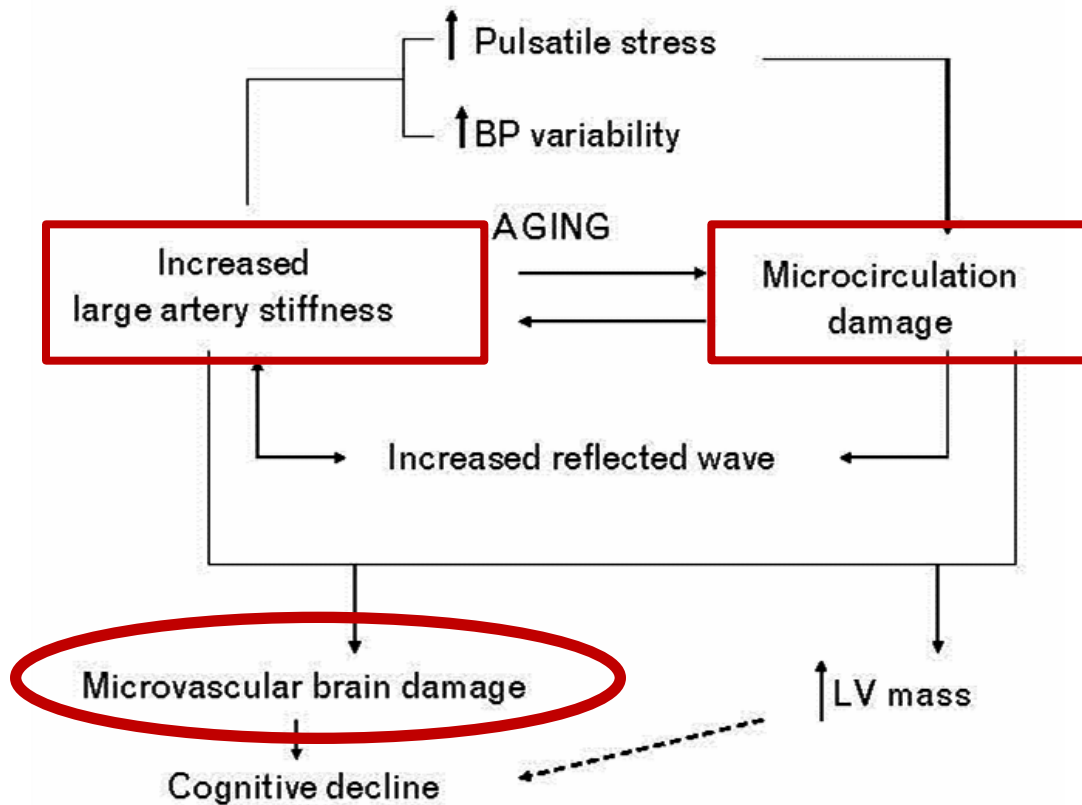




Revisiter le « neuro-VIH » par le microvasculaire

F-Xavier Lescure
SMIT Bichat, AP-HP, Paris

Lien macro-micro

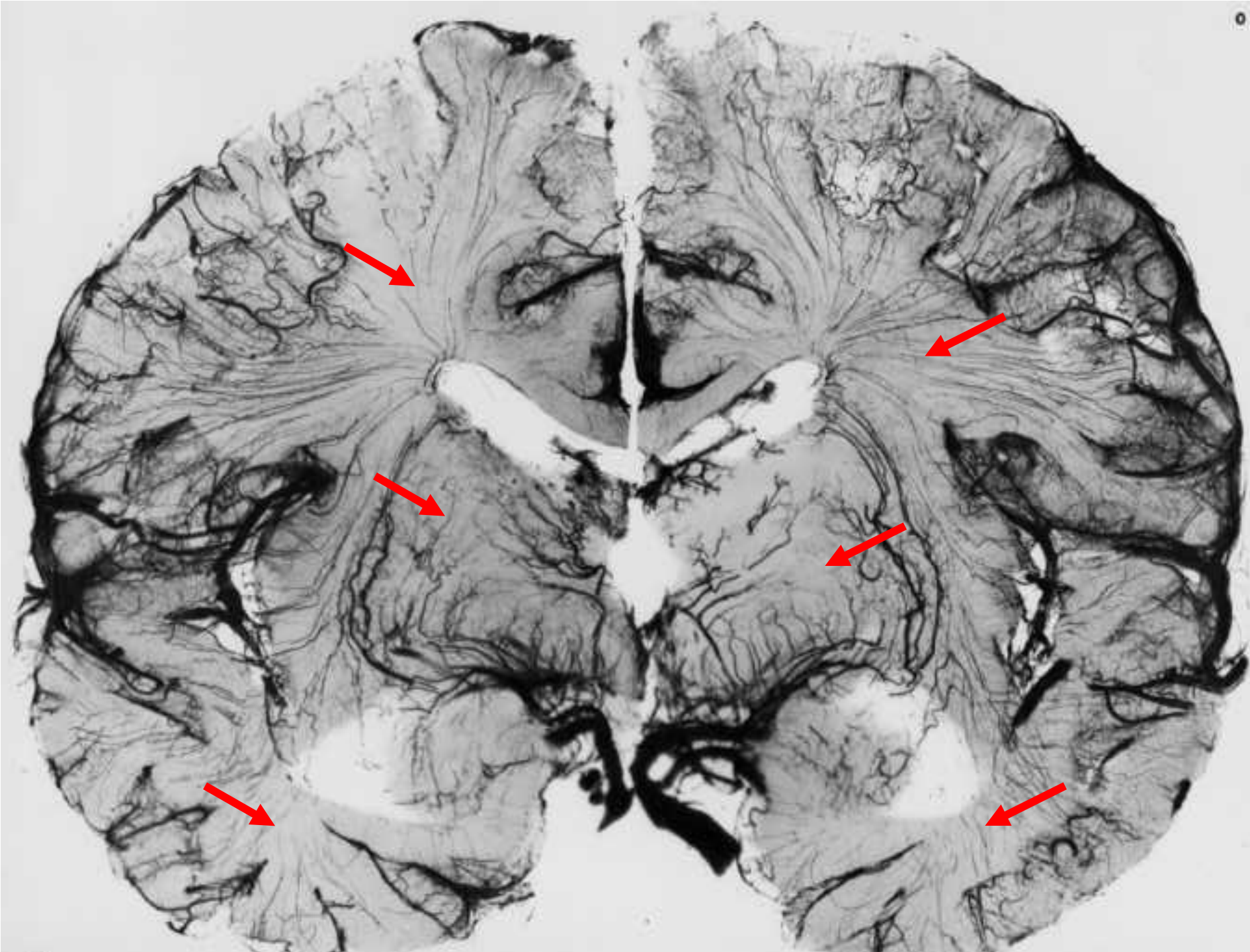


The cross-talk between large and small arteries and its effects on brain and heart with aging.

