27 | 0·71 (0·39–1·30) | 0·27 |
| All major occlusive vascular events (ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; deep vein thrombosis; pulmonary embolism; or carotid, coronary, or peripheral arterial revascularisation procedures) | 39 | 38 | 0·97 | 1·01 (0·65–1·58) | 0·97 | 1·02 (0·65–1·60) | 0·92 |
| All major haemorrhagic or occlusive vascular events | 54 | 61 | 0·42 | 0·86 (0·60–1·24) | 0·42 | 0·86 (0·60–1·24) | 0·43 |
| Major occlusive vascular events* | 45 | 52 | 0·39 | 0·84 (0·56–1·25) | 0·39 | 0·84 (0·56–1·25) | 0·39 |
| Major vascular events (as defined by the Antithrombotic Trialists' Collaboration) | 45 | 65 | 0·026 | 0·65 (0·45–0·95) | 0·027 | 0·65 (0·44–0·95) | 0·025 |

HR=hazard ratio. *As defined in the trial protocol.

***Table 3*: Risks of first occurrence of primary and secondary outcome events during follow-up**

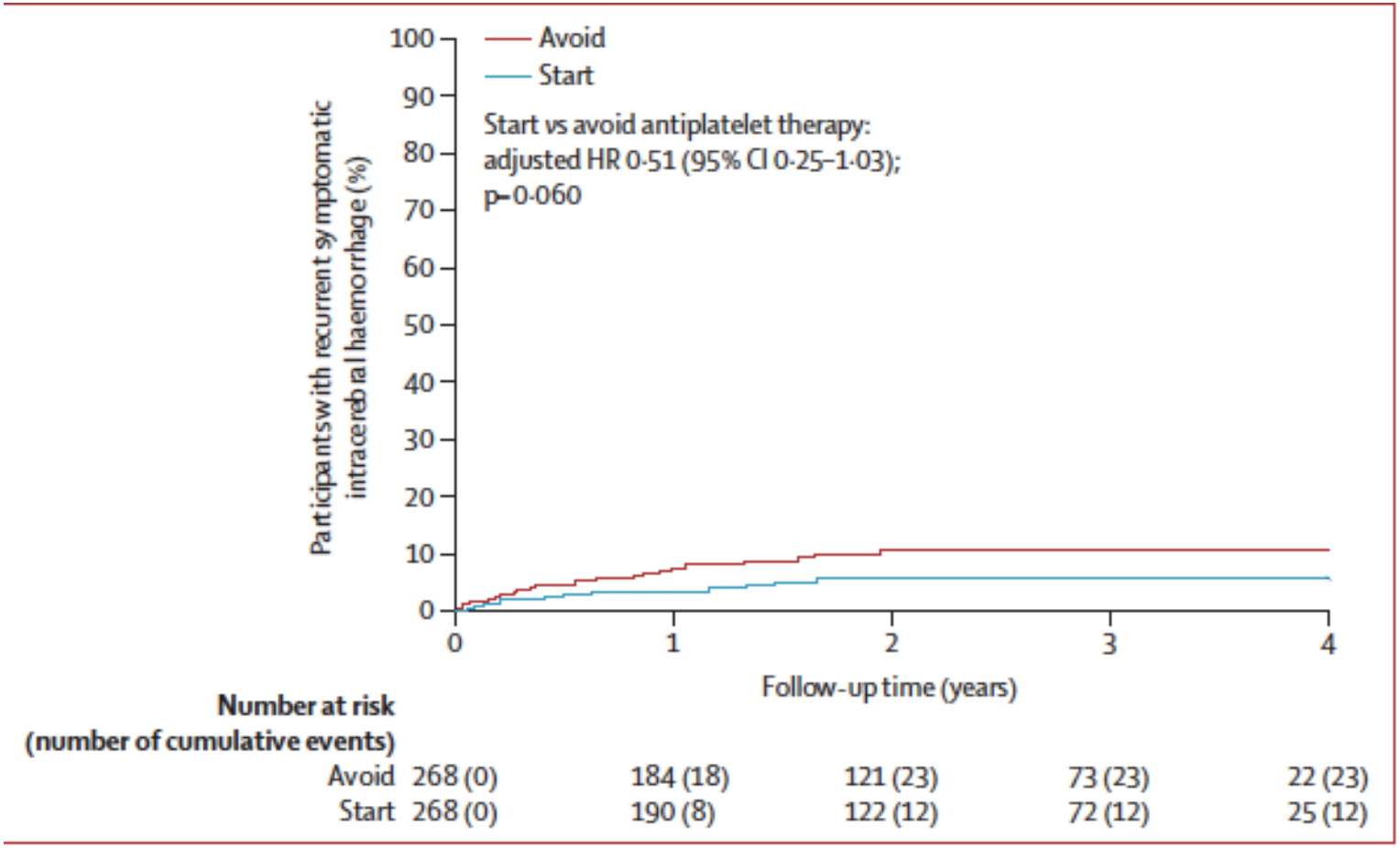



***Figure 2:*** **Kaplan-Meier plot of the first occurrence of recurrent symptomatic intracerebral haemorrhage**
Numbers at risk refer to survivors under follow-up at the start of each year according to treatment allocation. Cumulative events indicate the participants in follow-up with a first event. HR=hazard ratio.

