

Micro-saignements cérébraux: pertinence clinique



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Déclarations d'intérêt

Investigateur études cliniques (< 5 years) - Pas de financement personnel

BMS, Bayer, Biogen

Board d'experts

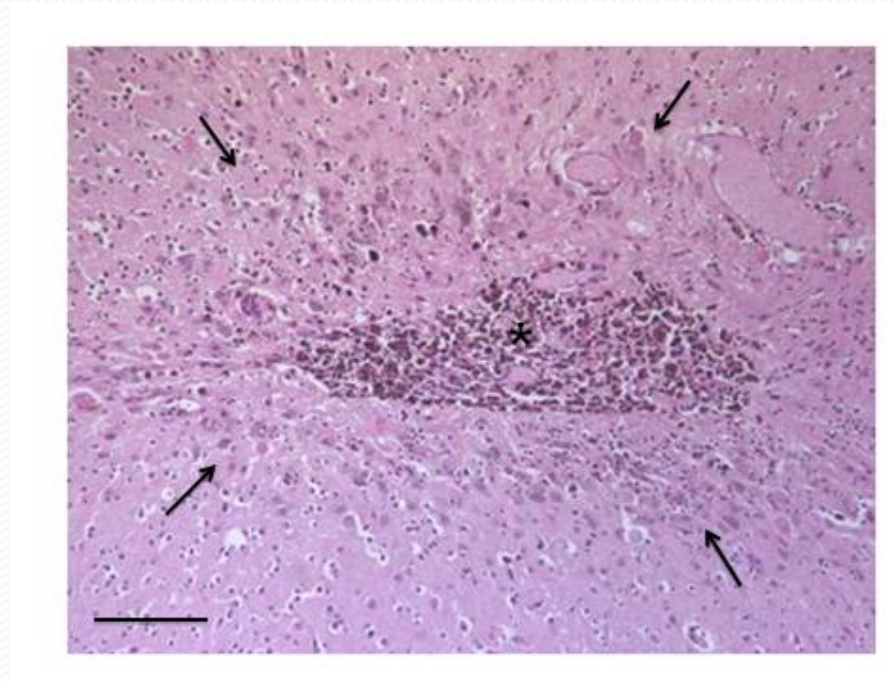
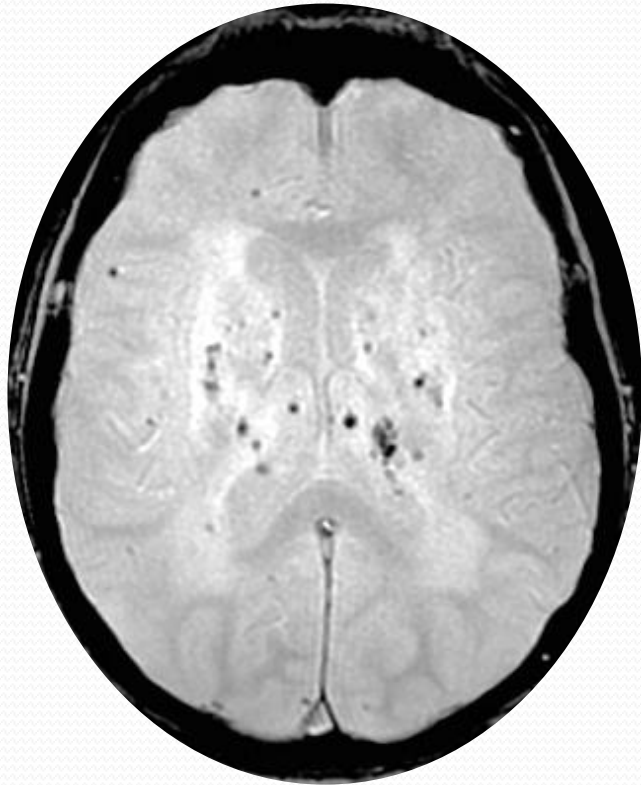
Bayer – Biogen - Amgen

Stocks, Travels

Aucun

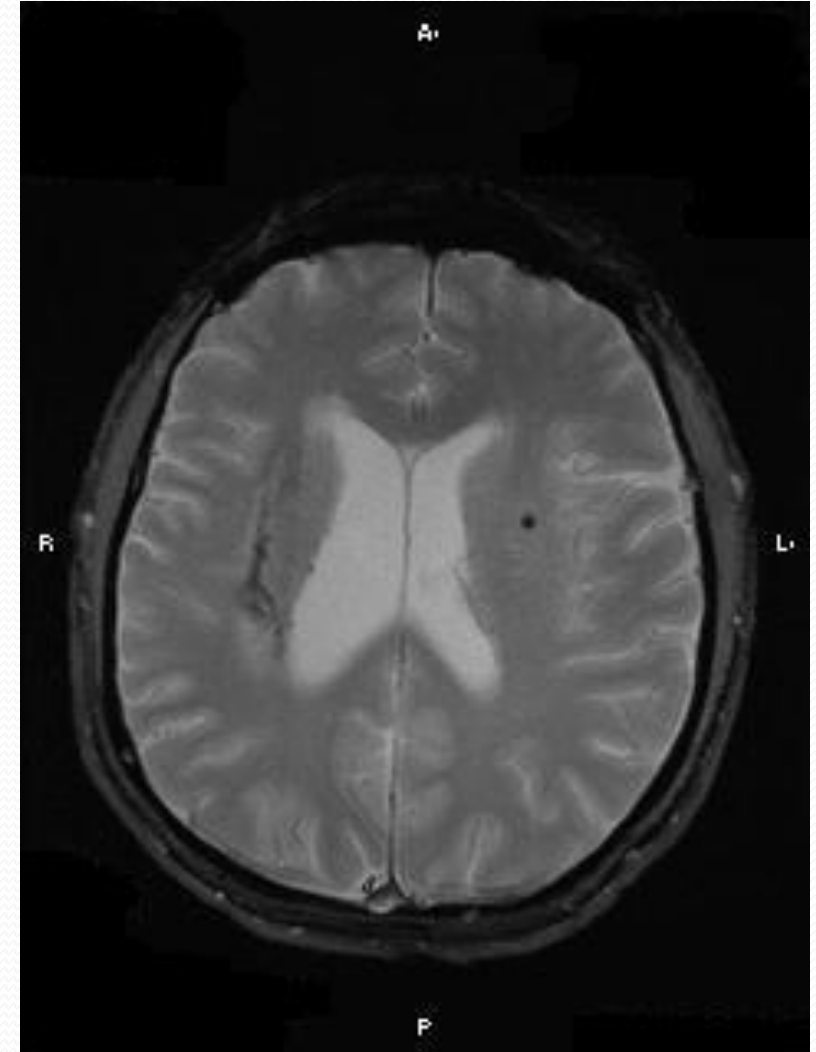
Financements via CHU Lille ou ADRINORD

Brain microbleeds: What are they?

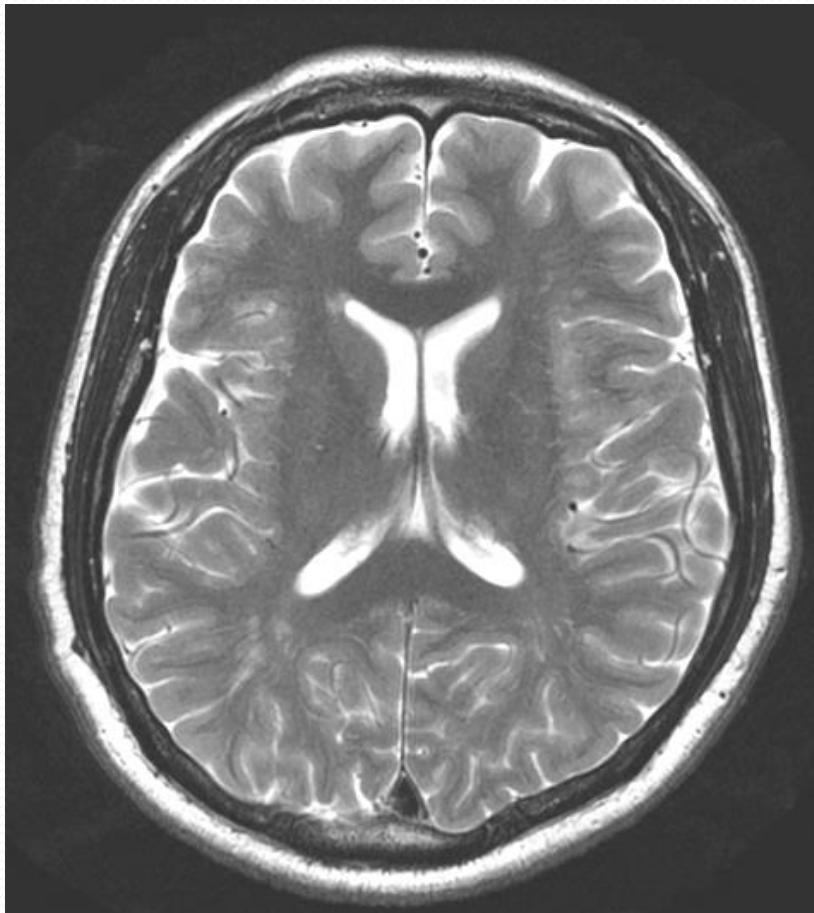


Criteria, imaging parameters

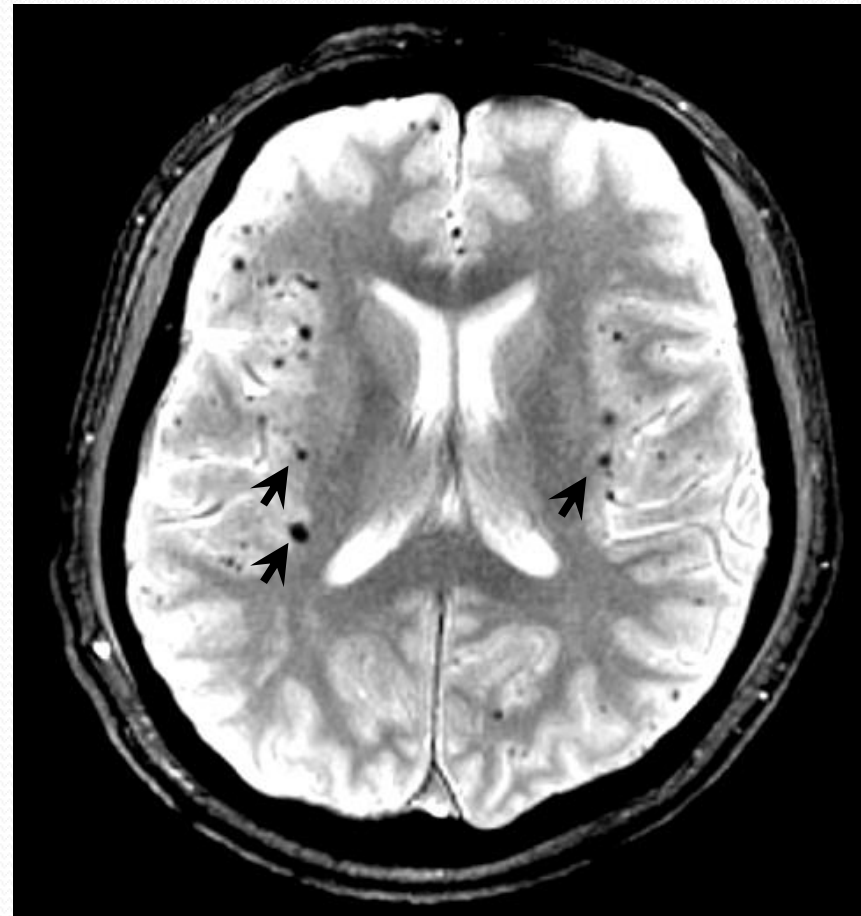
- Black & Blooming
- on GRE T2* or SWI MRI
- Round or ovoid
- Devoid of T2-weighted hyperintensity
- At least half surrounded by brain parenchyma
- Clinical history excluding traumatic diffuse axonal injury
- Less than 10mm