- Etude des 3 citées
- N=1800
- Age moyen 72 ans
- Ajustement sur âge, sexe et FdR CV

Plaque carotidienne :
ORa 1.32 microvasculopathie

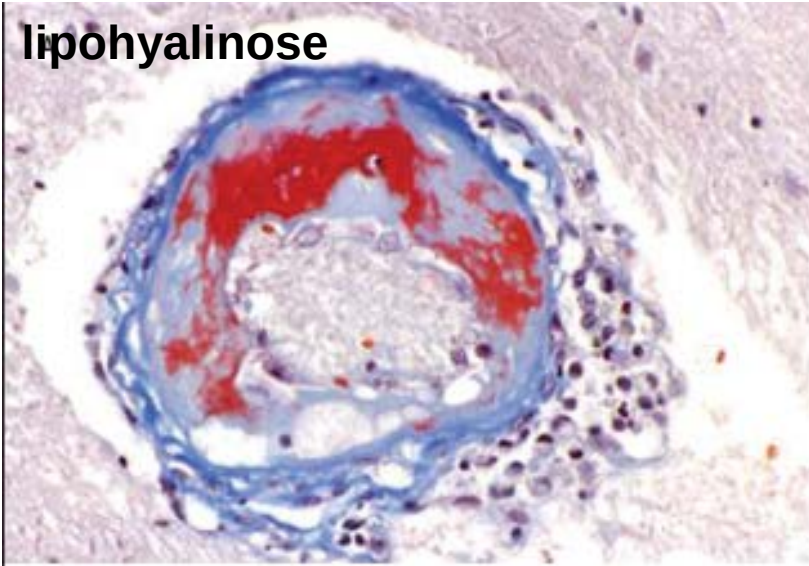
Indices de raideur carotidienne :
ORa 1.22 microvasc.



DEFINITION

Sclérose pariétale des artérioles

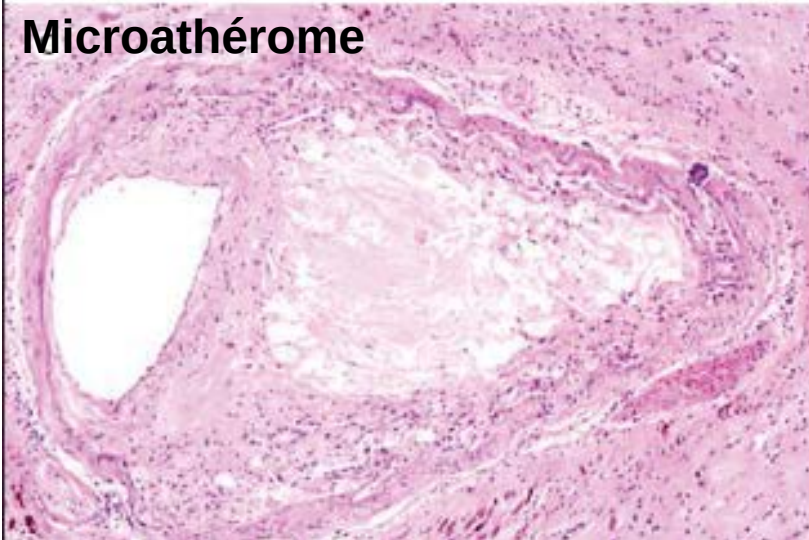
lipohyalinose



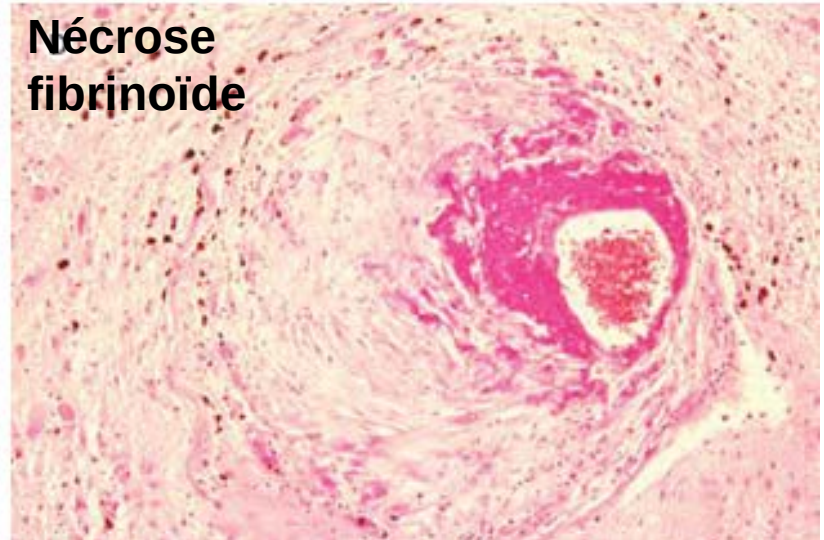
Microanévrisme



Microathérome



**Nécrose
fibrinoïde**



Classification étiopathogénique MPAC

Type 1: arteriolosclerosis (or age-related and vascular risk-factor-related small vessel diseases)

Fibrinoid necrosis

Lipohyalinosis

Microatheroma

Microaneurysms (saccular, lipohyalinotic, asymmetric fusiform, bleeding globe)

Segmental arterial disorganisation

Type 2: sporadic and hereditary cerebral amyloid angiopathy

Type 3: inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy

For example, CADASIL, CARASIL, hereditary multi-infarct dementia of the Swedish type, MELAS, Fabry's disease, hereditary cerebroretinal vasculopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, small vessel diseases caused by *COL4A1* mutations

Type 4: inflammatory and immunologically mediated small vessel diseases

For example, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the CNS, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis

Type 5: venous collagenosis

Type 6: other small vessel diseases

For example, post-radiation angiopathy and non-amyloid microvessel degeneration in