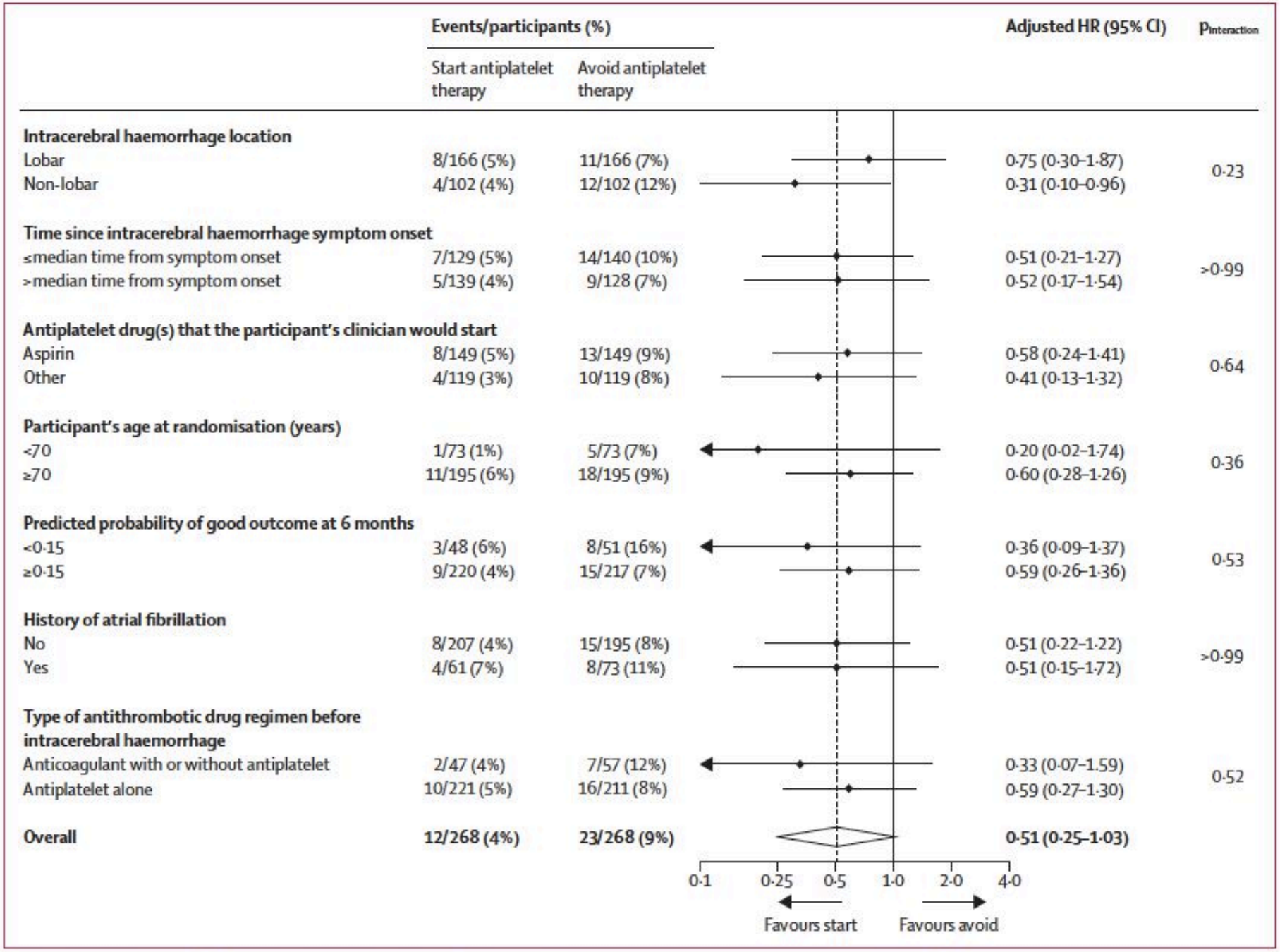



*Figure 3:* **Prespecified exploratory subgroup analyses of the risk of first recurrent symptomatic intracerebral haemorrhage**

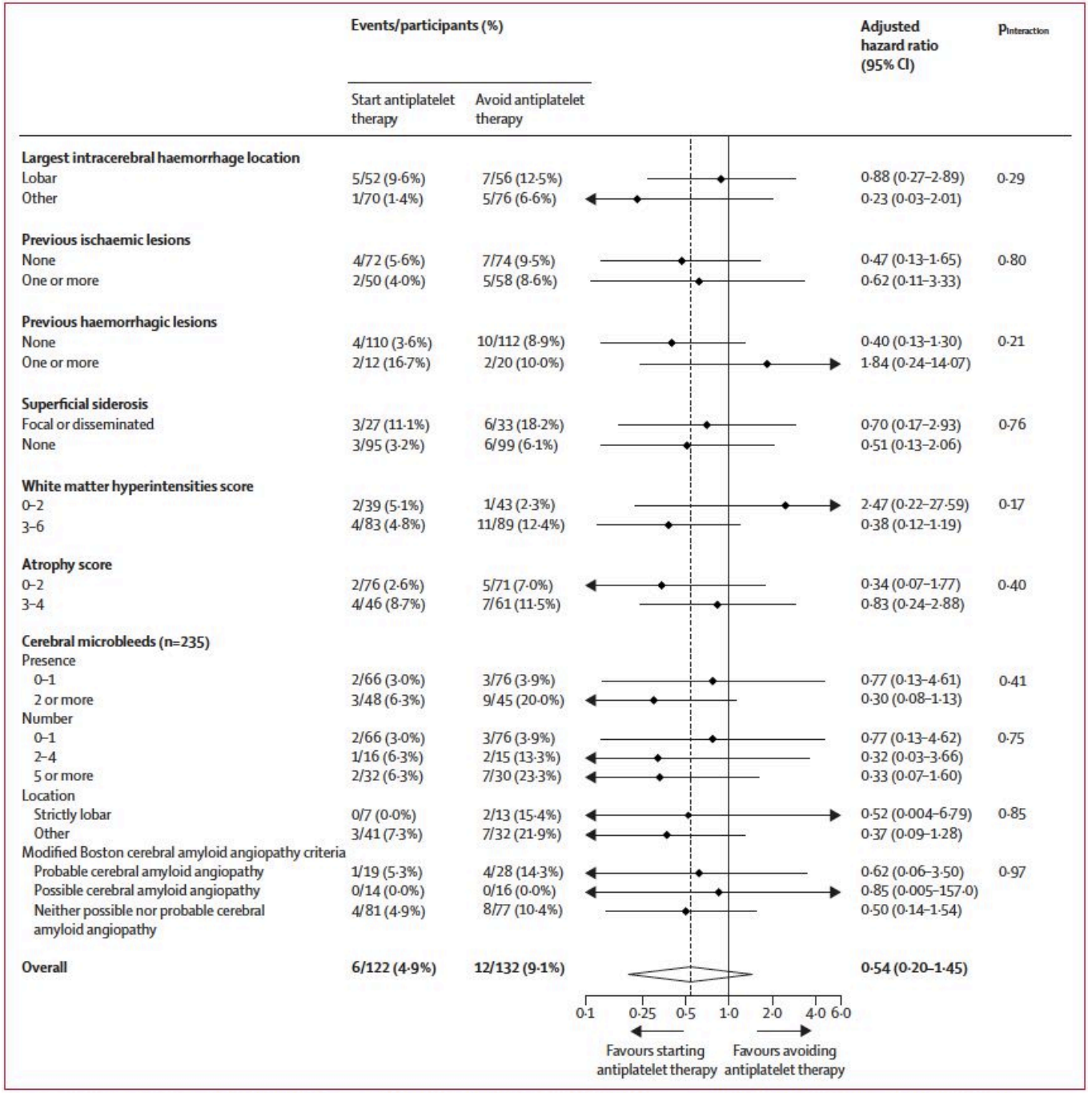



*Figure 3*: **Prespecified primary and exploratory subgroup analyses of the risk of first recurrent symptomatic intracerebral haemorrhage (the primary outcome) by brain MRI features**