Microbleeds: a radiological construct

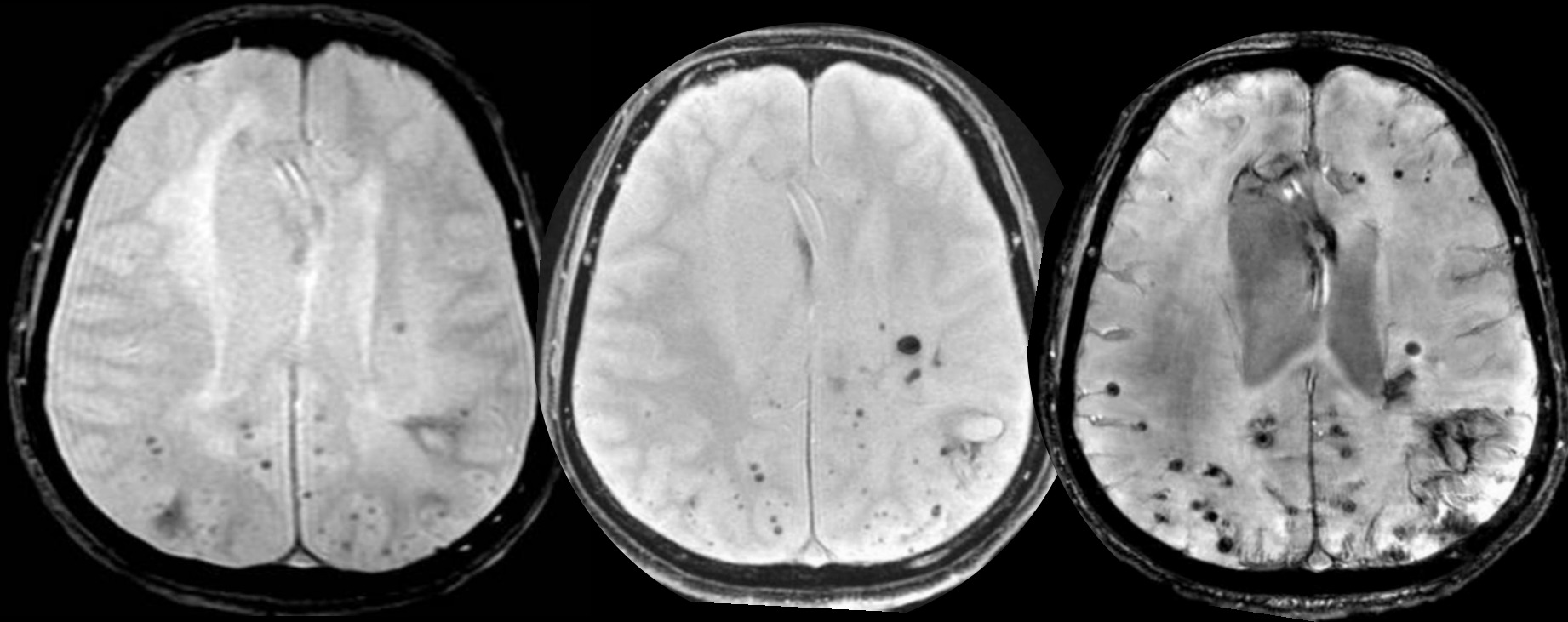


T2



T2*

Influence of radiological parameters on detection rate



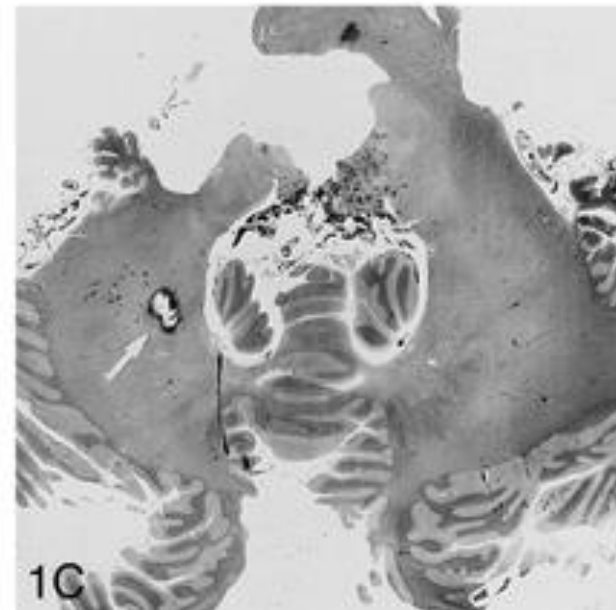
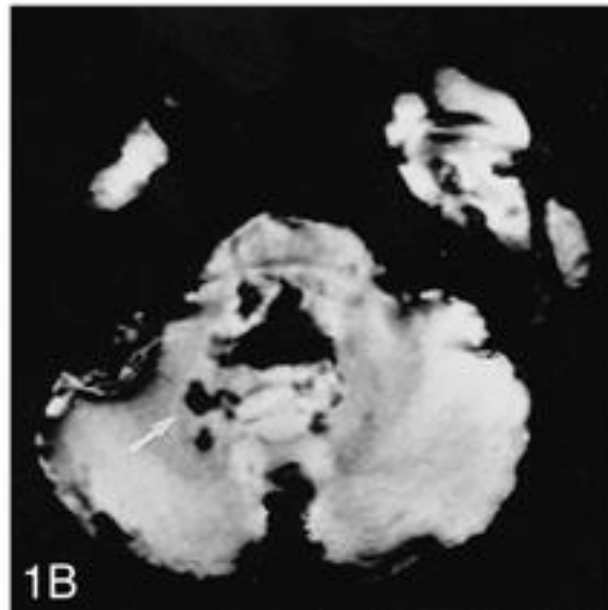
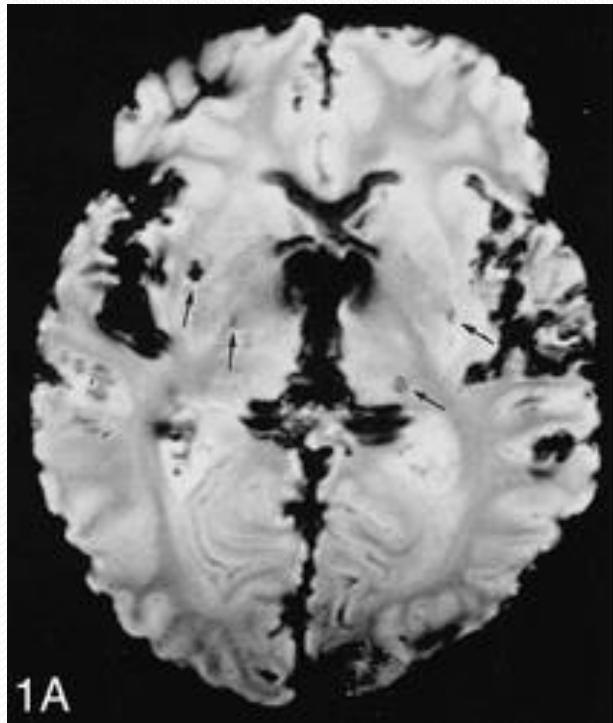
1,5 T GRE

3 T GRE

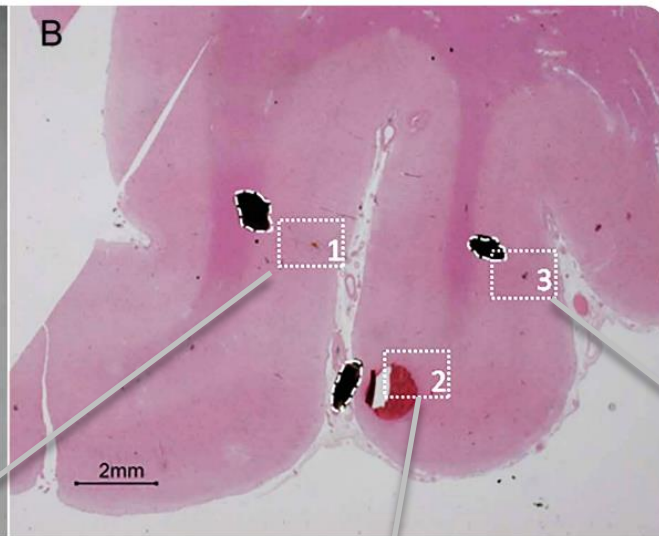
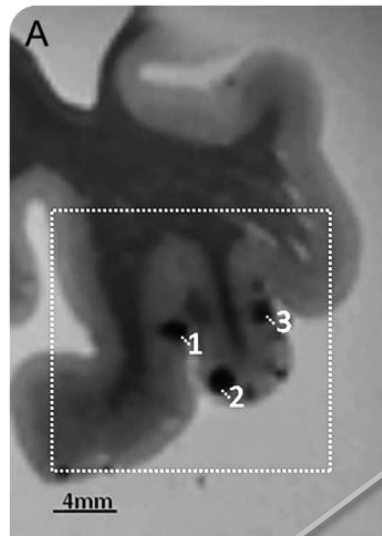
3 T SWAN

Histological substrate

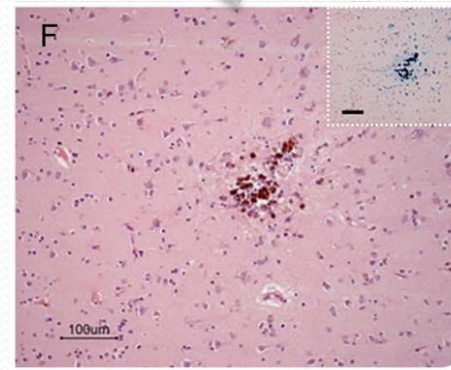
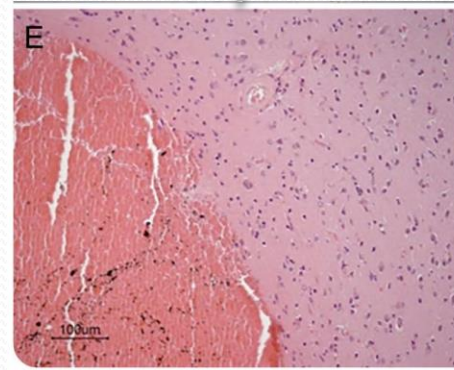
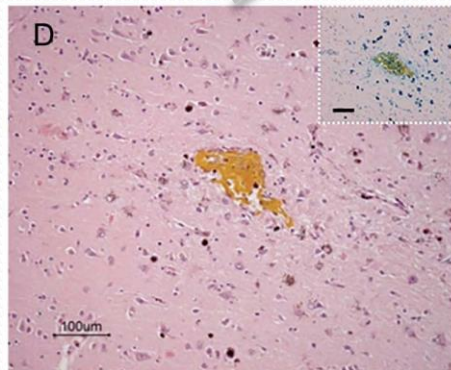
Focal leakage of haemosiderin from abnormal small blood vessels affected by lipohyalinosis or arising from arteries affected by amyloid deposition



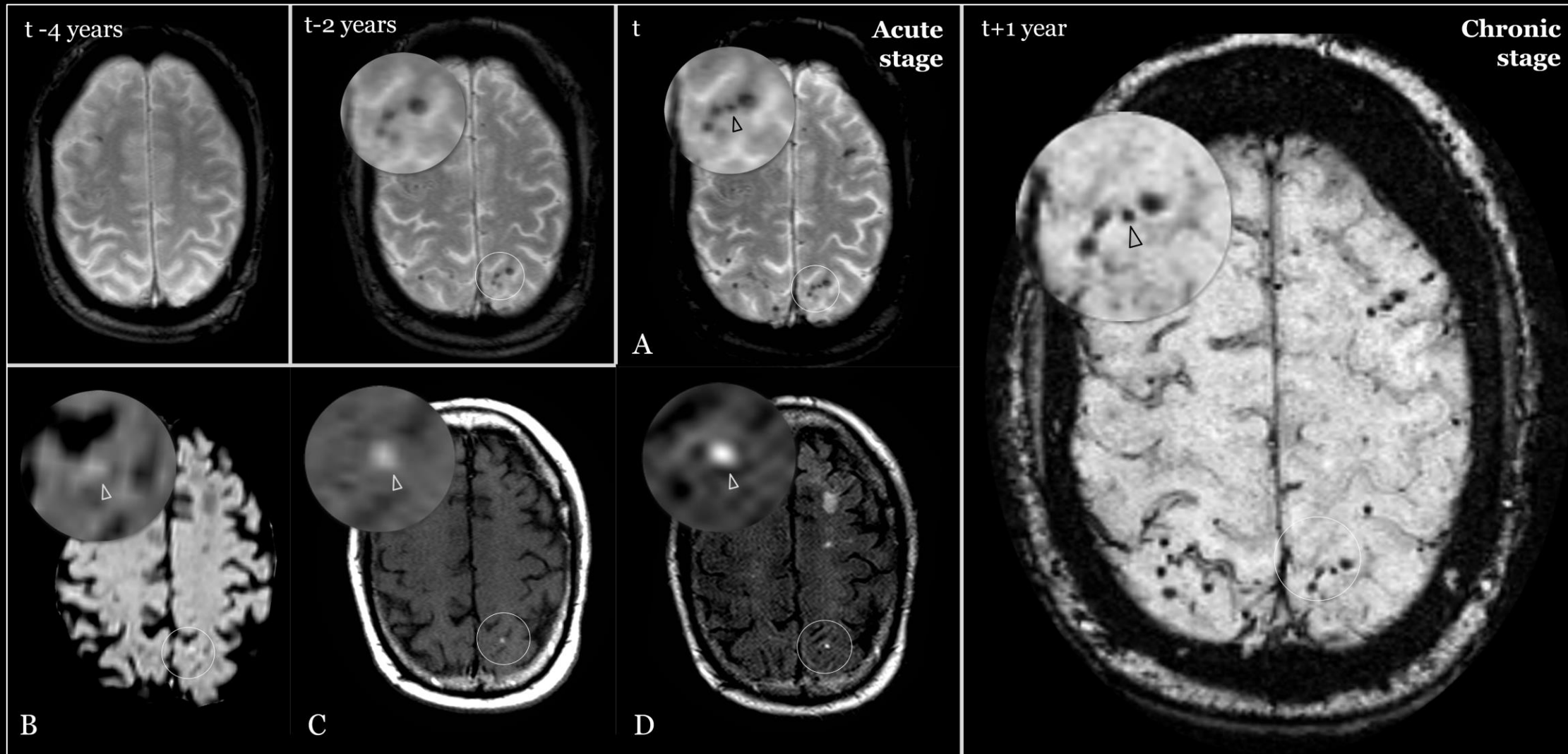
From a radiological construct to histological correlates



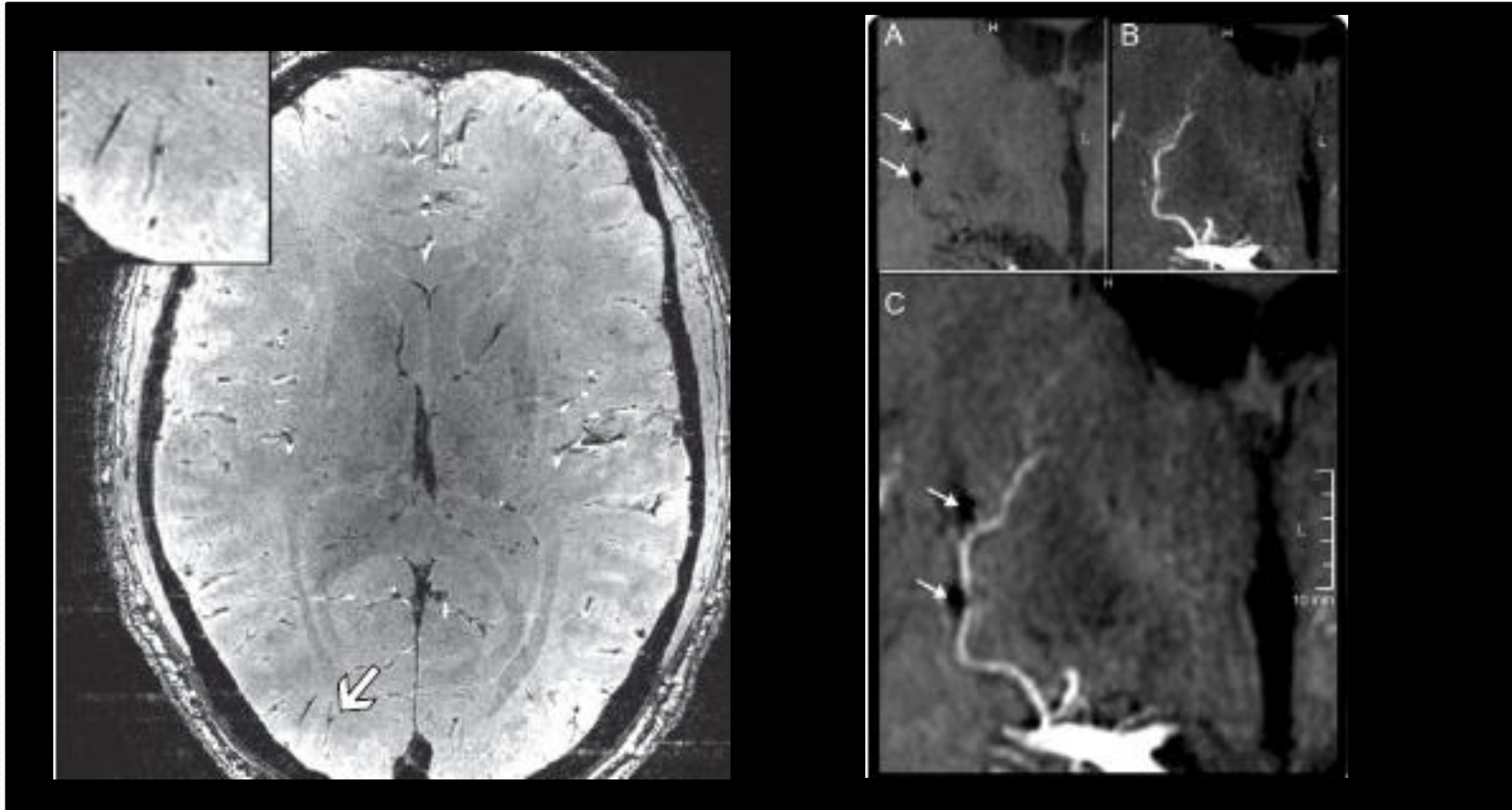
- Rupture microvessel wall
- Blood extravasation
- Iron deposition (old BMBs)



Birth of a Brain MicroBleed



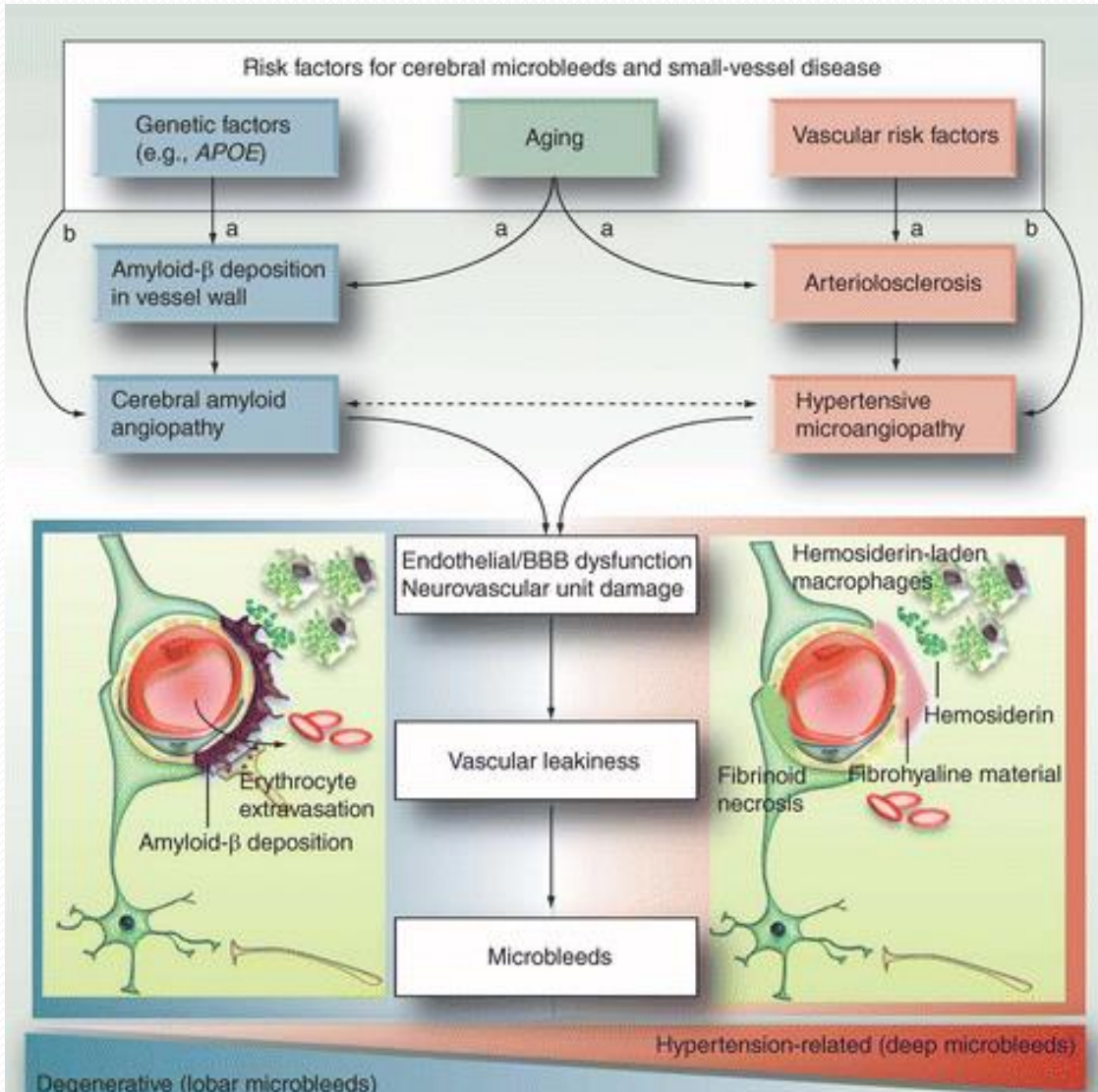
Bleeding or leaking?