Alzheimer's disease

MPAC

Définition IRM



Microsaignements

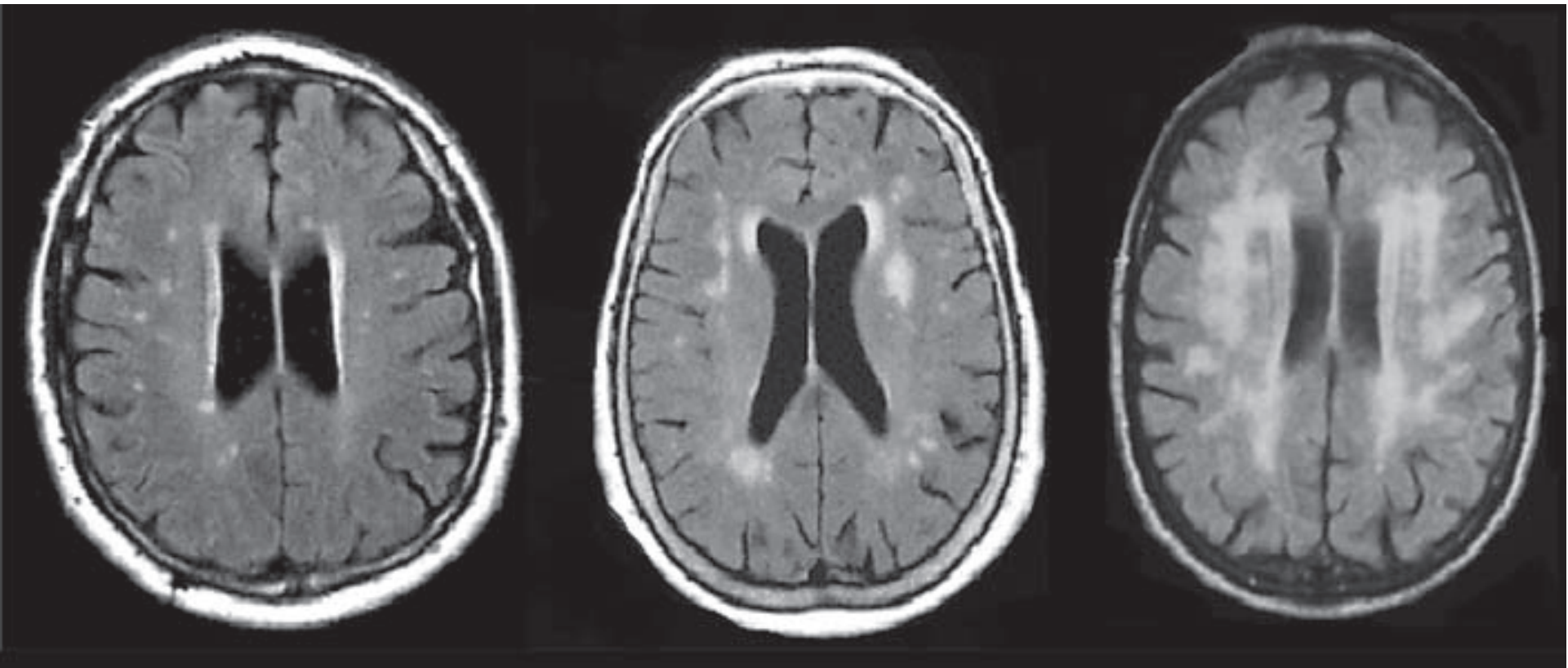


Hypersignaux SB



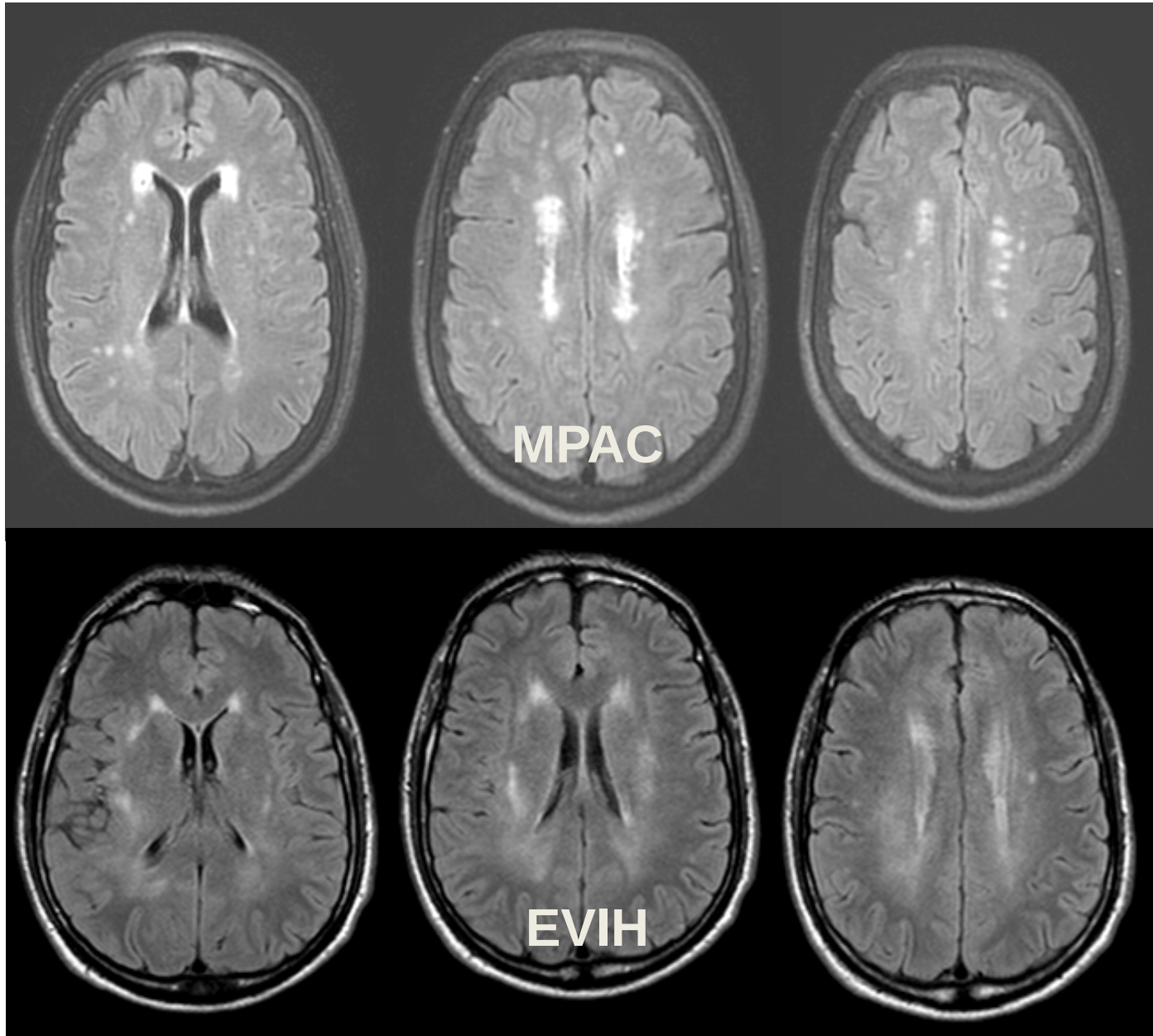
AVC méconnus

3 stades IRM des anomalies de la SB



Classification Fazekas modifiée

Remarque...