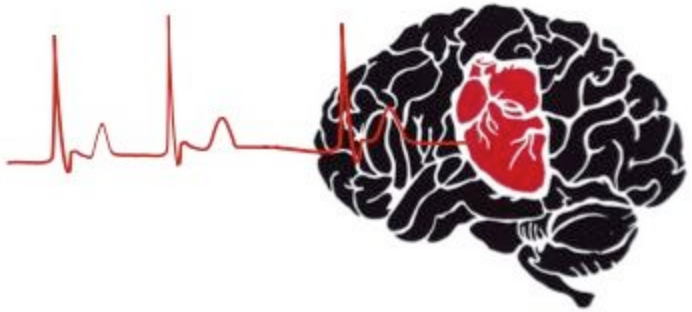
**Comorbid Atrial Fibrillation in Cerebral Amyloid Angiopathy-related Intracerebral Hemorrhage: Between a Rock and a Hard Place**

Ashkan Shoamanesh, MD,* Andreas Charidimou, MD, PhD,† and Kevin N. Sheth, MD‡

*Journal of Stroke and Cerebrovascular Diseases,*

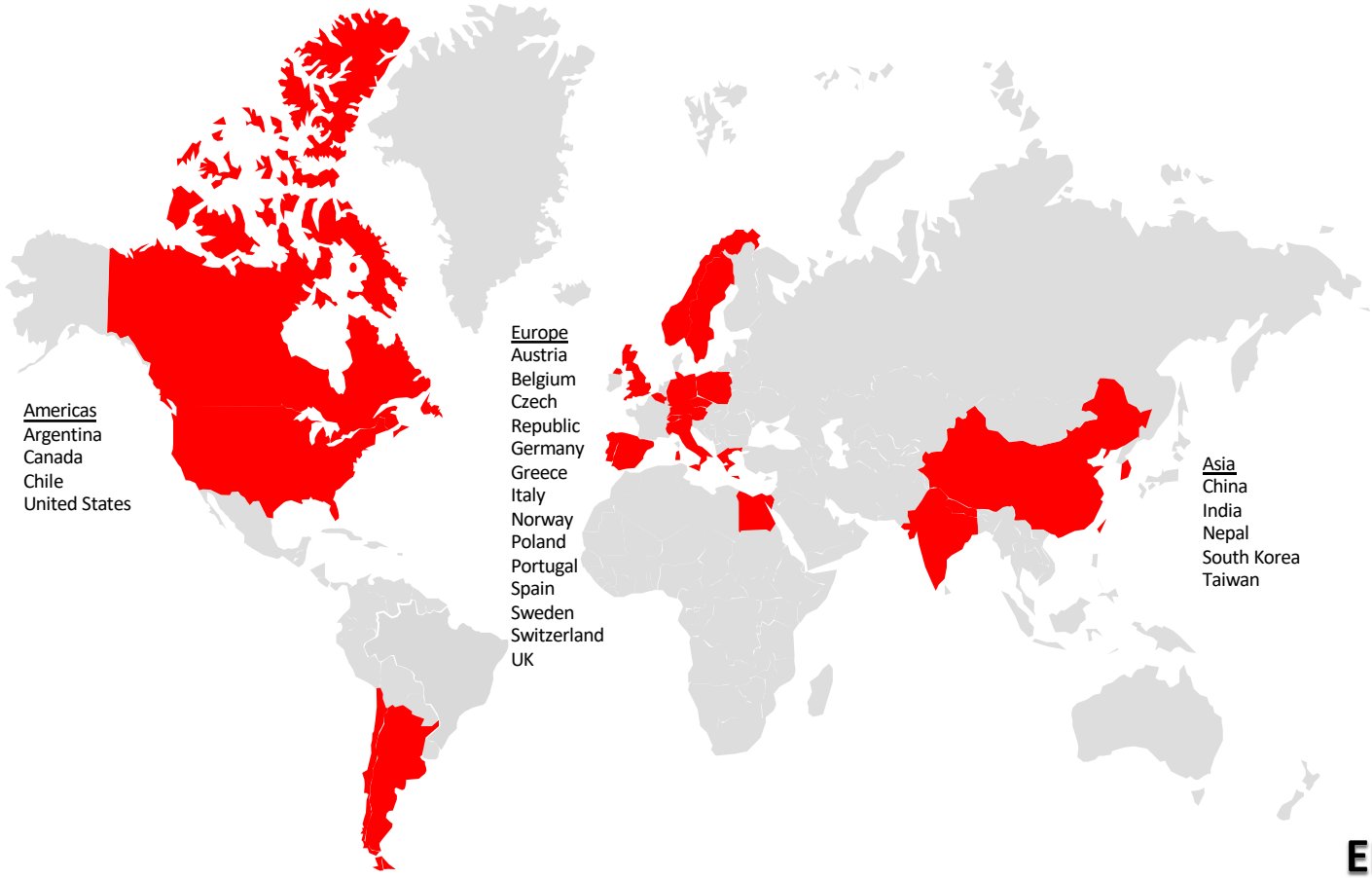
~20-25% of CAA-lobar ICH patients have AF