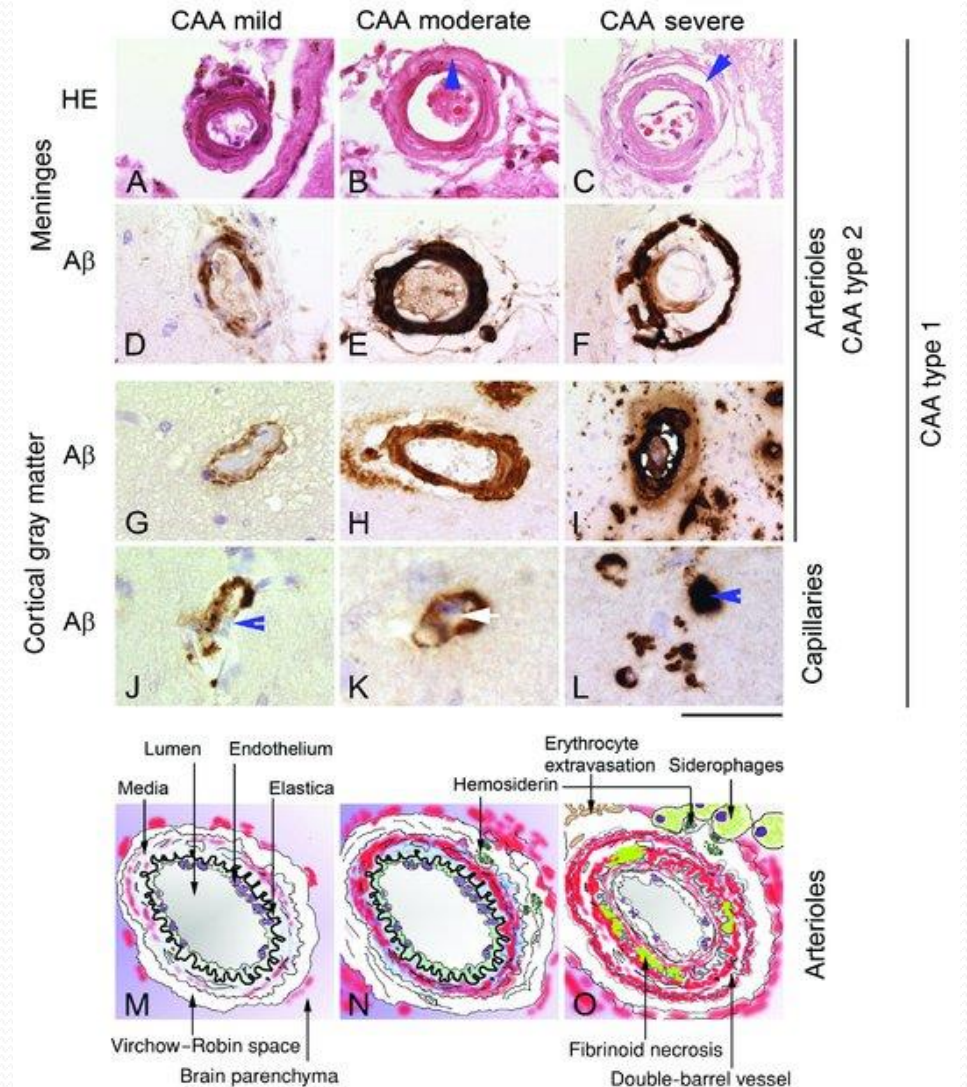
Kuijf HJ. Neuroimage 2012

Biessels GJ. Neurology 2011

What are the mechanisms underlying BMBs?



Microvessel wall fragility

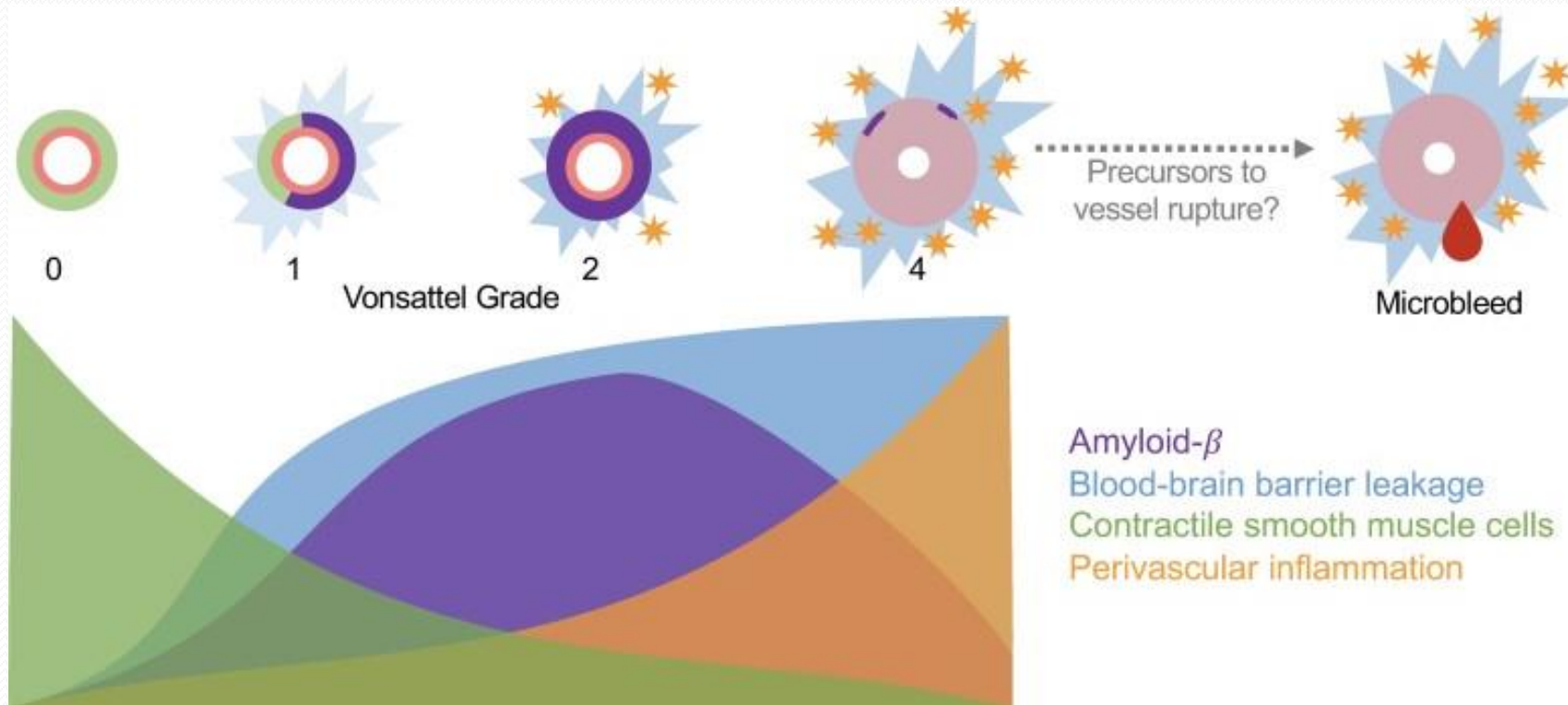


What are the mechanisms underlying BMBs ?

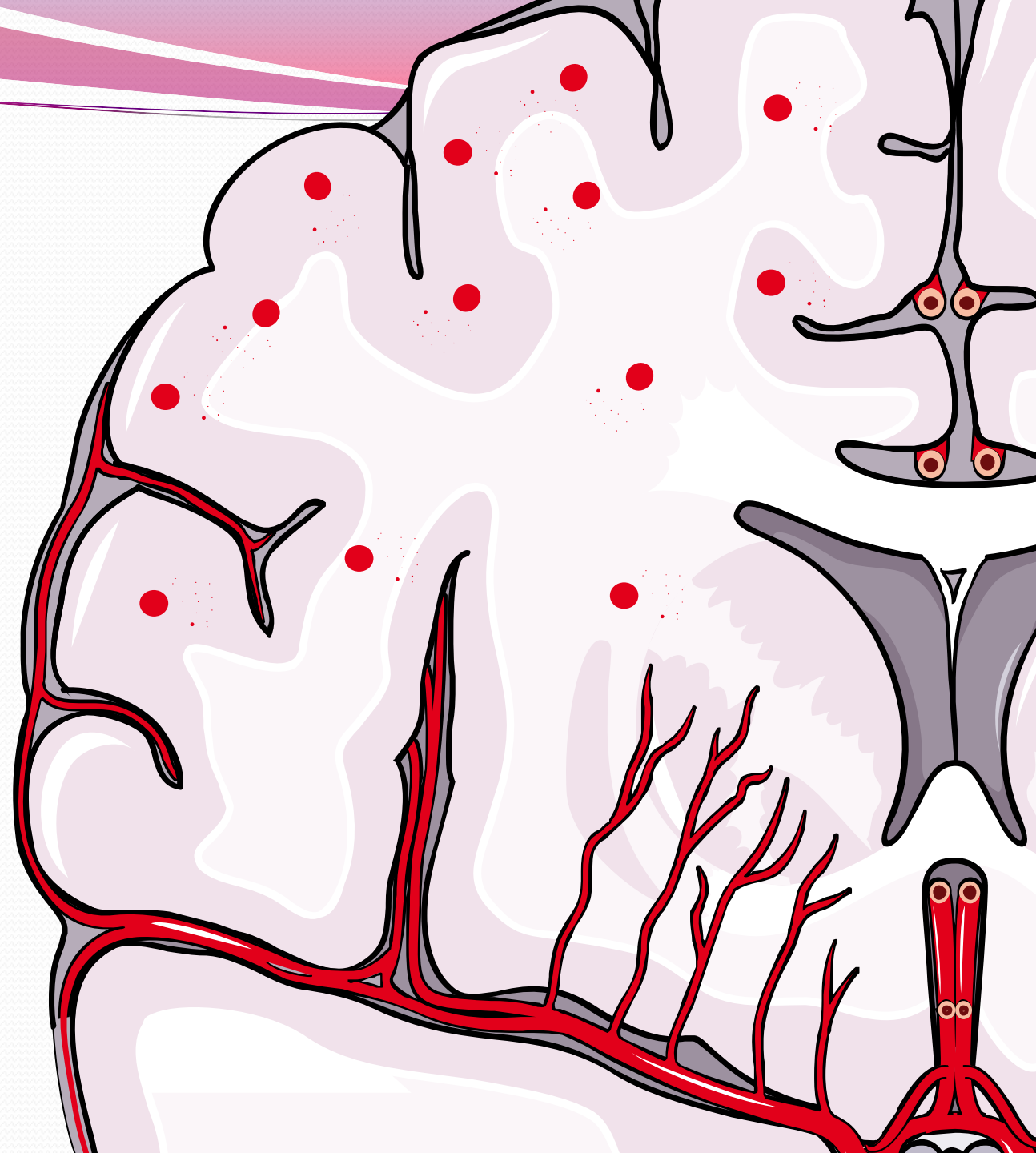
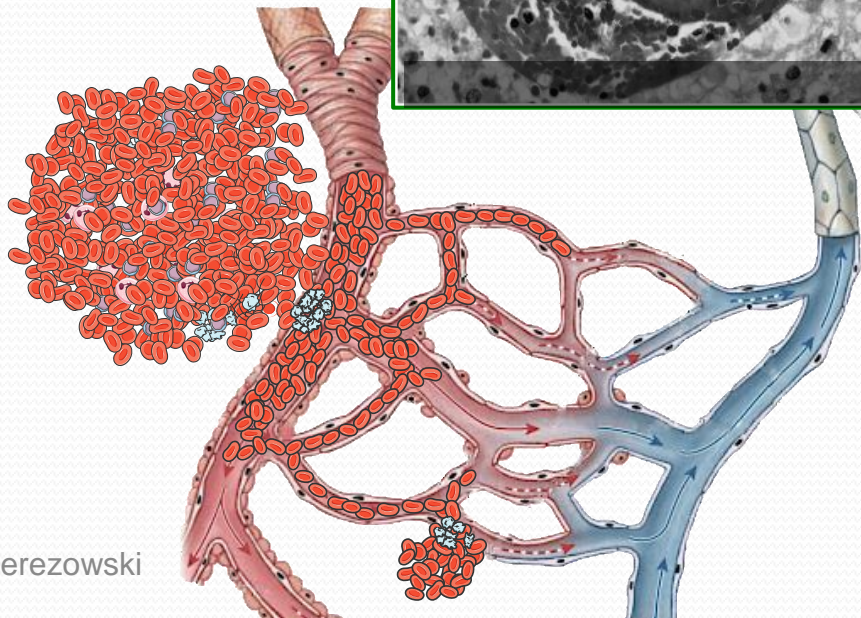
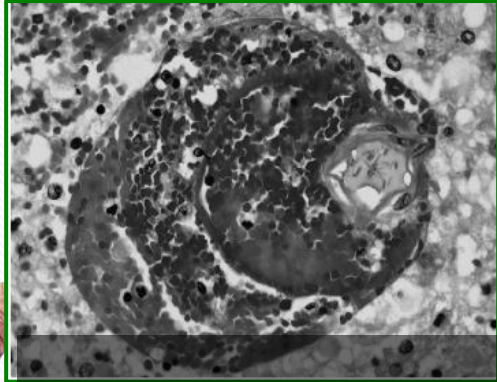
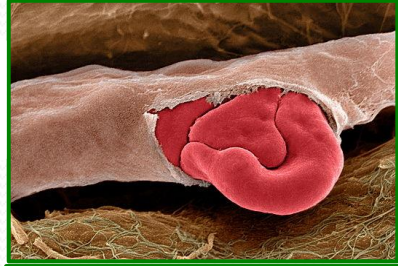
Neuroinflammation

Contribution to BMB occurrence

Blood Brain Barrier leakage and perivascular inflammation in Cerebral Amyloid Angiopathy

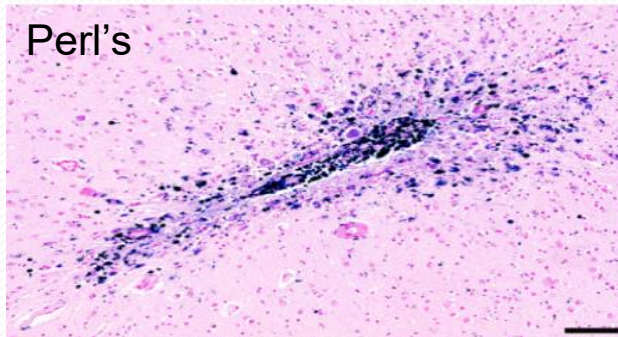


Potential focal toxicity

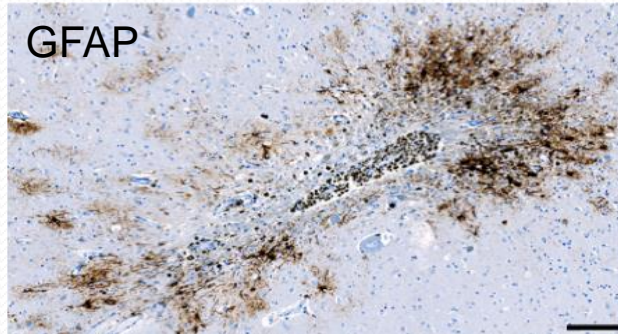


What are the mechanisms underlying BMBs ?