FREQUENCY

Plan National AVC 2010-2014

France

(Rapport ministériel 2009 ; Chevreul, 2013)

Prévalence : 800 000 cas

Incidence : 145 000/an

5,3 milliards d'euros (2007)

OMS (AVC)

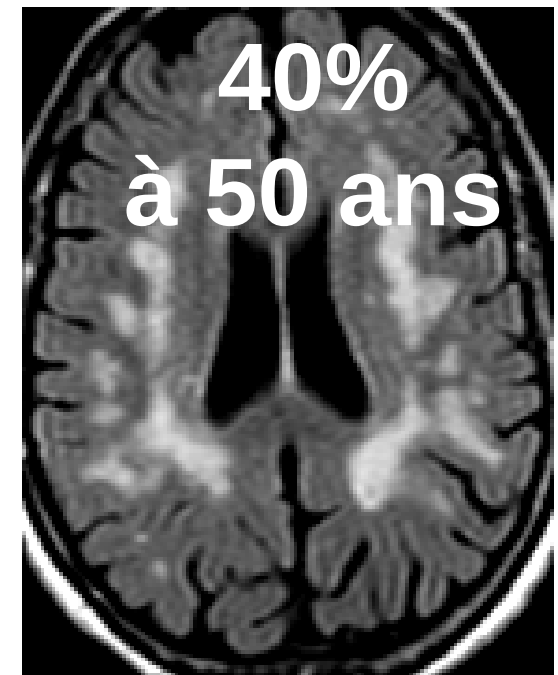
2008 : 16 millions

2030 : 23 millions

Incidence, prévalence : x 5 à 10 AVC

Prévalence des hypersignaux de la SB

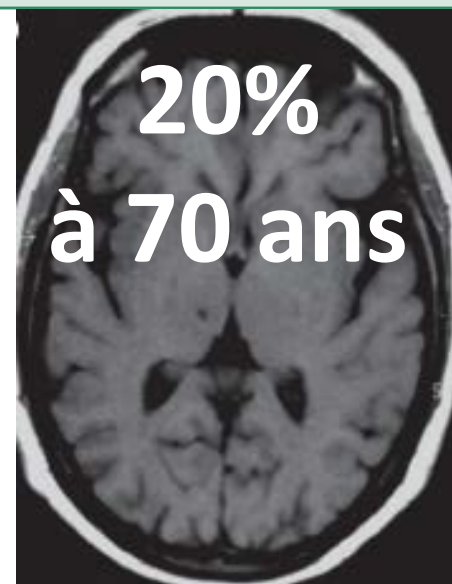
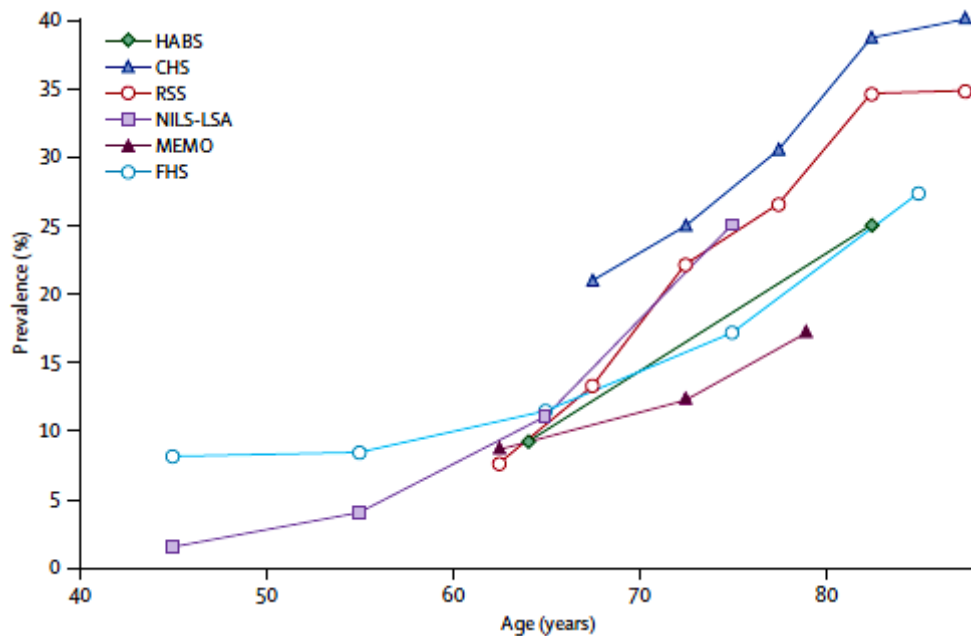
Characteristic	Controls (n = 140)	Patients With Migraine Without Aura (n = 134)	Patients With Migraine With Aura (n = 161)
Age, mean (SE), y	48.0 (0.7)		
Female, No. (%)	100 (71)		
Maastricht research center, No. (%)	75 (54)		
Low education, No. (%)†	72 (51)		
Body mass index, mean (SE)	24.4 (0.3)		
Blood pressure, mean (SE), mm Hg			
Systolic	134.8 (1.5)		
Diastolic	90.8 (0.8)		
Hypertension, No. (%)§	45 (32)		
Cholesterol, mean (SE), mmol/L	5.2 (0.1)		
Diabetes, No. (%)	5 (4)		
Smoking			
Never, No. (%)	48 (34)		
Pack-years, mean (SE)	11 (1.2)		
Alcohol use, No. (%)			
None	21 (15)		
≥3 units/d	22 (16)		
≥15 Years of oral contraceptive use (women only), No. (%)	24 (24)		



Prévalence des infarctus méconnus

	N	Mean age (range), years	SBI (range), %
Ischaemic stroke patients (including cardioembolic stroke) ³⁴	171	69 (26–93)	57 (NA)
Patients with coronary artery disease ^{35–37}	493	60 (34–84)	32 (17–60)
Patients with atrial fibrillation ³⁸	72	68 (?)	32 (NA)
Patients with cardiovascular risk factors ^{39–43}	788	67 (40–93)	39 (21–51)
Patients with asymptomatic carotid stenosis ⁴⁴	189	68 (45–82)	23 (NA)
Patients with hypertension ^{45–58}	1003	69 (40–88)	43 (20–86)
Patients with diabetes mellitus ^{59–63}	685	62 (41–88)	38 (13–82)
Patients with chronic renal failure ^{55,61,64,65}	296	58 (48–74)	51 (25–85)
Patients with dementia ⁶⁶	143	73 (?)	33 (NA)
Patients with depression ^{67–69}	131	63 (50–76)	46 (39–49)
Patients with migraine ⁷⁰	295	48 (30–60)	8 (NA)
Patients with sickle cell disease ^{71,72}	94	24 (16–44)	30 (20–36)

Table 2: Prevalence of MRI-defined silent brain infarcts (SBIs) among selected populations

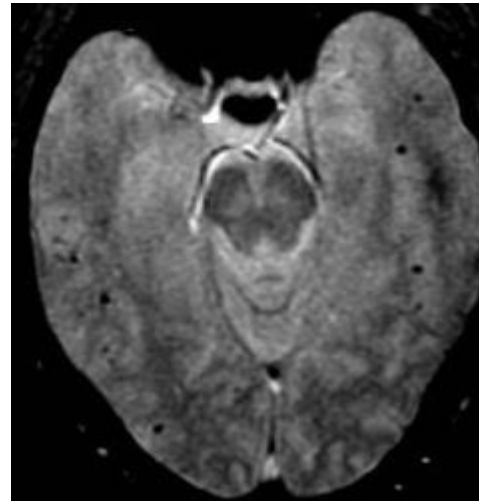
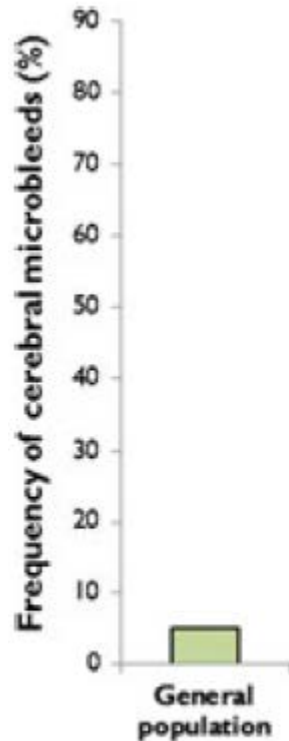