# ENRICH-AF



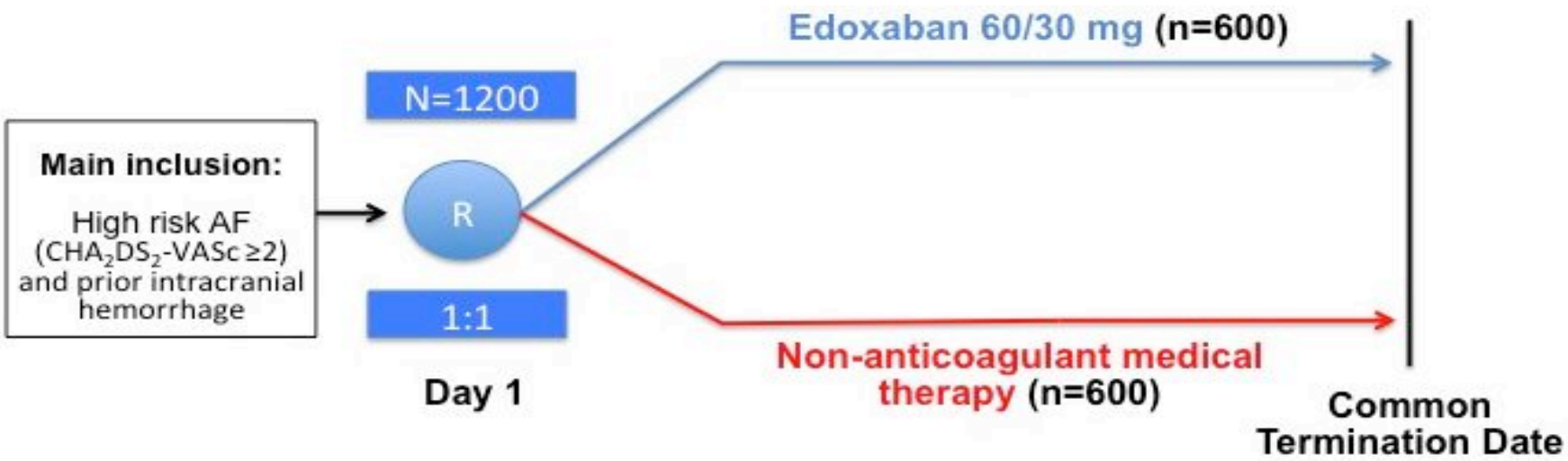
EdoxabaN foR IntraCranial Hemorrhage survivors with Atrial Fibrillation

October 4rth, 2019


Americas
Argentina
Canada
Chile
United States
Europe
Austria
Belgium
Czech Republic
Germany
Greece
Italy
Norway
Poland
Portugal
Spain
Sweden
Switzerland
UK
Asia
China
India
Nepal
South Korea
Taiwan