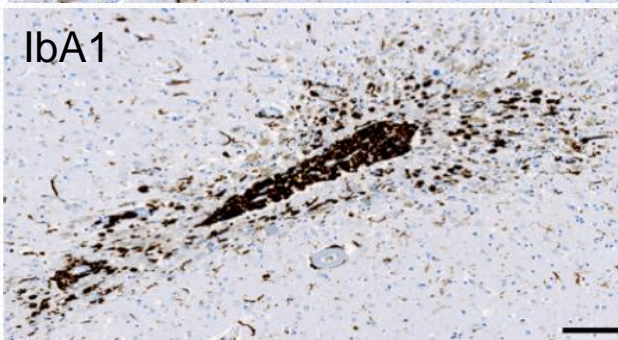
BMB in histology



GFAP



IbA1

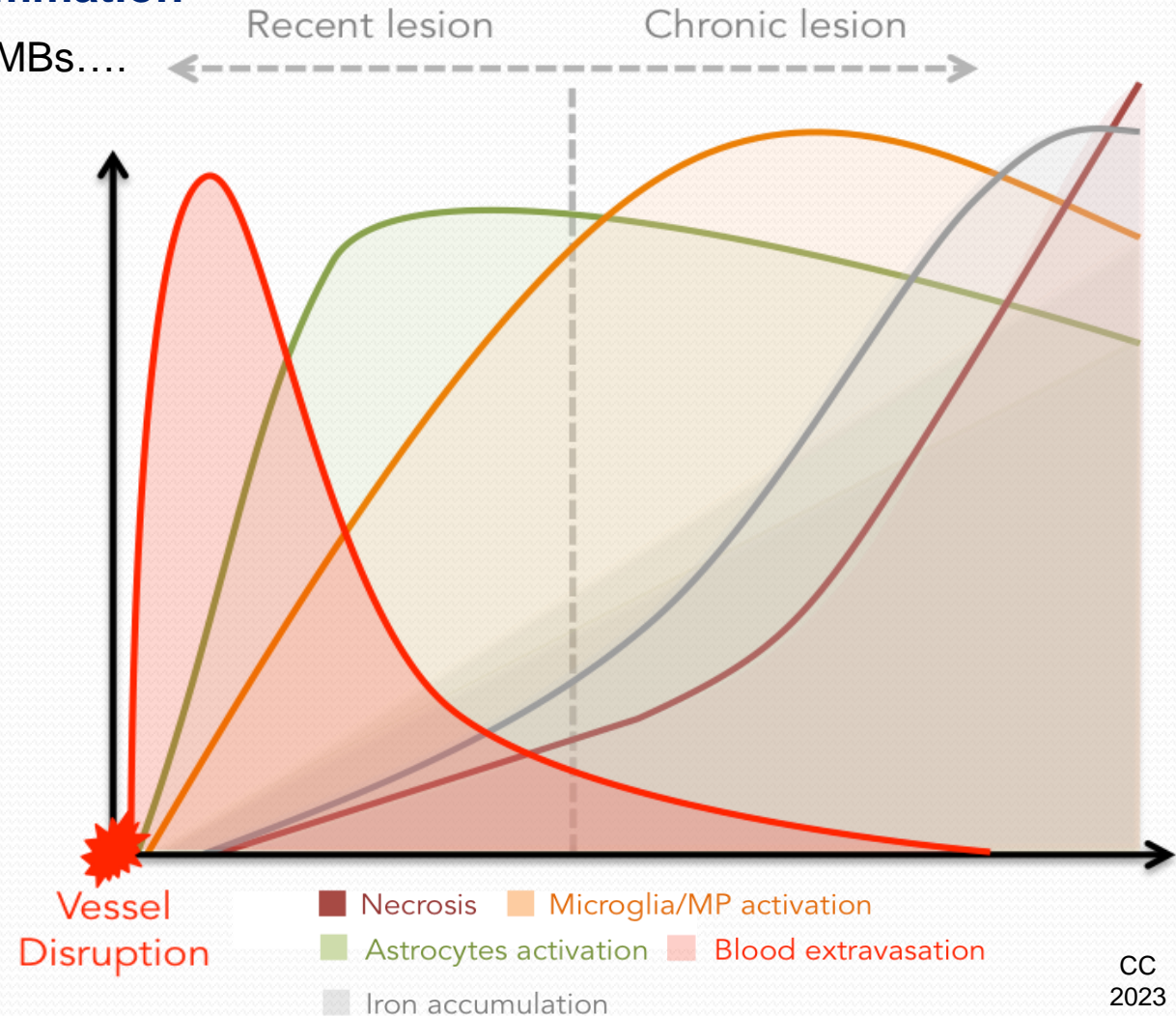


— = 100 µm

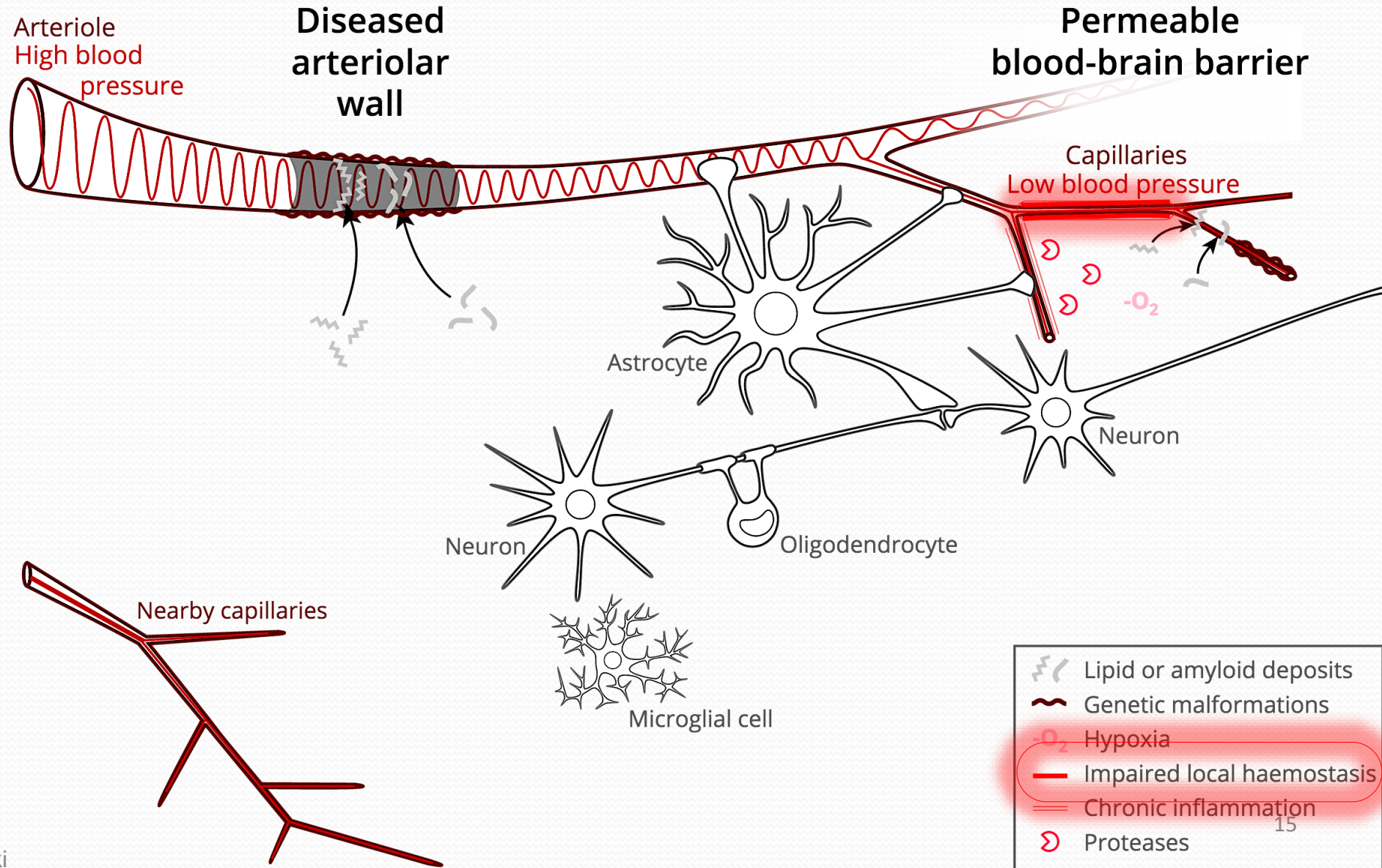
Puy L et al.; unpublished data

Neuroinflammation

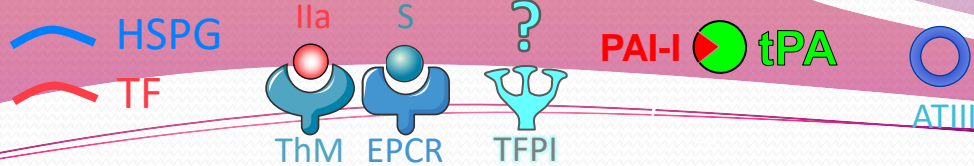
Consequence of BMBs....



A. Events leading to microbleeds



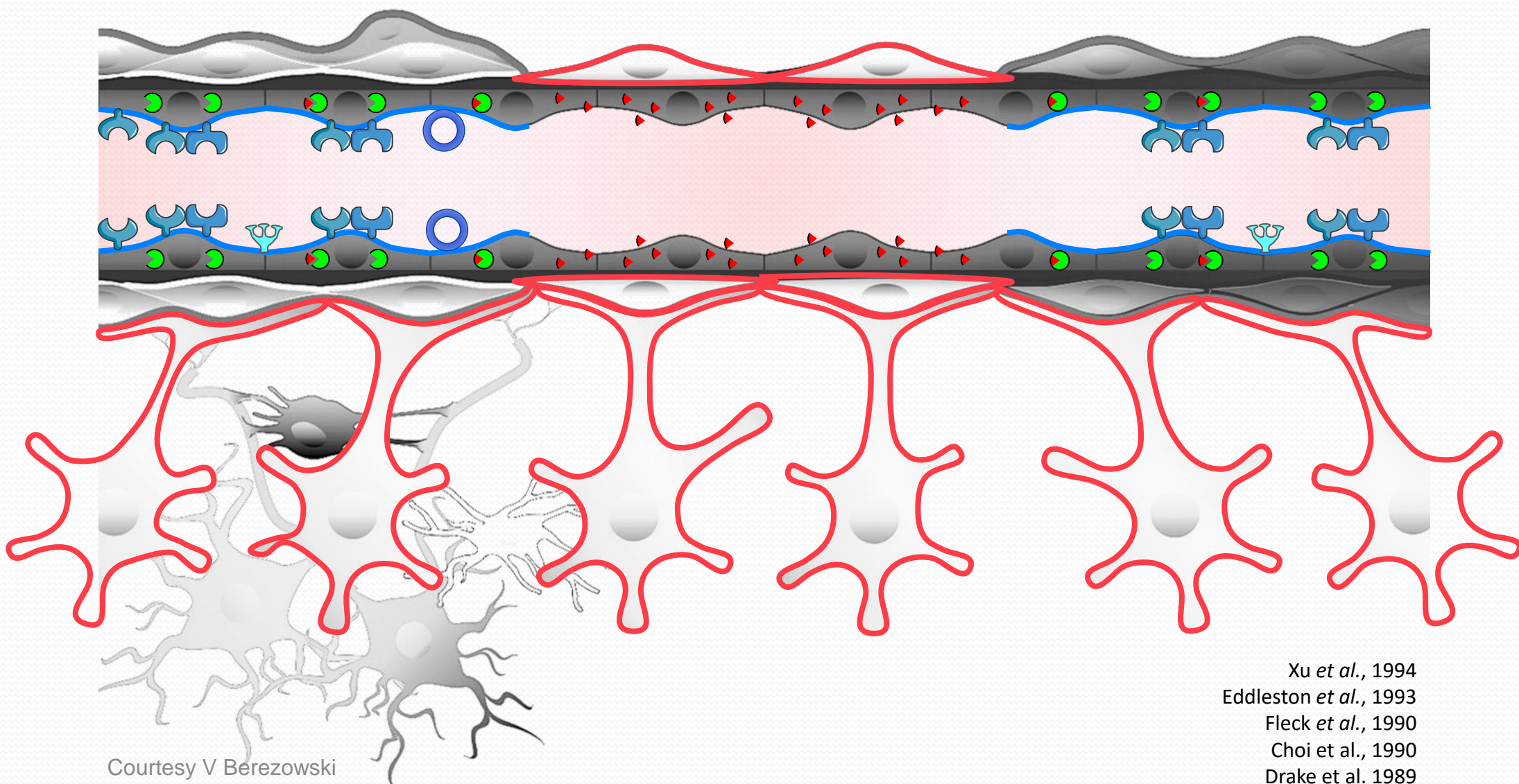
- Lipid or amyloid deposits
- Genetic malformations
- Hypoxia
- Impaired local haemostasis
- Chronic inflammation
- Proteases



Arteriole

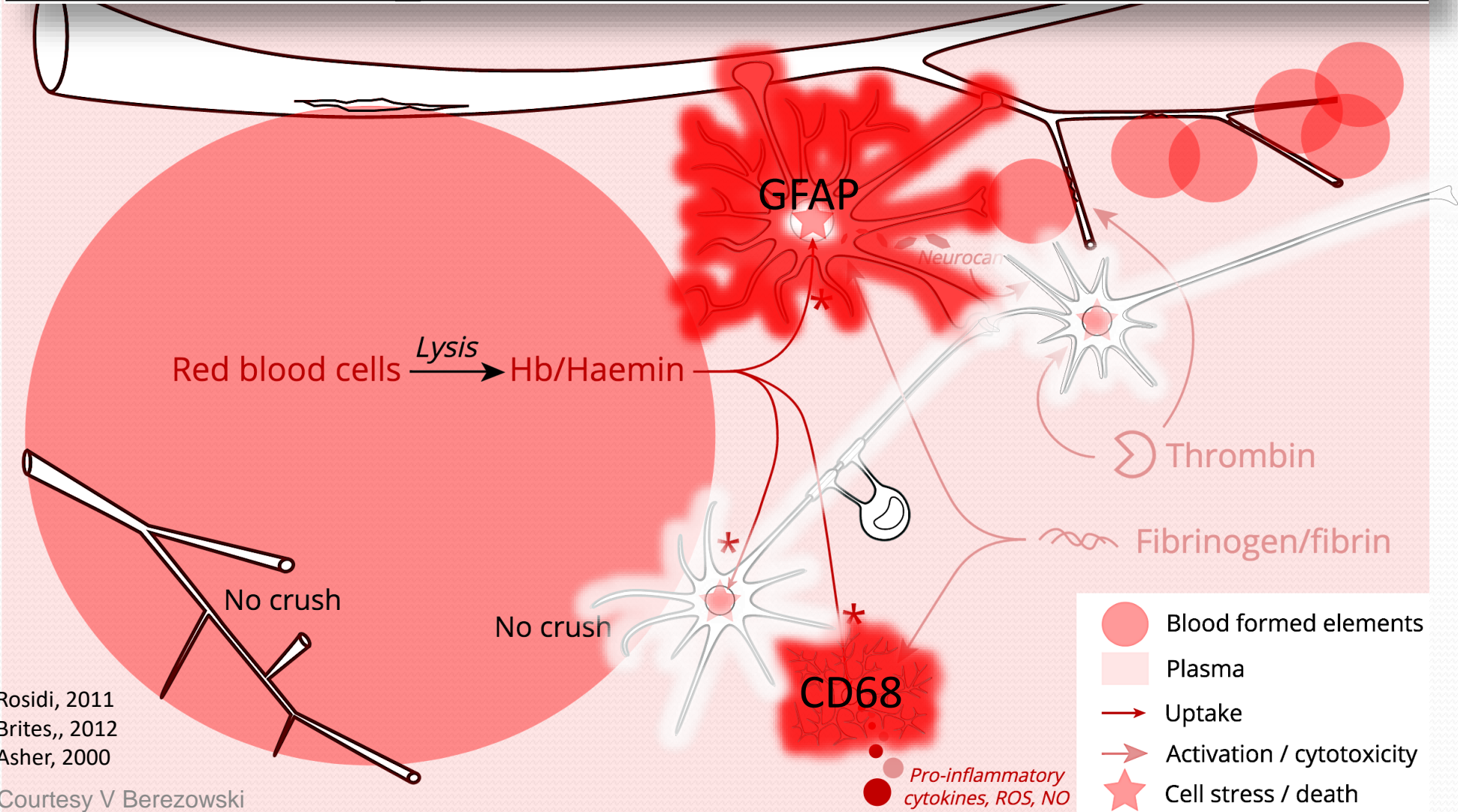
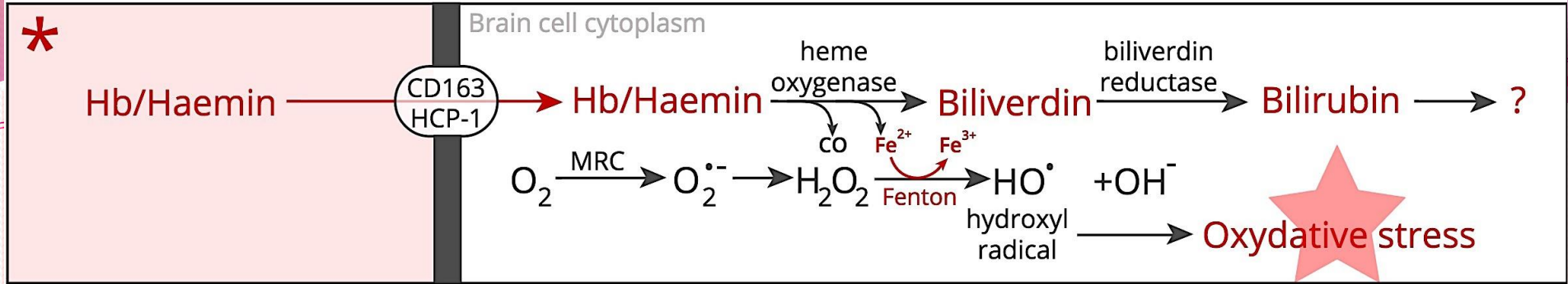
Capillary