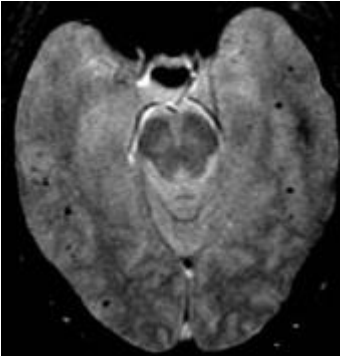
20%
à 70 ans

Vermeer et al. Lancet Neurol 2007

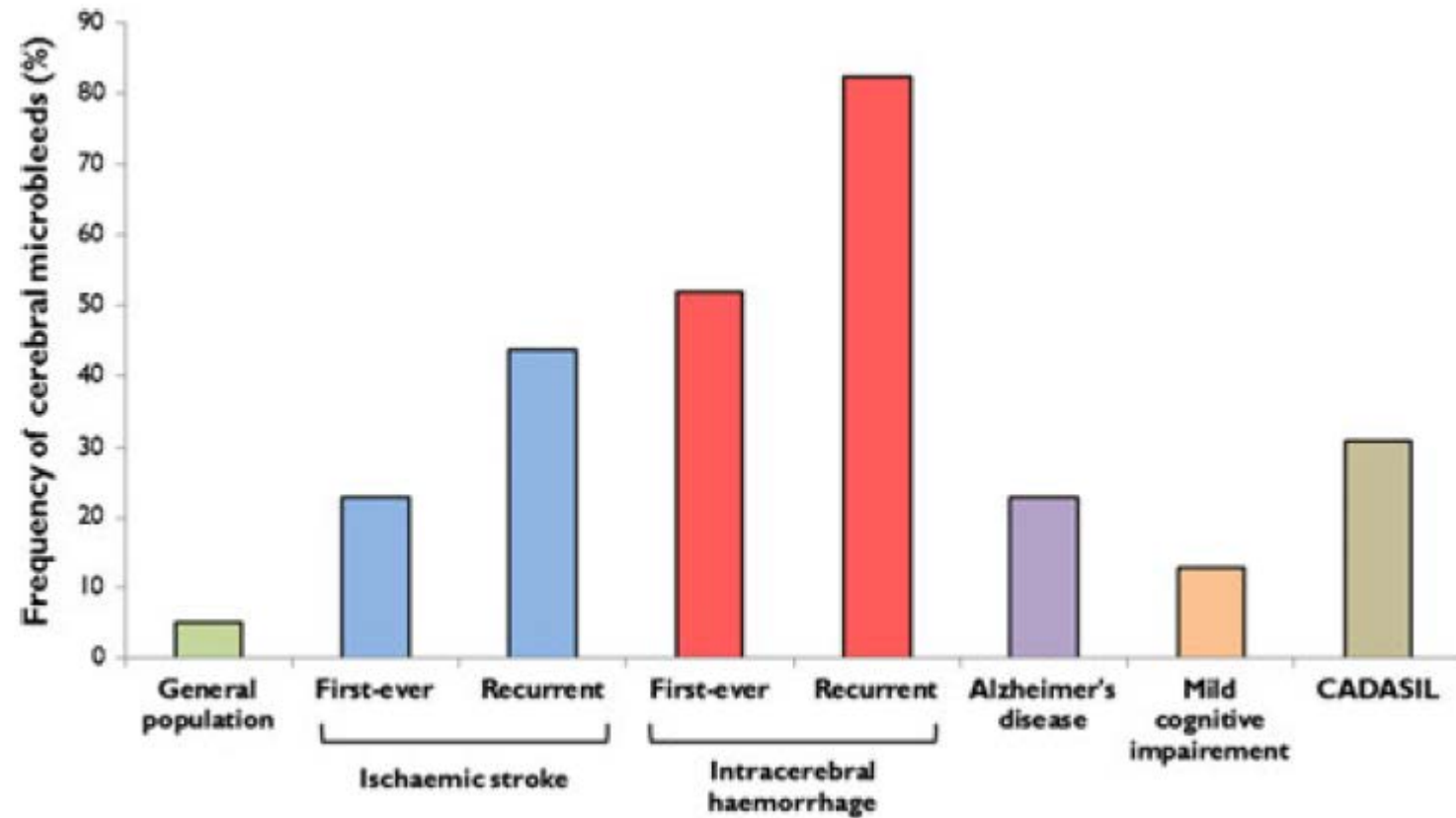
Prévalence des microsaignements

40% à 80 ans





Prévalence des microsaignements



GRAVITE
IMPACT

***Small vessels disease
(stroke world day 2008)***

« Little stroke, big trouble »