ENRICH-AF

# Design




**Recruitment period:** 24 months

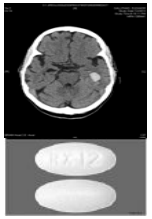
**Last participant followed:** common study termination once 123 primary events have accrued; estimated to occur 12 months following end of recruitment

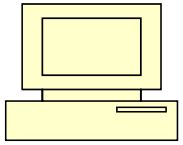
**Total study duration**: ~ 36 months

**Mean follow-up per participant:** 24 months (range 12 – 36 months)

# Statins?: SATURN

## Study Procedures





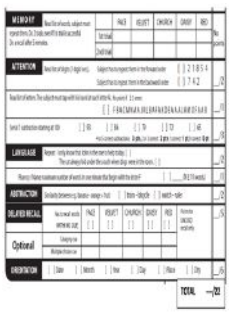
Randomization | D/C | 1, 2, 3, 6, 9, 12, 18, 24 months*

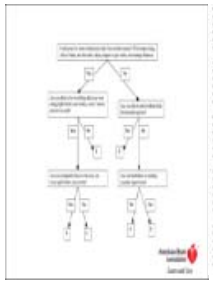
Screening


- Screening: ✓ Inclusion ✓ Exclusion
- Randomization: ✓ ICH score ✓ NIHSS
- D/C: ✓ mRS ✓ NIHSS
- 1, 2, 3, 6, 9, 12, 18, 24 months*: ✓ MACCE; SAEs; mRS; TMoCA; QoL (EQ-5D); Review of prescription refills; Pill count; BP reporting

**All follow-up assessments will be performed by centralized evaluators. A central adjudication committee blinded to treatment allocation will adjudicate all outcome events and imaging data.*

*Each subject will be followed for 24 months, including those who experience a recurrent ICH, to standardize the timing of final assessments of quality of life and functional/cognitive outcomes among all participants.*





# Spectrum of Transient Focal Neurological Episodes in Cerebral Amyloid Angiopathy

## Multicentre Magnetic Resonance Imaging Cohort Study and Meta-Analysis

Andreas Charidimou, MSc; Andre Peeters, Zoe Fox, PhD; Simone M. Gregoire, MD; Yves Vandermeeren, PhD; Patrice Laloux, PhD; Hans R. Jäger, PhD; Jean-Claude Baron, PhD; David J. Werring, PhD

- 25 of 172 CAA patients (15%) had TFNE
- 70% multiple stereotyped episodes lasting 10 – 30 mins duration
- 50% positive symptoms/50% negative symptoms (TIA-like)
  - 32% marching parasthesias
  - 28% dysphasia
  - 16% focal weakness
  - 16% limb jerking
  - 16% visual (mostly positive)

(*Stroke*. 2012;43:2324-2330.)

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- Superficial siderosis: 50% of CAA patients with TFNE vs. 19% in patients without (p=0.001)

(*Stroke*. 2012;43:2324-2330.)

# Spectrum of Transient Focal Neurological Episodes in Cerebral Amyloid Angiopathy

## Multicentre Magnetic Resonance Imaging Cohort Study and Meta-Analysis

Andreas Charidimou, MSc; Andre Peeters, Zoe Fox, PhD; Simone M. Gregoire, MD; Yves Vandermeeren, PhD; Patrice Laloux, PhD; Hans R. Jäger, PhD; Jean-Claude Baron, PhD; David J. Werring, PhD

- 2 month risk of ICH: 38%

- Risk equal between positive and negative symptoms.

- Only 1 patient had an ischemic stroke over mean follow up of 14 months.

(*Stroke*. 2012;43:2324-2330.)

# TFNE: Management

- AED effective for cortical spreading depression (Topamax, valproic acid, gabapentin)