Venule



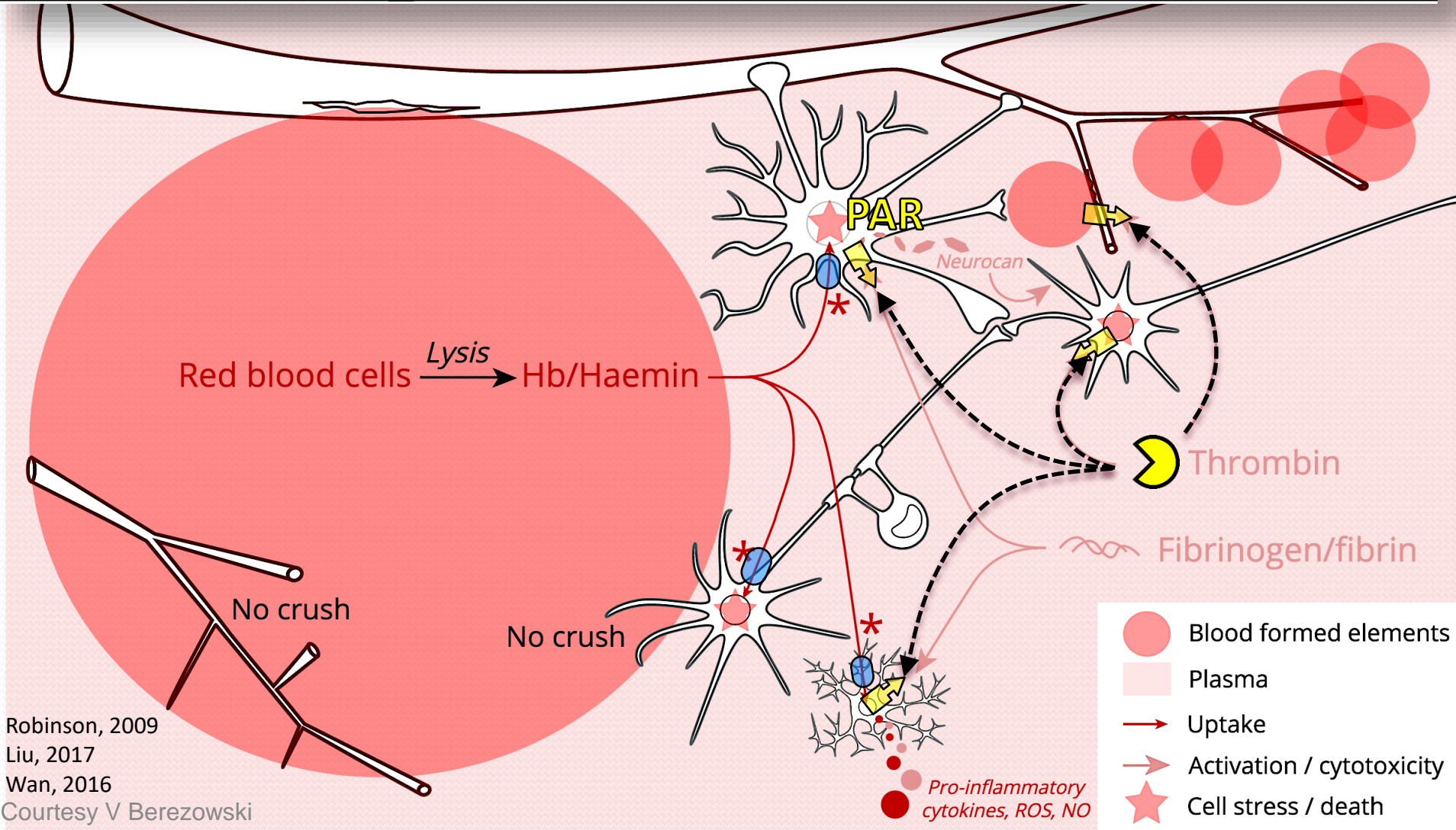
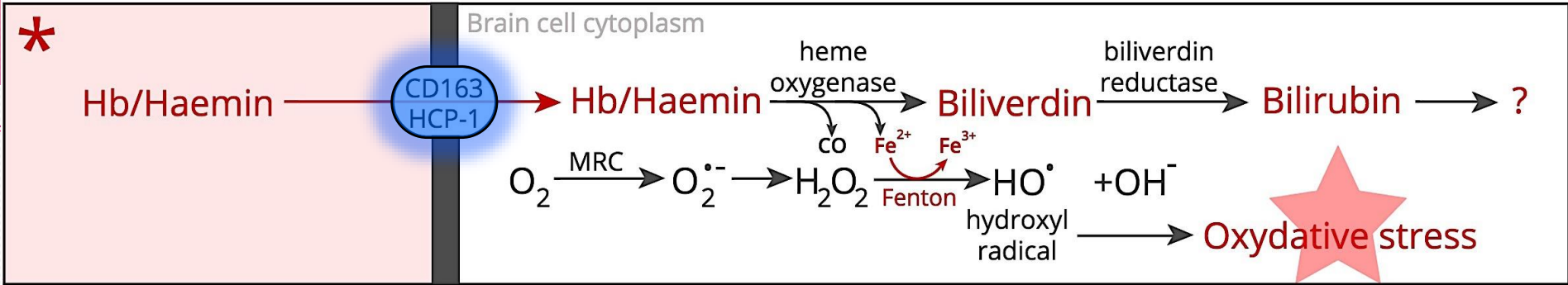
Courtesy V Berezowski

Xu *et al.*, 1994
 Eddleston *et al.*, 1993
 Fleck *et al.*, 1990
 Choi *et al.*, 1990
 Drake *et al.* 1989



Rosidi, 2011
 Brites,, 2012
 Asher, 2000
 Courtesy V Berezowski

Pro-inflammatory cytokines, ROS, NO



Robinson, 2009
 Liu, 2017
 Wan, 2016
 Courtesy V Berezowski

Multiple settings

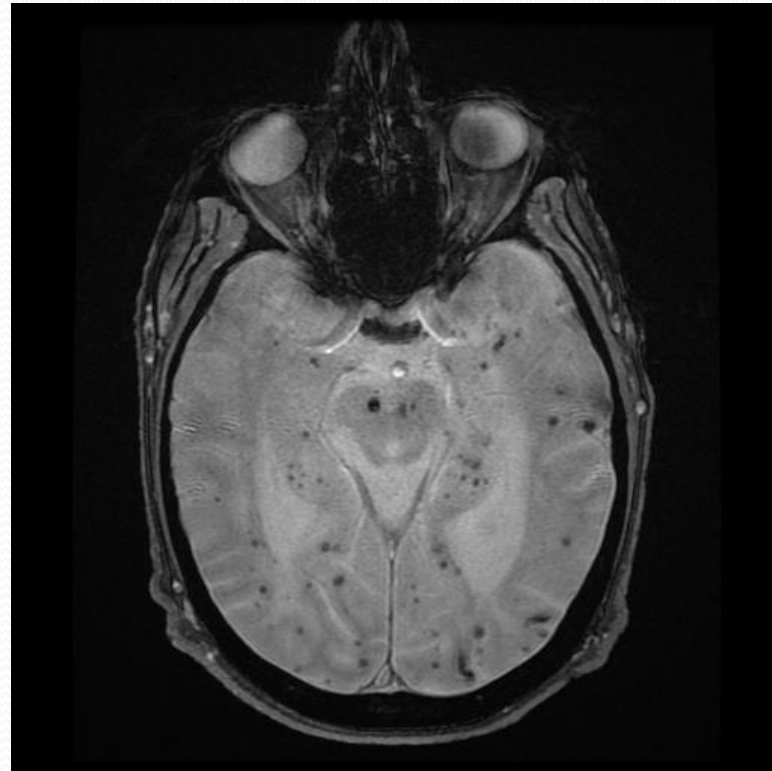
Stroke

Hypertension

Brain Aging

Haemophilia

TAVI

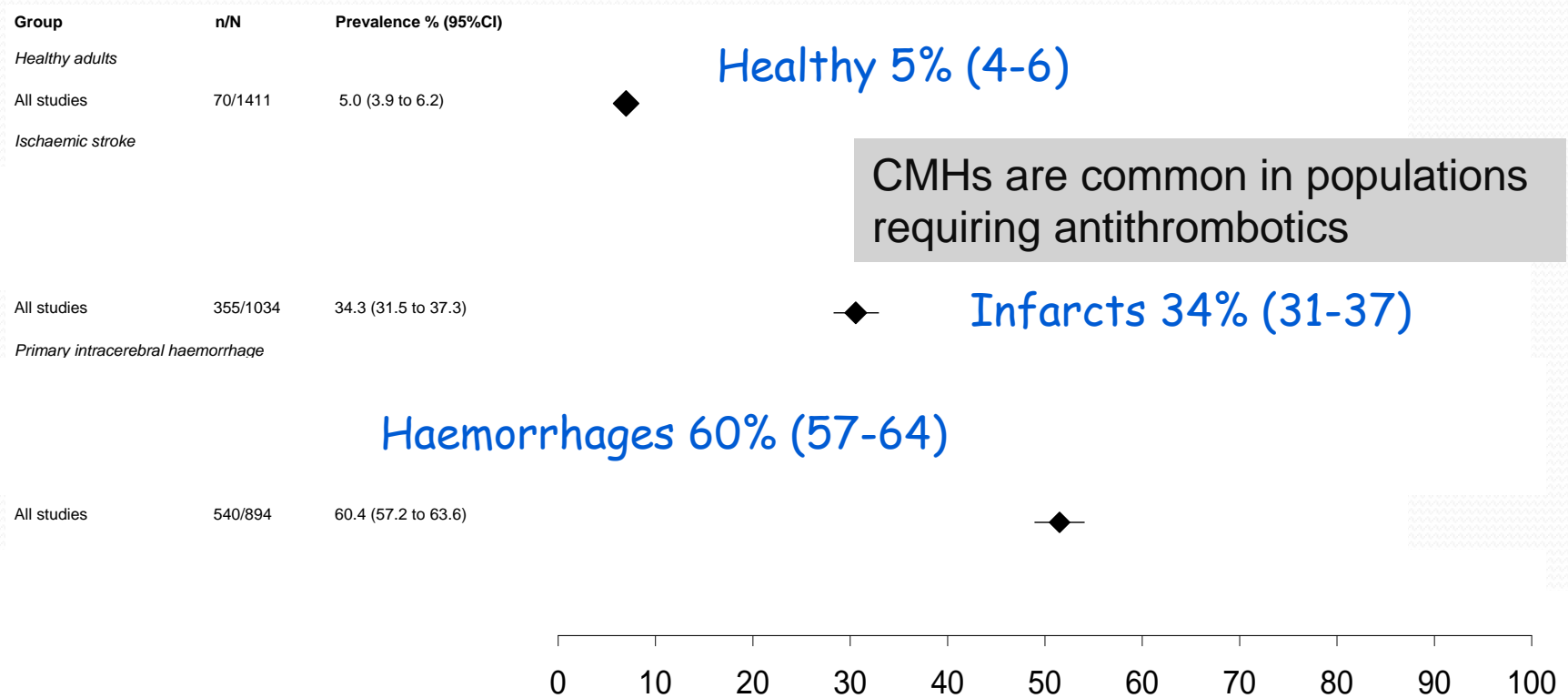


Cerebral Amyloid Angiopathy

Alzheimer's disease

Dementia

Prevalence

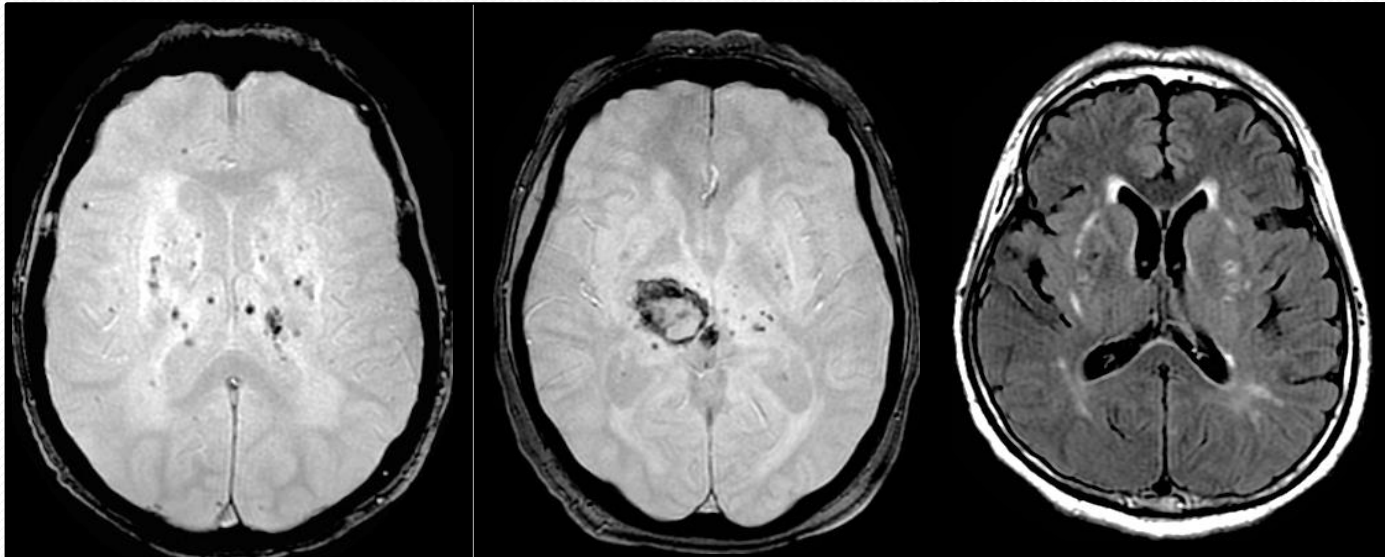


What do BMBs mean?