HS SB = facteur prédictif

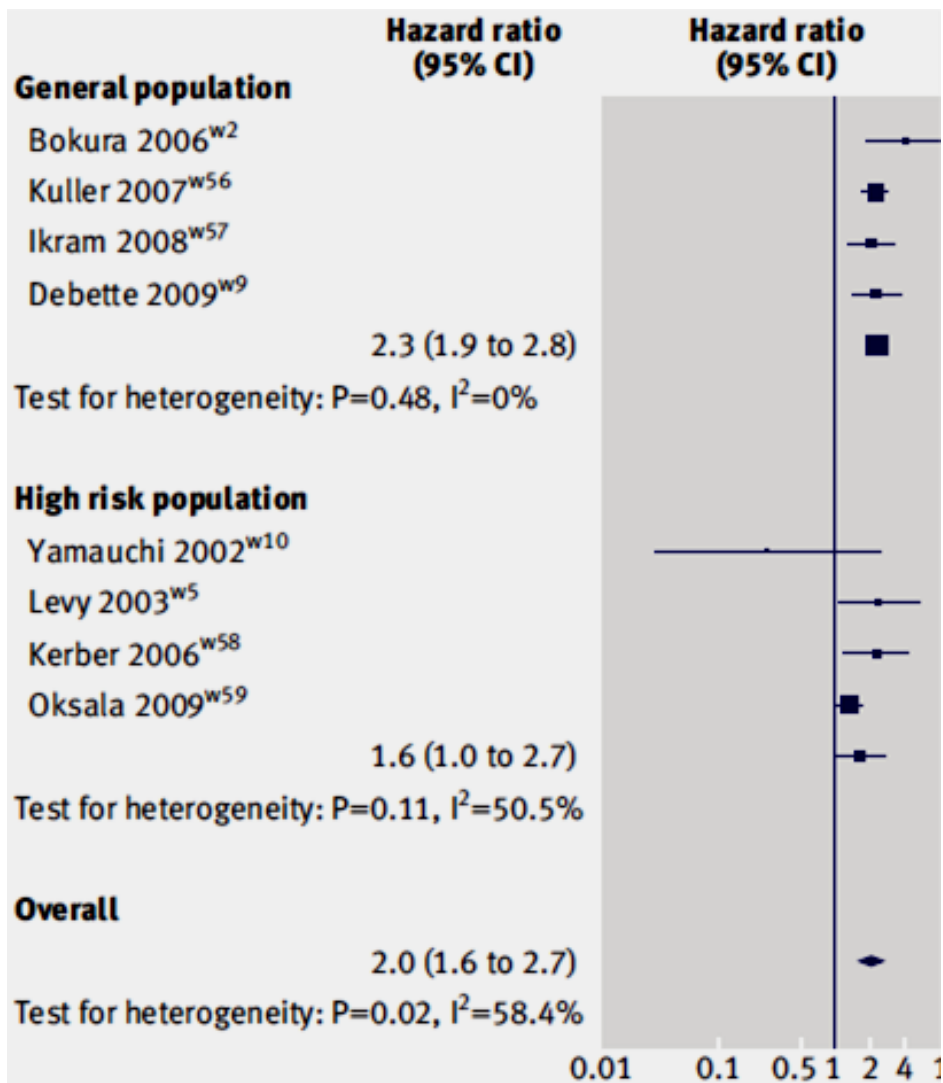


Fig 4 | Inverse variance meta-analysis of studies testing association of white matter hyperintensities with mortality

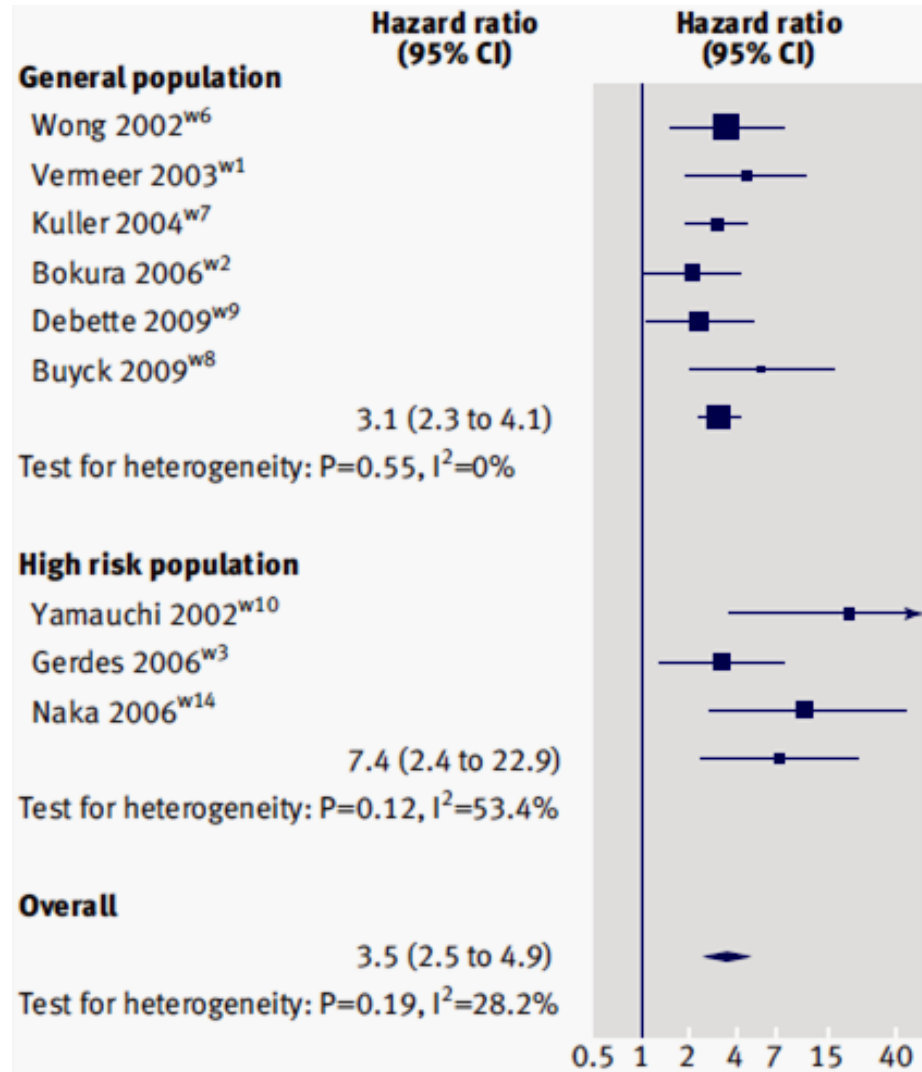


Fig 2 | Inverse variance meta-analysis of studies testing association of white matter hyperintensities with incident stroke

Principaux résultats LADIS 2001-2011

Impact des anomalies de la SB

- **Déclin cognitif**

- ASB (Fazekas 3) multiplie par 3 le risque de développer une démence et demeure l'un des facteurs prédictifs les plus forts de déclin cognitif
- Vasculopathie cérébrale // AVC, ASB, atrophie corticale

Jokinen H et al. Cerebrovasc dis. 2009, Verdelho A et al. Neurology 2010

- **Perte d'autonomie, frailty**

- Perte d'autonomie ou décès annuel (suivi de 3 ans) de 11%, 15% et 30% en fonction des 3 stades de sévérité
- HRa (Cox) pour Fazekas 3 vs Fazekas 2 : 2,4 (1,7-3,5)
- ASB associée aux troubles moteurs

Inzitari et al. BMJ 2009

Blahak C et al. J Neurol Neurosurg Psy 2009

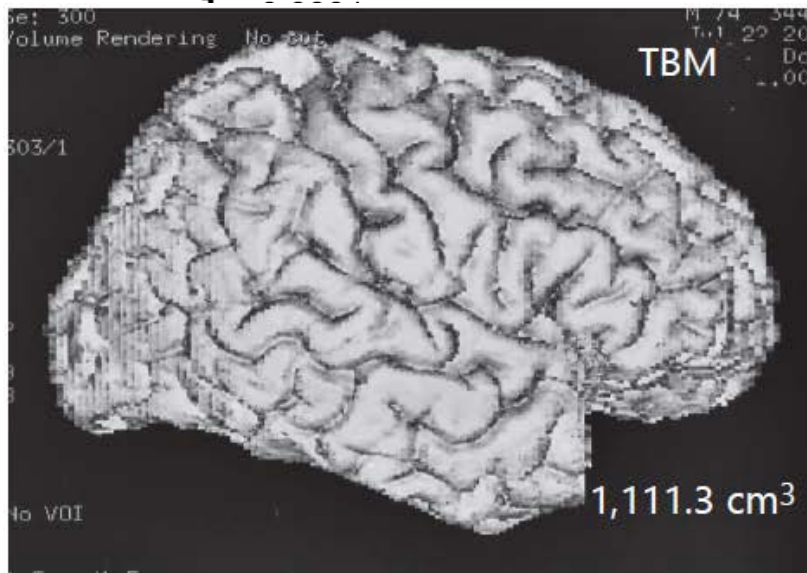
- **Dépression**

- ASB associée aux symptômes dépressifs et à la qualité de vie
- Hypothèse de la « dépression vasculaire »