- Taper off after 3 months

Original Investigation

# Validation of Clinicoradiological Criteria for the Diagnosis of Cerebral Amyloid Angiopathy–Related Inflammation

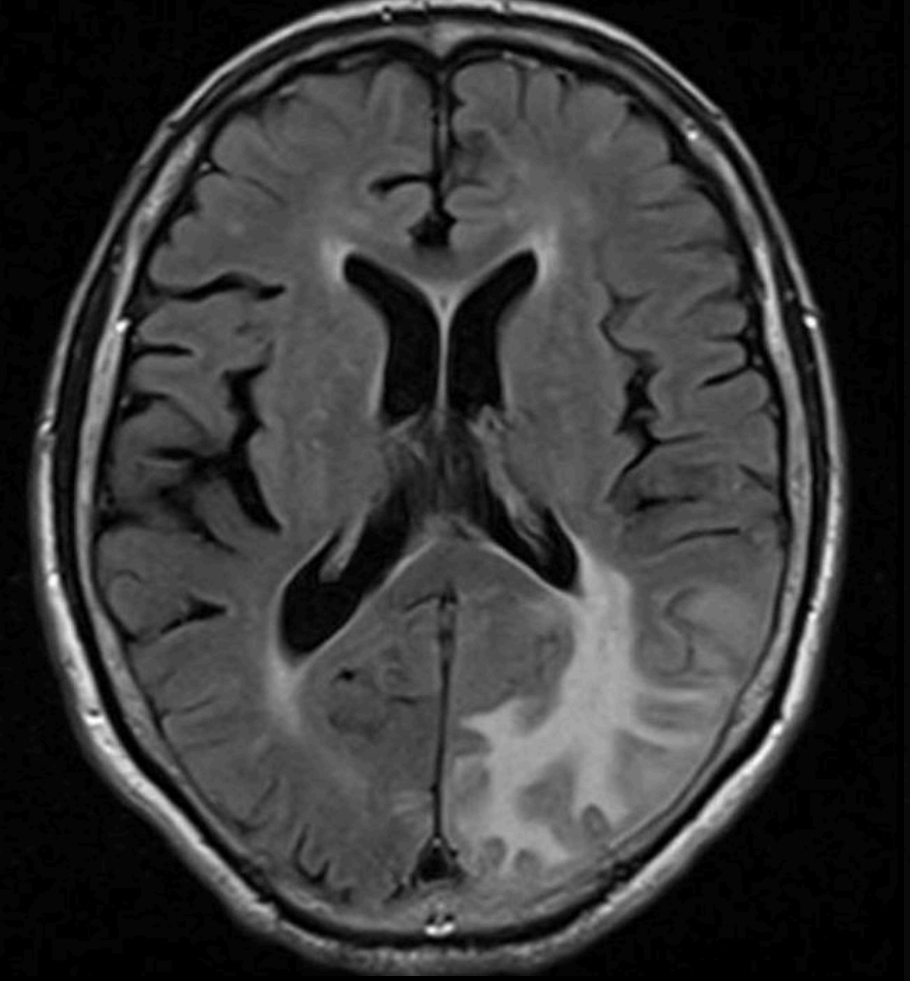
Eitan Auriel, MD, MSc; Andreas Charidimou, MD, PhD; M. Edip Gurol, MD, MSc; Jun Ni, MD; Ellis S. Van Etten, MD; Sergi Martinez-Ramirez, MD; Gregoire Boulouis, MD; Fabrizio Piazza, PhD; Jacopo C. DiFrancesco, MD, PhD; Matthew P. Frosch, MD, PhD; Octávio M. Pontes-Neto, MD, PhD; Ashkan Shoamanesh, MD; Yael Reijmer, PhD; Anastasia Vashkevich, BA; Alison M. Ayres, BA; Kristin M. Schwab, BA; Anand Viswanathan, MD, PhD; Steven M. Greenberg, MD, PhD