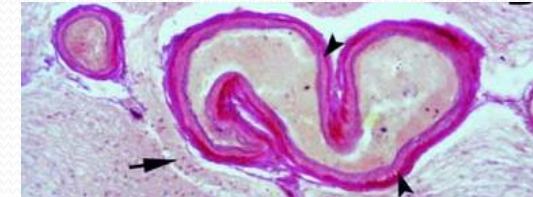
Markers of vessel disease

Importance of the anatomical distribution

DEEP BMBS

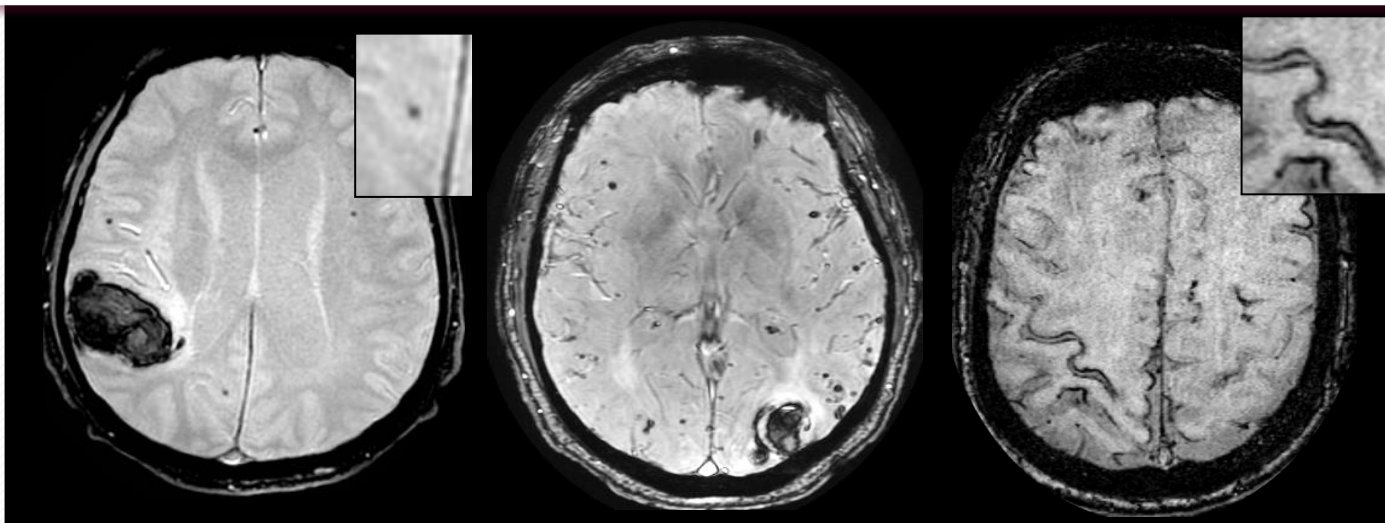


Deep perforating
vasculopathy

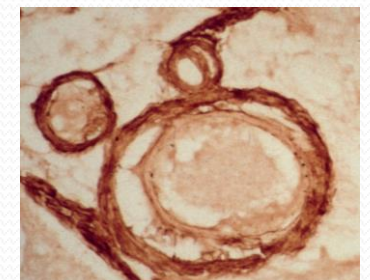


Thal JNEN 2003

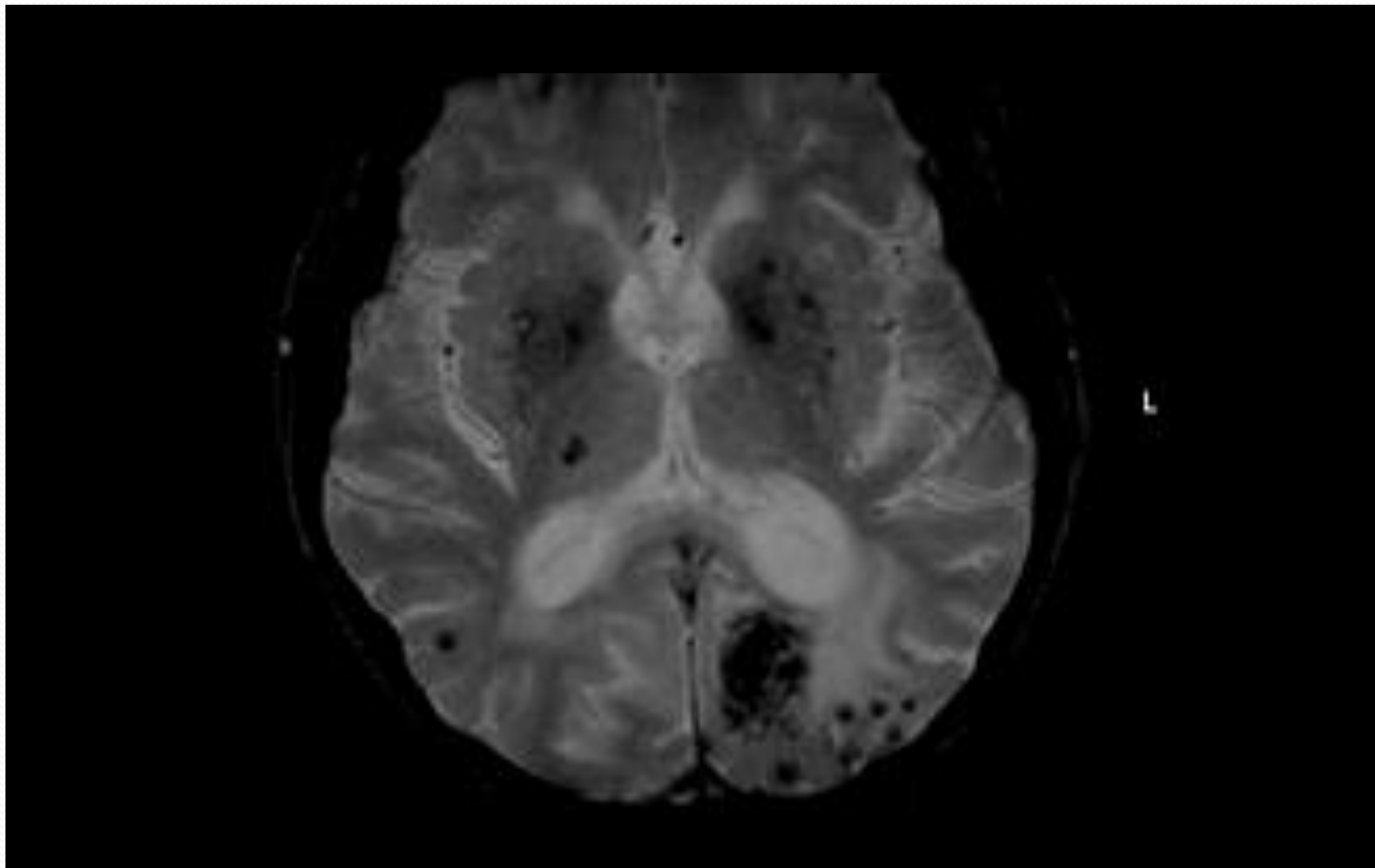
LOBAR BMBS



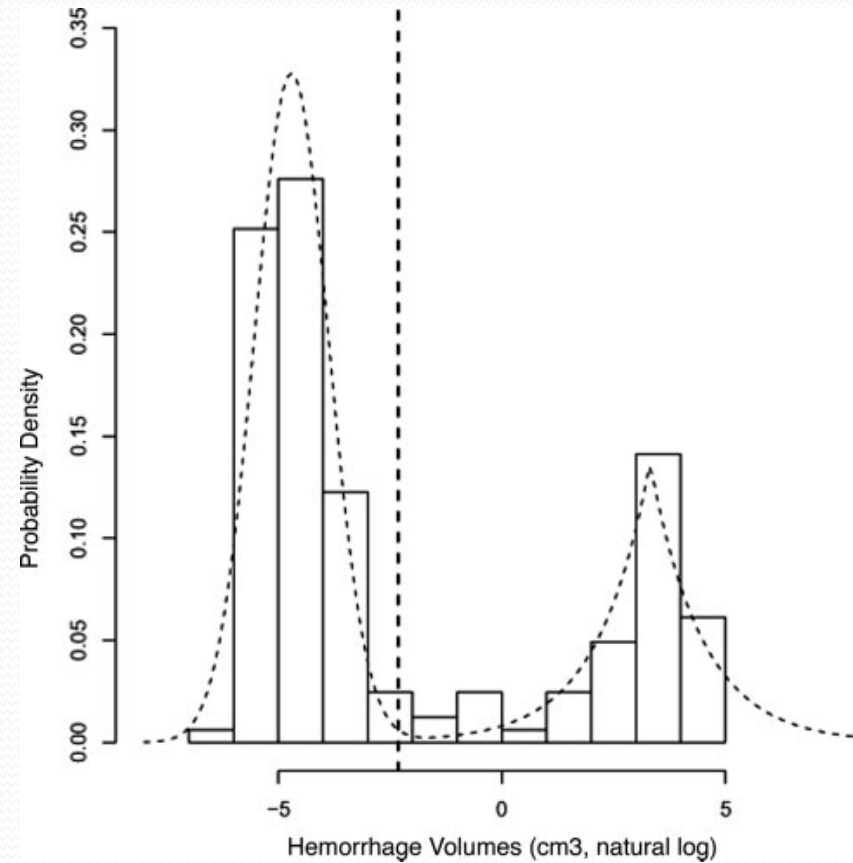
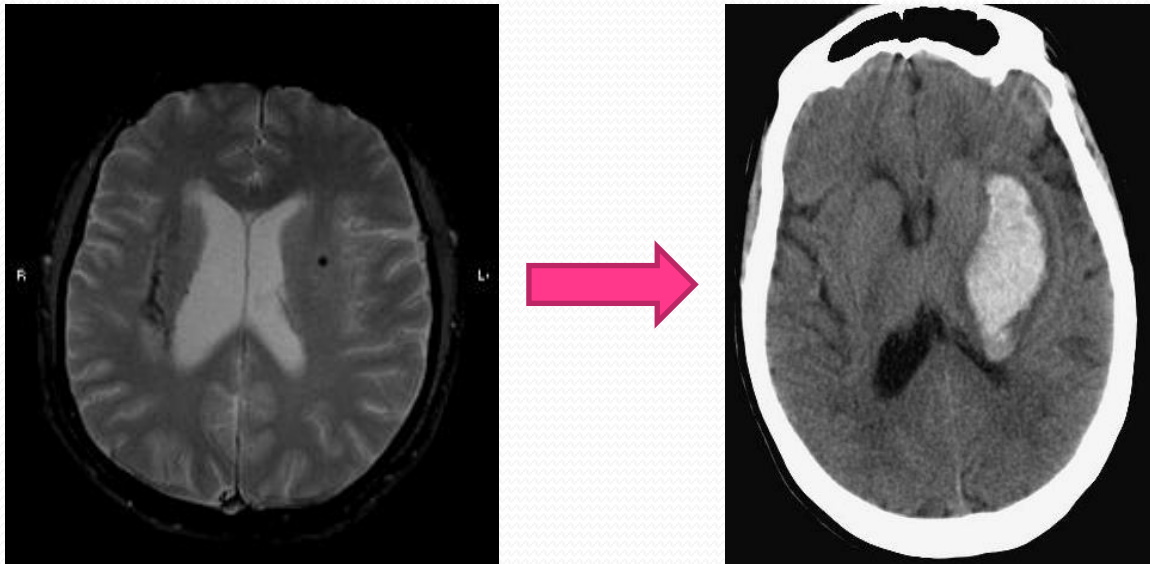
Cerebral amyloid
angiopathy



Markers of disease



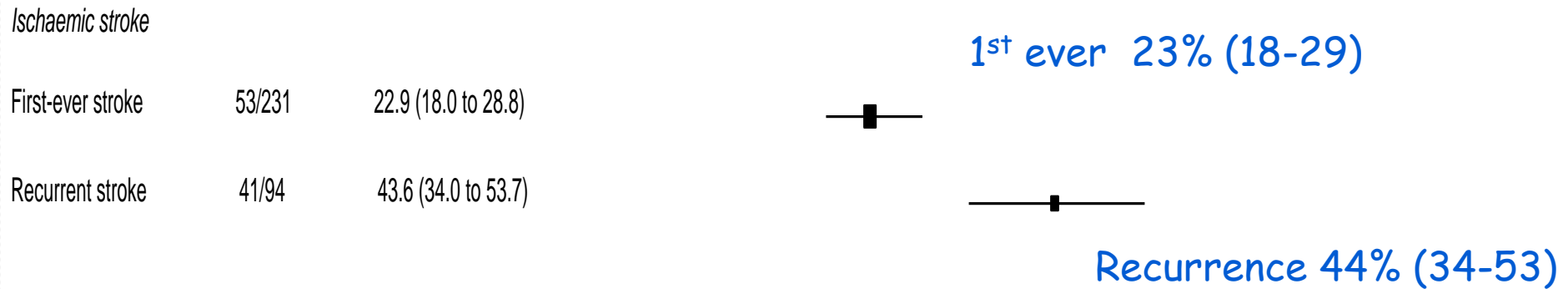
From micro to macro: is there a continuum?



How to interpret BMBs?

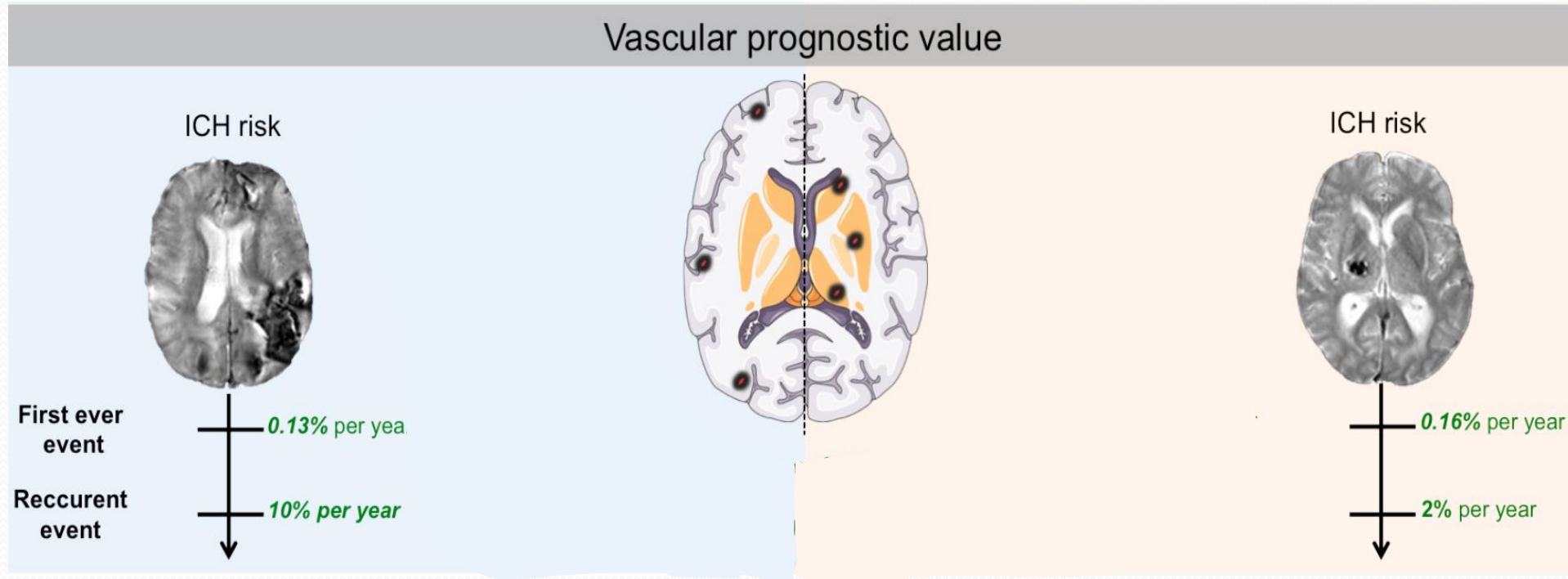
Markers of the SEVERITY
of the underlying vessel disease

Prevalence



First ever < Recurrence
**CMHs could be a biomarker of the evolutivity,
severity of the cerebrovascular disease**