Firbank MJ et al. Int J Ger psy 2005

CAUSES

FdR MPAC et distribution des comorbidités chez les PvVIH

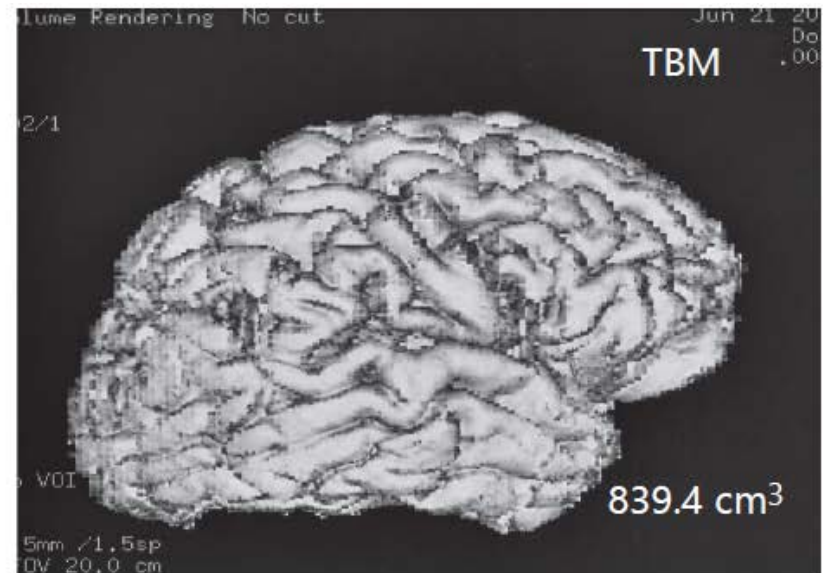


74-year-old male

24-hour SBP: 124 mm Hg
Awake SBP: 139 mm Hg
Sleep SBP: 118 mm Hg

Nocturnal SBP dipping: 15%
MMSE score: 29

Hypertension
Angina
Myocardial infarction
Periph. arterial insufficiency
Cerebrovascular disease
Diabetes mellitus



73-year-old male

24-hour SBP: 144 mm Hg
Awake SBP: 138 mm Hg
Sleep SBP: 158 mm Hg

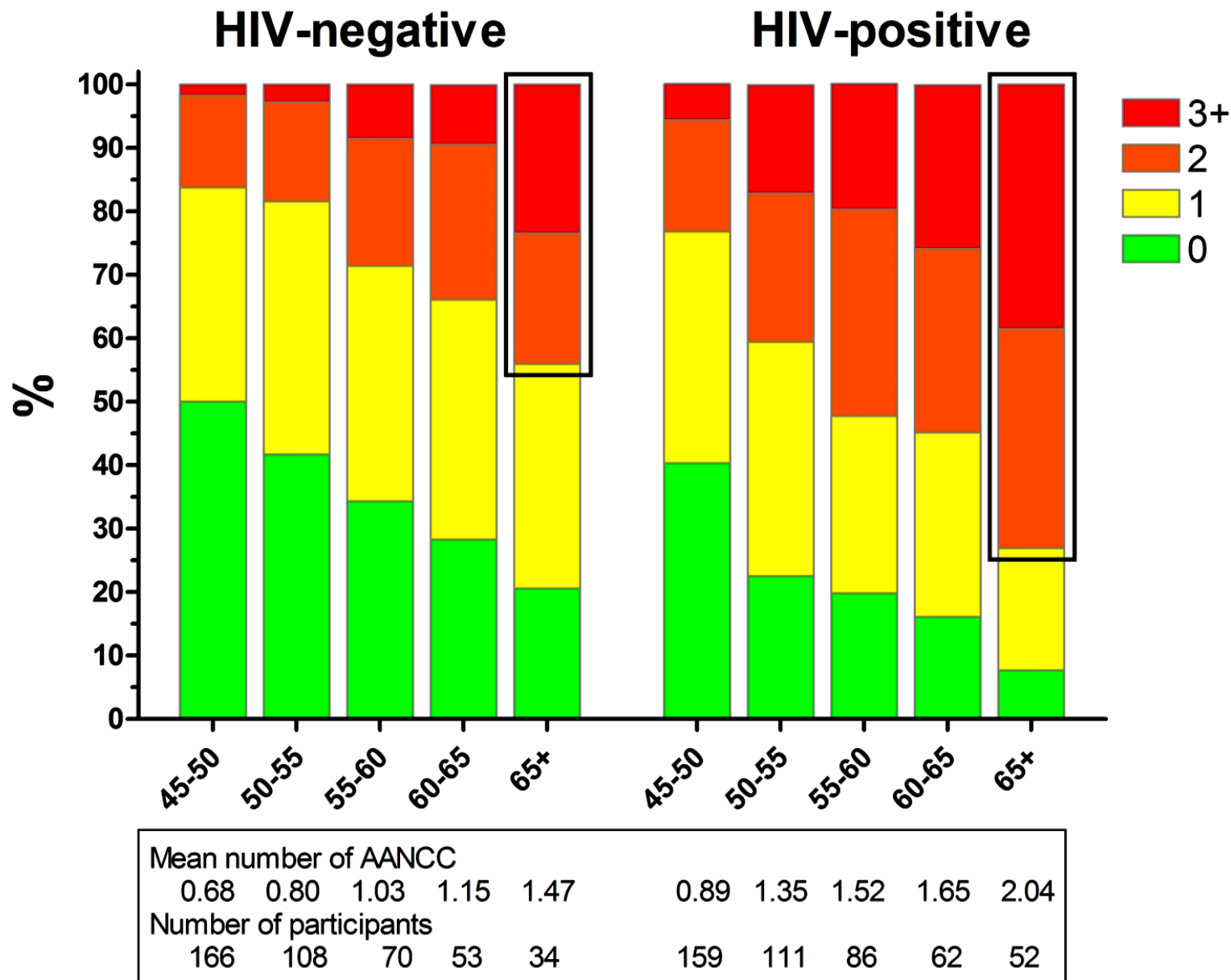
Nocturnal SBP dipping: -14%
MMSE score: 22