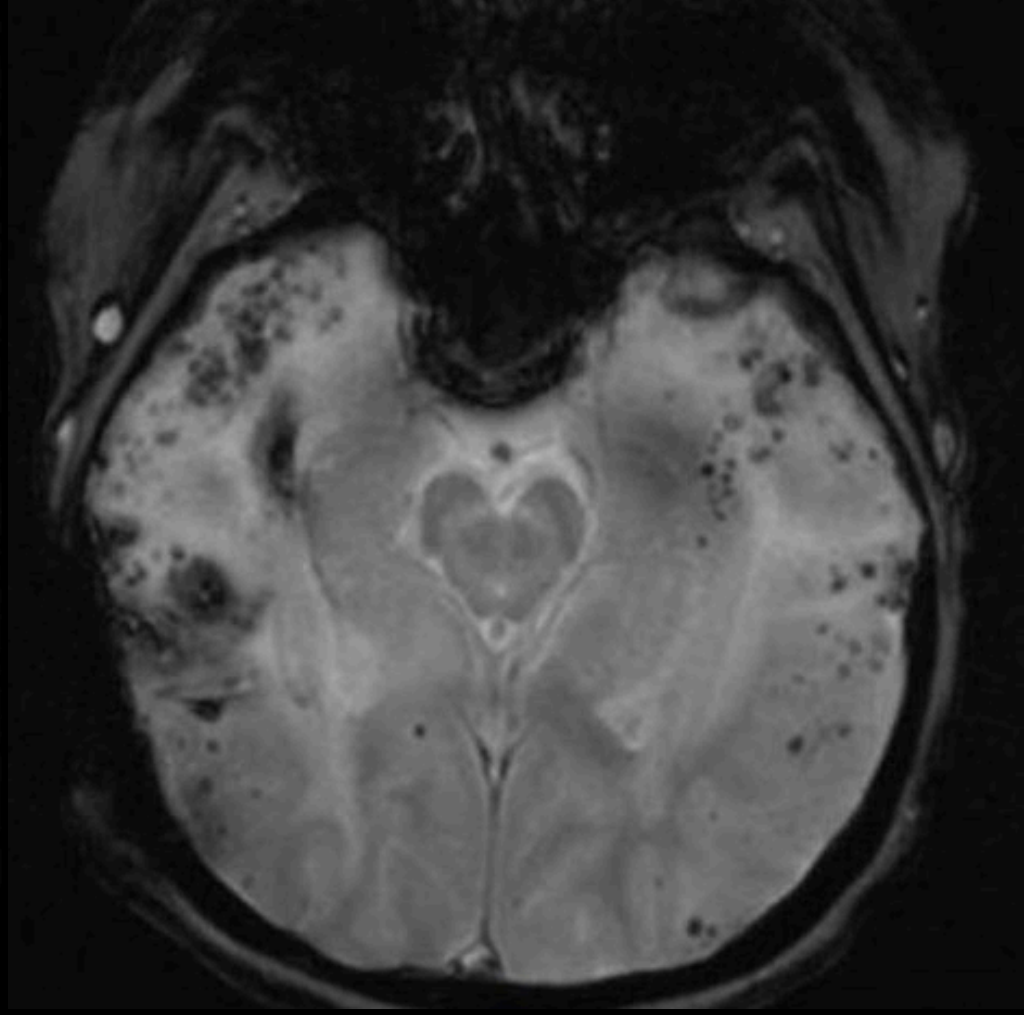
97% Specificity
82% Sensitivity

Table 1. Criteria for the Diagnosis of CAA-ri

JAMA Neurology February 2016 Volume 73, Number 2

| Diagnosis | Criteria |
|---|---|
| Probable CAA-ri | 1. Age ≥40 y<br>2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH<br>3. MRI shows unifocal or multifocal WMH lesions (corticosubcortical or deep) that are asymmetric and extend to the immediately subcortical white matter; the asymmetry is not due to past ICH<br>4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8]<br>5. Absence of neoplastic, infectious, or other cause |
| Possible CAA-ri | 1. Age ≥40 y<br>2. Presence of ≥1 of the following clinical features: headache, decrease in consciousness, behavioral change, or focal neurological signs and seizures; the presentation is not directly attributable to an acute ICH<br>3. MRI shows WMH lesions that extend to the immediately subcortical white matter<br>4. Presence of ≥1 of the following corticosubcortical hemorrhagic lesions: cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis[8]<br>5. Absence of neoplastic, infectious, or other cause |





CTA: negative
MRI post Gad: negative/mild leptomeningeal enhancement
LP: elevated protein
APOE genotyping: APOE ε4

Rx: IV methylprednisolone x 3-5 days followed by rapid prednisone taper
Full remission: 2/3
Relapse: 1/3

# Conclusions

- Sporadic CAA is a common age-related disease that will be an increasingly important health care challenge as our population ages further
- CAA is an important contributor to neurologic functional decline in the elderly and lobar ICH
- In vivo diagnostic criteria for CAA are continually evolving and will likely expand to include other biomarkers of disease.
- Evidence-based treatment is lacking, highlighting need to include CAA patients in targeted randomized trials.

# Questions?

- ashkan.shoamanesh@phri.ca