Prognostication : risk of macrobleeding

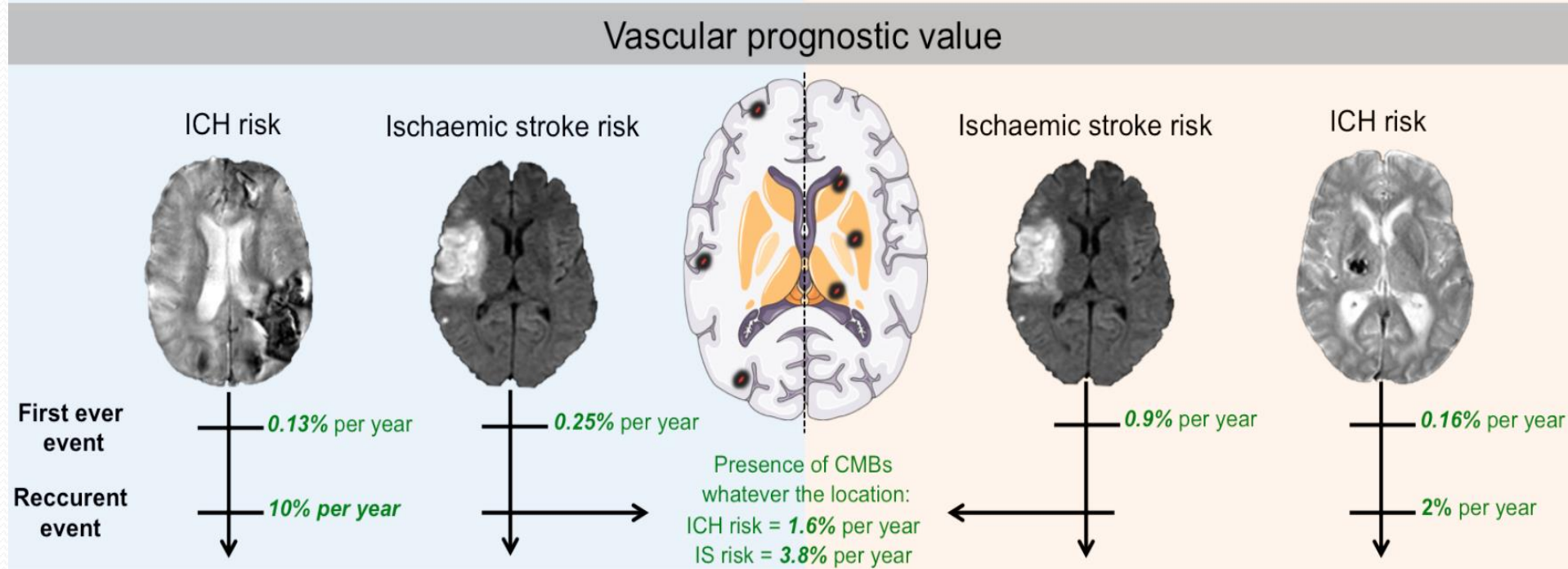


Importance of anatomical distribution

BMB presence exposes to an increased relative risk of :

ICH × 6

Prognostication : markers of bleeding, but not only...



Importance of anatomical distribution

BMB presence exposes to an increased relative risk of :

ICH × 6

Ischemic stroke × 2



BMB: silent lesions?

BMB are not silent lesions!

- BMB could have direct effects on neurologic function, cognition, and disability (with interactions)

Choi, Stroke 2012

- BMB were associated with clinical disability in CADASIL

Viswanathan, Brain 2006

- Patients with BMB performed worse in executive function

Werring, Brain 2004

- BMB influence cognition

Infratentorial

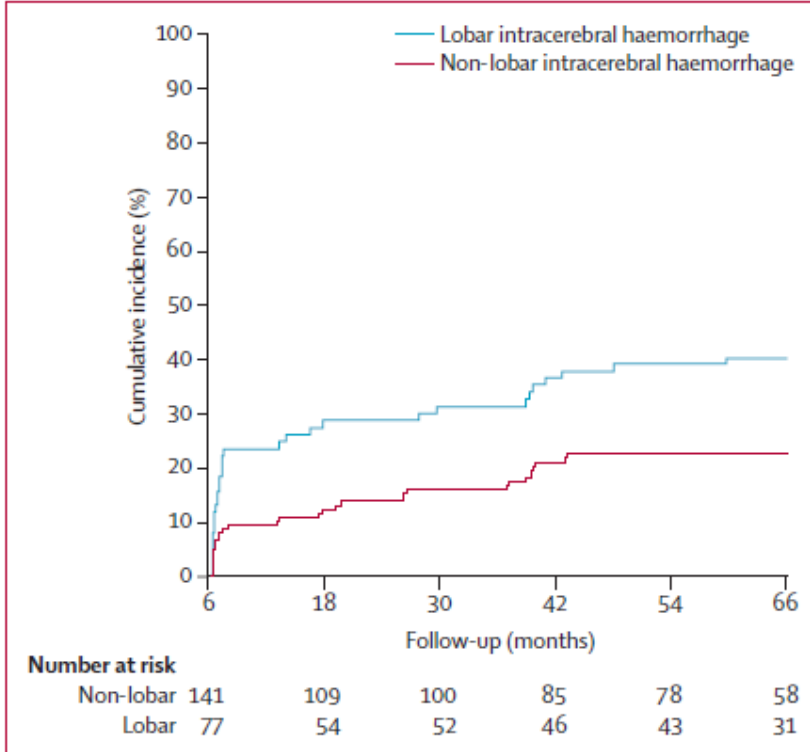
Frontal, temporal or deep

van Es, Neurology 2011

van Norden, Stroke 2011

BMB predictors of dementia after ICH

- Predictors amongst others



	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

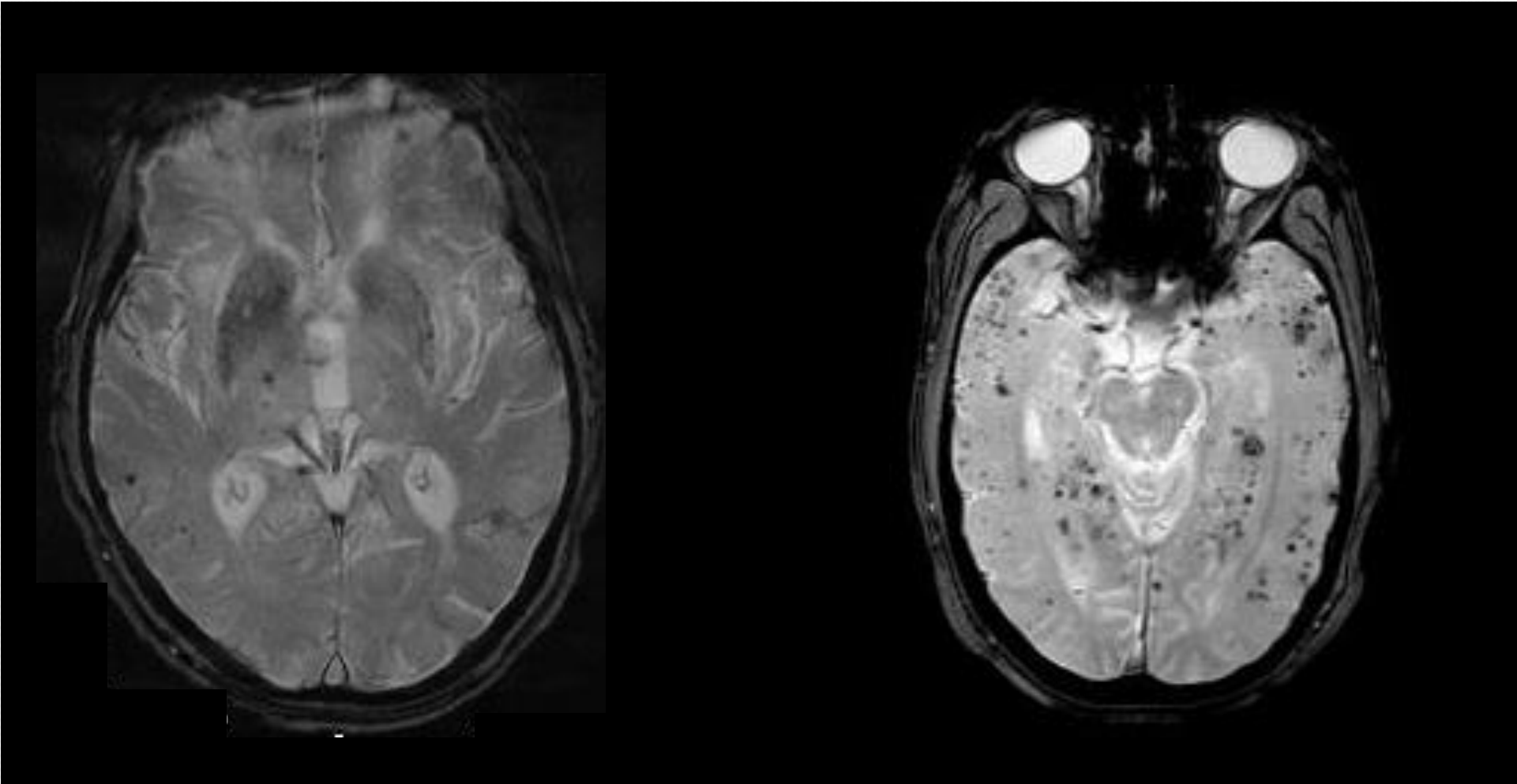
218 ICH patients

Median FU: 6 years

Incidence rate 28% (95%CI 22-35) @ Y4

Influence on cognition

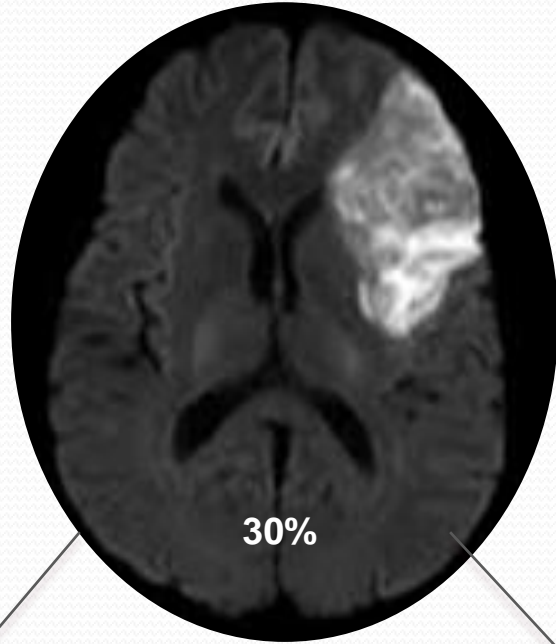
- Potential impact of the number & location of microbleeds





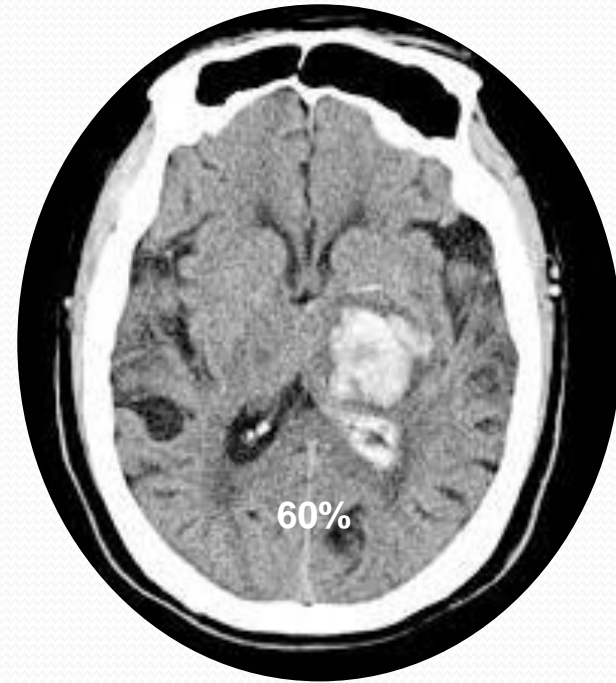
BMBs & treatment decisions

BMB and treatment decisions in the context of stroke



Acute care
Reperfusion therapies

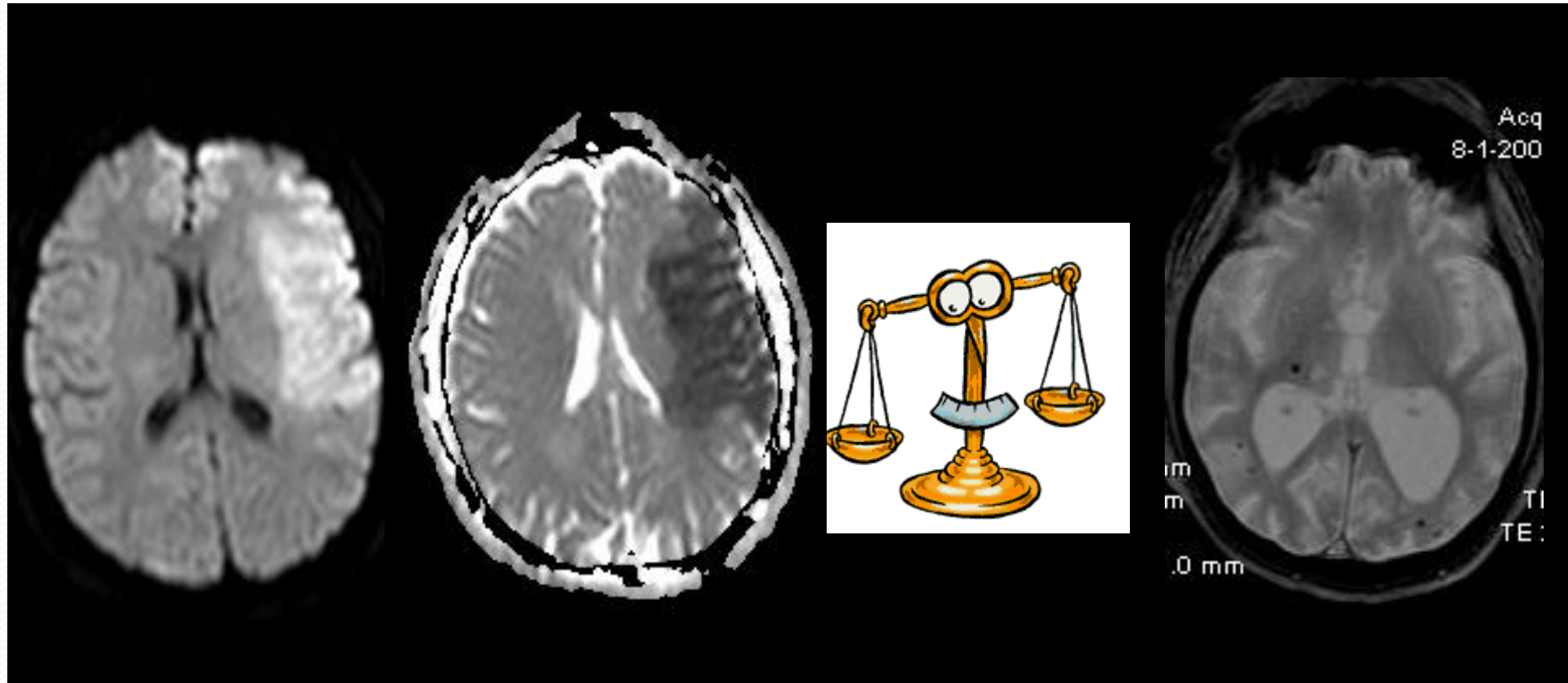
Long term:
Risk of future ICH



Long term:
Risk of recurrent ICH

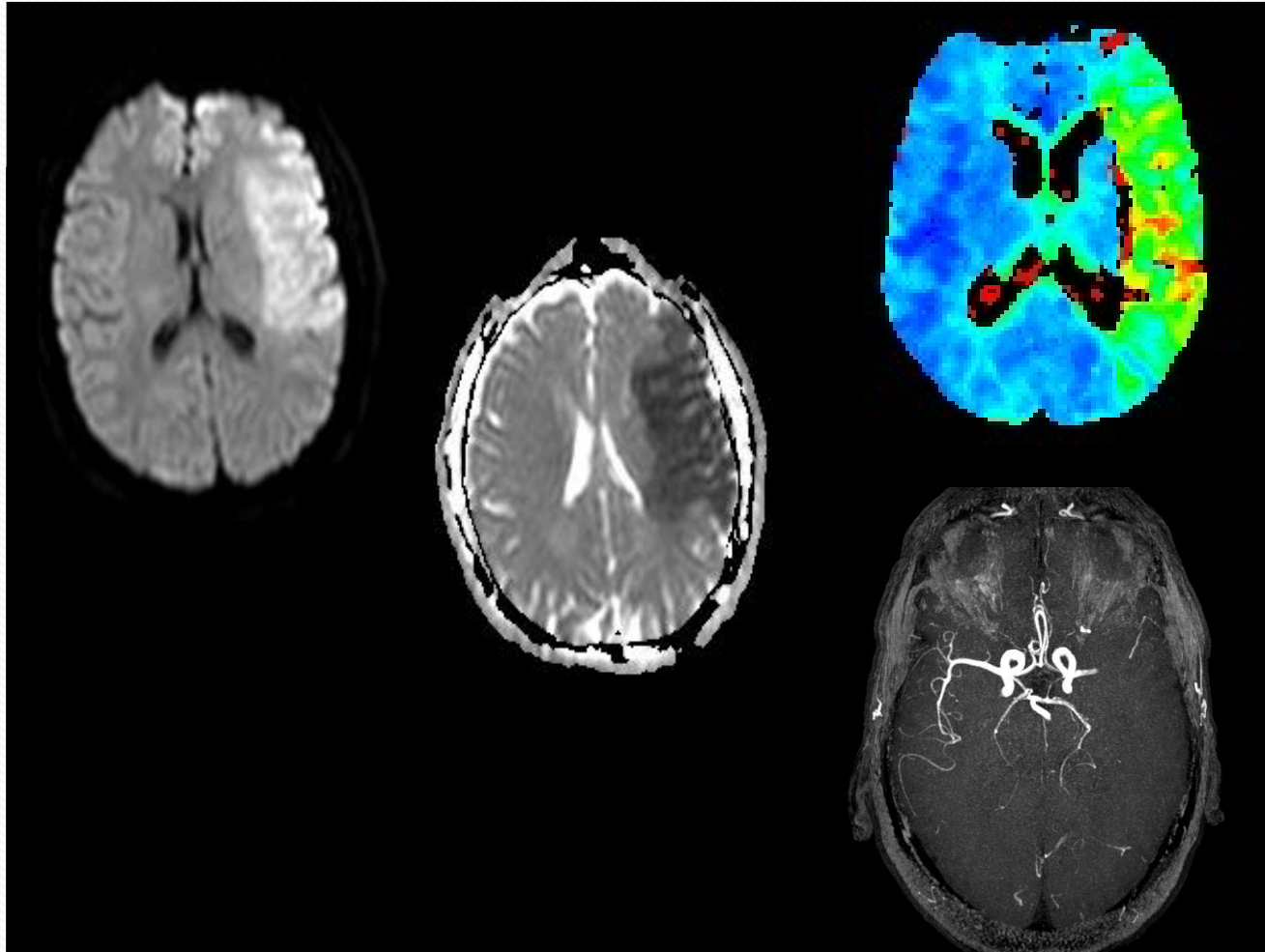
BMBs & i.v. rtpa

- i.v r-tpa or not?



BMBs & mechanical thrombectomy

- To reperfuse or not?



Should we start anti-thrombotic agents after ischaemic stroke in the presence of BMBs ?

Study	Population n, n	Type of stroke	Proportion baseline CMBs	Therapeutic arms	Follow-up	Main results
SPS3 trial	1278	Lacunar strokes	30%	Aspirin Vs Aspirin + Clopidogrel	3.3 y	no significant interactions noted between baseline CMB presence and random assignment Tt for the outcomes of recurrent stroke
PICASSO trial	1534	IS with a history of ICH or > 1 CMB	60%	Aspirin Vs Cilostazol	1.9 y	-risk of sICH was lower with cilostazol than aspirin in participants with CMBs (0.12%/year vs. 1.49%/year) -No difference in participants with prior sICH (1.26%/year vs. 0.79%/year)
NAVIGATE ESUS	3699	ESUS	11%	rivaroxaban 15 mg daily compared with aspirin	11 Mo	-No suggestion of a treatment effect for the outcome sICH between baseline presence, location or severity of CMBs (participants with CMBs: HR 3.1, 95%CI 0.3 - 30.0; without CMBs: HR 3.0, 95%CI 0.6 - 14.7; interaction p=1.0).

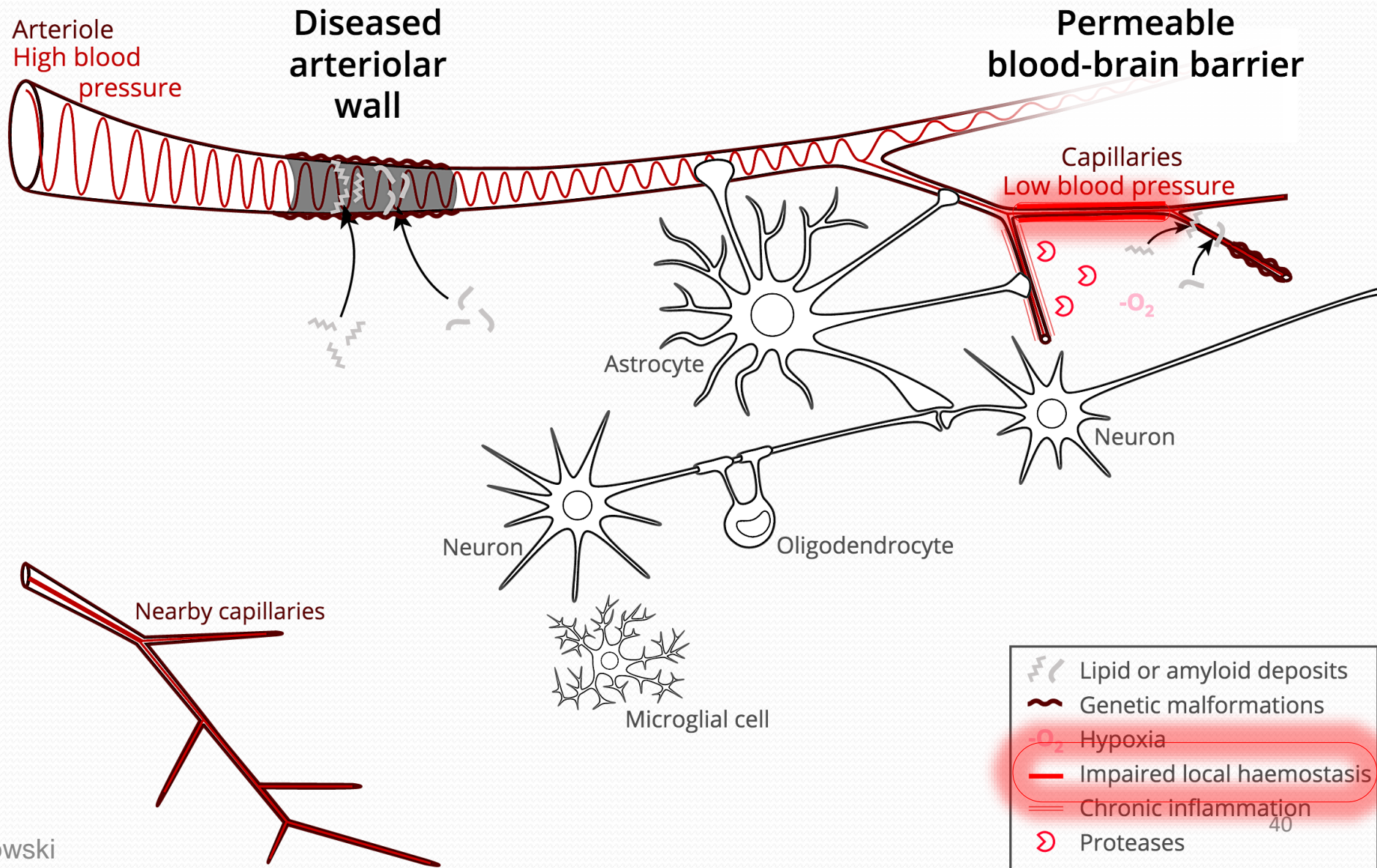
- **No interaction between baseline presence, location and severity of MBs for the outcome « recurrent stroke » or « ICH » and antithrombotic drug (AAP or OAD)**

Should we start anti-thrombotic agents after ischaemic stroke in the presence of BMBs ?

- BMBs does not seem to modify the effect of antithrombotic agents on the risk of ICH
- Current evidence does not justify withholding the evidence-based treatments from stroke patients solely on the basis of BMBs on MRI
- It is not recommended to always perform an MRI before introducing anti thrombotic agents to screen for BMBs



Time to look beyond the vessel



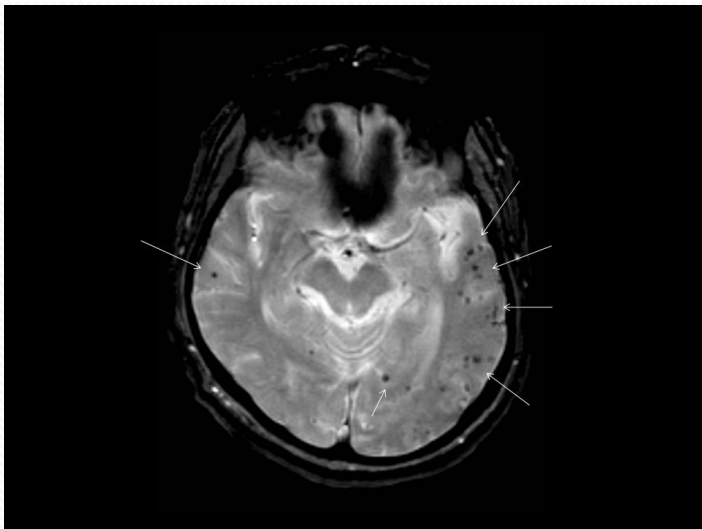
Importance of haemostasis?

- Influence of haemostatic disorders per se?
- Or do you need an underlying vessel defect?
- Very few data available on this topic

BMB in haemophilia

- N=31
- mean age 43 years
- 23% hypertension)
- 35% with at least one BMB

Husseinzadeh H et al., Haemophilia 2018



- N=44
- mean age 35 years
- 20% hypertension
- 3/44 had BMB
- Mild cognitive impairment is frequent

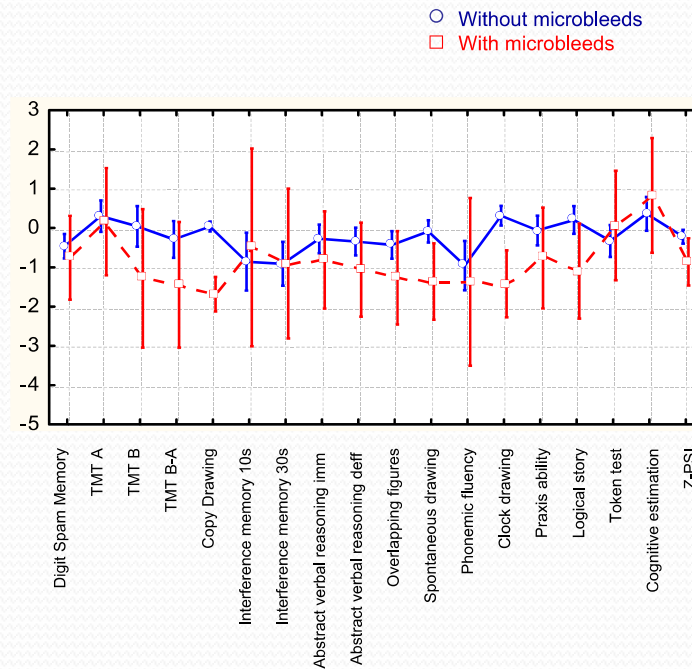


Fig. 3. Cognitive profile in subjects with and without microbleeds on brain MRI. The vertical bars show confidence intervals of 0.95.

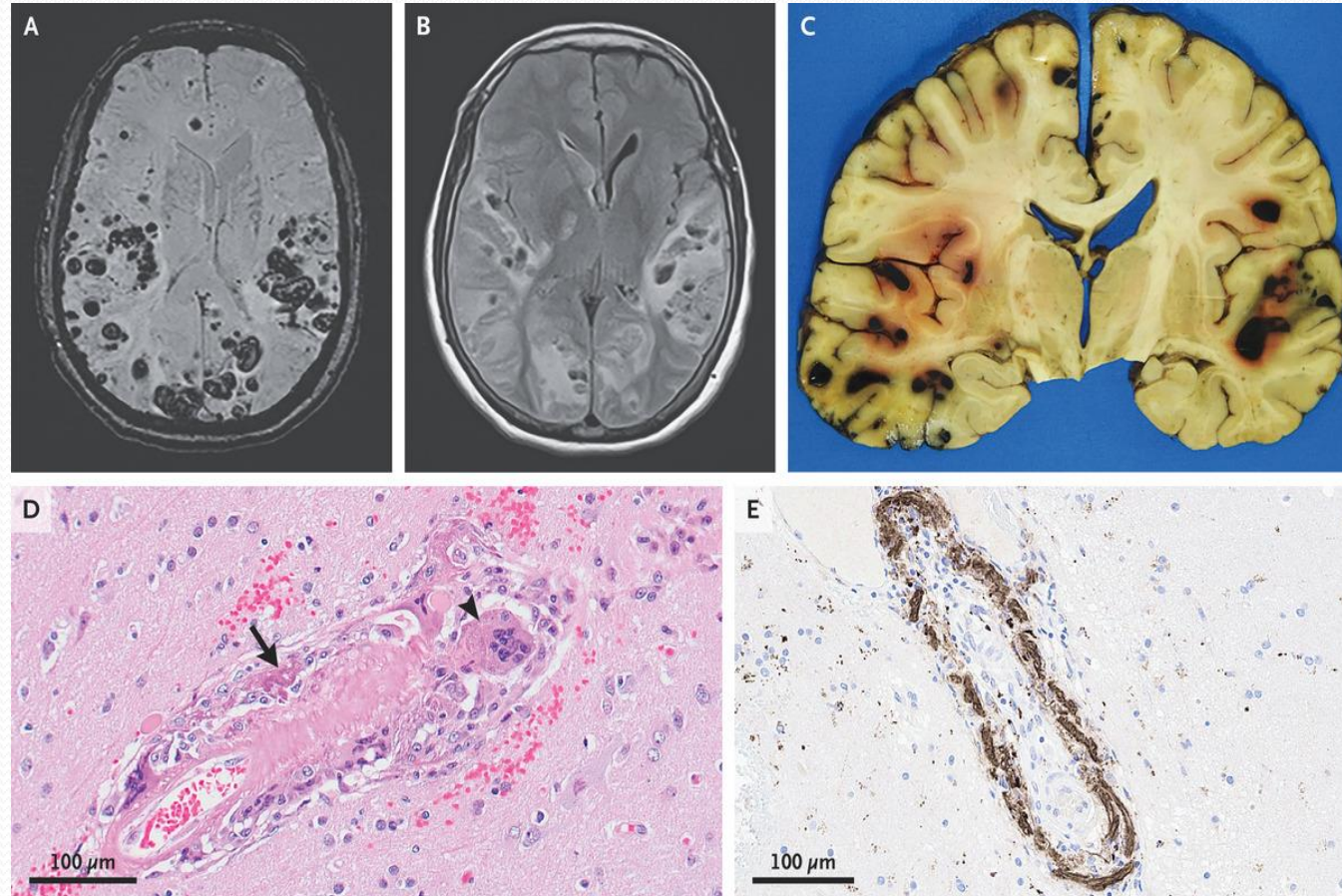
Zanon E et al., Thromb Research 2014

BMB in transcatheter aortic valve replacement

- 1 patient out of 4 has BMB before
- 1 patient out of 4 has BMB after
- Associated factors with new BMB
 - Prolonged procedure → Anticoagulation management
 - vWF multimer defect
- Long term impact of function and future stroke risk unknown

BMB: risk markers for future anti-amyloid treatment in Alzheimer's disease

Screening for BMB at enrollment
With specific MRI sequences
Monitoring during treatment
Risk of serious adverse events



Take home message

- Radiological construct
- Markers of vessel disease : diagnostic tool
- Markers of the severity of the vessel disease: prognostic tool
- Not a silent lesion
- No interaction with antiplatelet agents
- Possible interaction with anticoagulants: but benefit > risk ?
- Interaction with haemostatic defects → ? Interaction with vessel disease ?



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INSERM U1172- Lille Neurosciences & Cognition