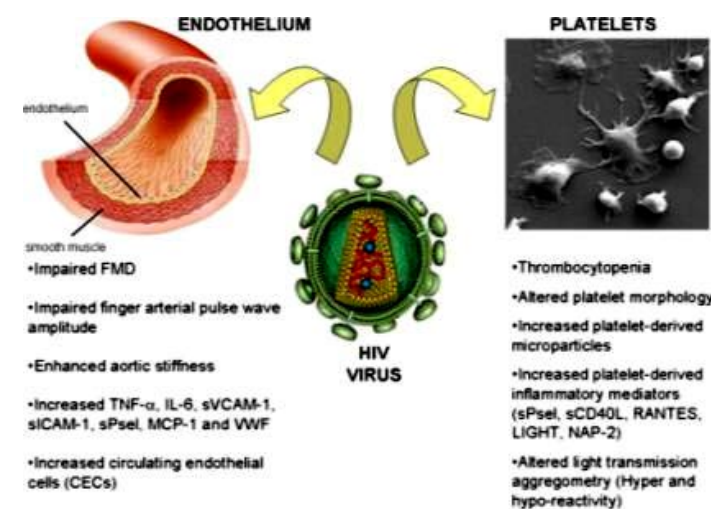
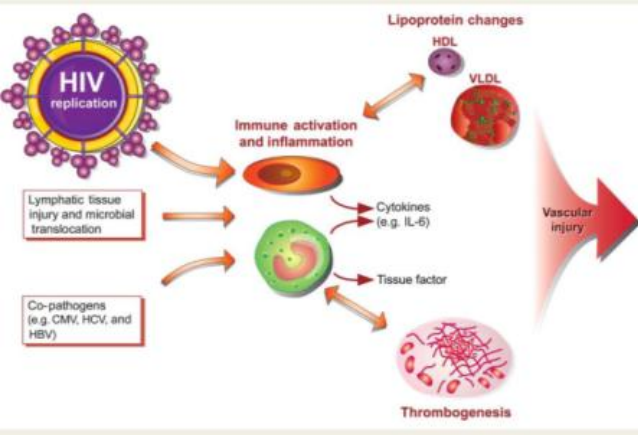
Chronic kidney disease
Reduced bone density
Fracture

Nagay M et al. Contrib Nephrol 2013

Schouten, 2012

Comorbidity in relation to age





Microbleeds et inflammation en population générale

Model 1*

Model 2†

hsCRP	1.85 (1.41–2.45)§	1.81 (1.35–2.46)§
IL-6	1.97 (1.36–2.90)§	1.73 (1.18–2.61)‡
IL-18	2.48 (1.40–4.49)§	2.41 (1.44–4.52)‡

N=431
70 ans
15% MBC

*Model 1: Adjusted for age and sex.

†Model 2: Adjusted for age, sex, hypertension, diabetes, hyperlipidemia, eGFR, IMT, the presence of SLI, and the WMH (PVH, DWMH) grade.

**microvasculaire
et VIH**

Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons

N=292

CD4 médian 536/mm³

CV VIH<400/mL : 88%

TNC : 14%

FdR classiques HAND NS

ARV CPE NS

Factors ^b	% of population	NCI ^c
Age (per 10 y)		NS
Gender (female vs male)	41.7	NS
Race/ethnicity (black vs other)	19.7	p=0.08 2.25
Education (>12 y)	46.6	NS
Location		NS
Brazil ^d	15.2	
Thailand ^d	50.0	
Prior AIDS	20.7	p=0.08 0.41
Hepatitis B	2.1	—
Prior CVD	3.5	p=0.01* 6.17
Blood pressure-lowering drugs	11.0	—
Total cholesterol (per 10 mg/mL)		p=0.06 1.08
HDL (per 10 mg/mL)		—
Depression (CES-D ≥ 16)	23.8	—

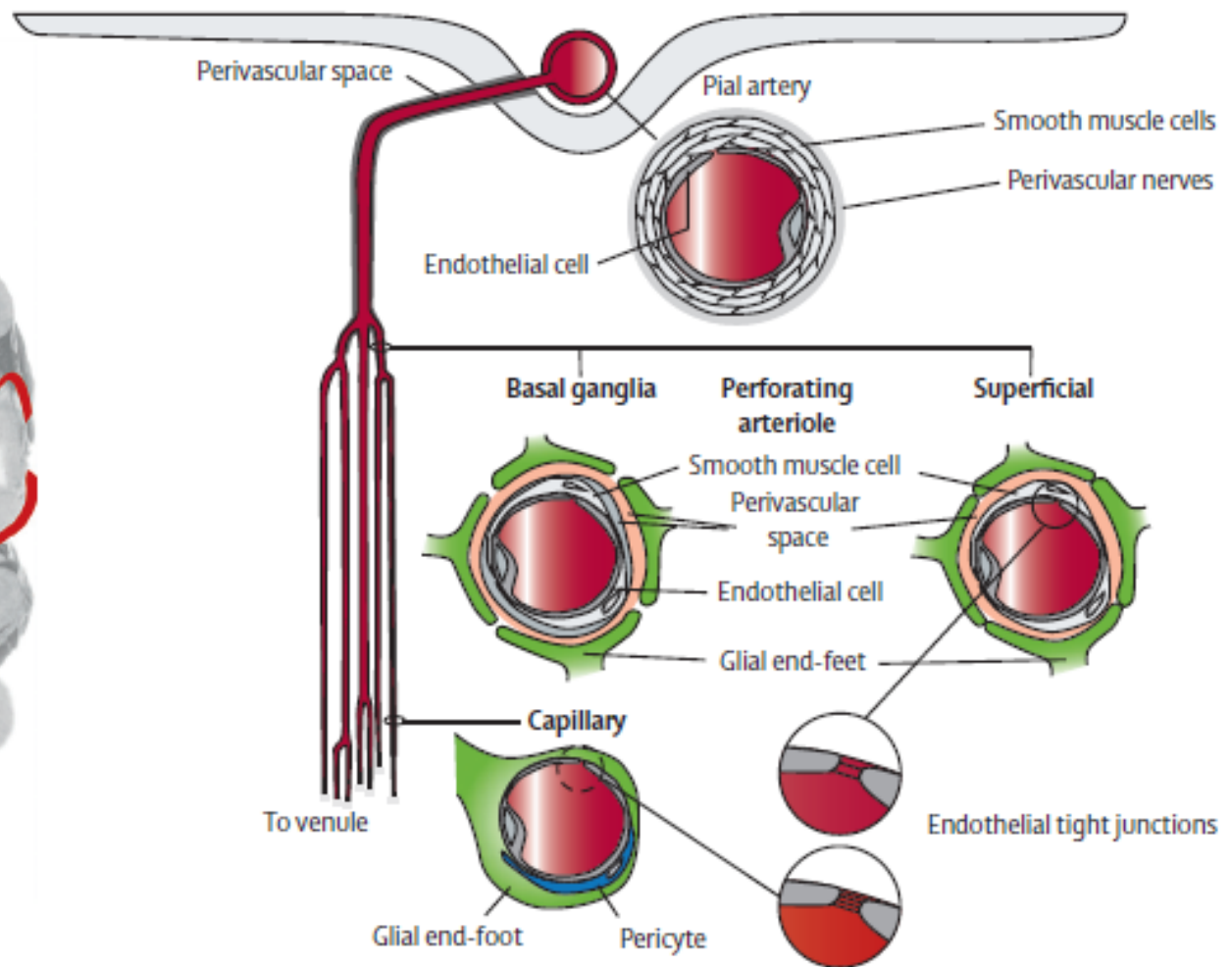
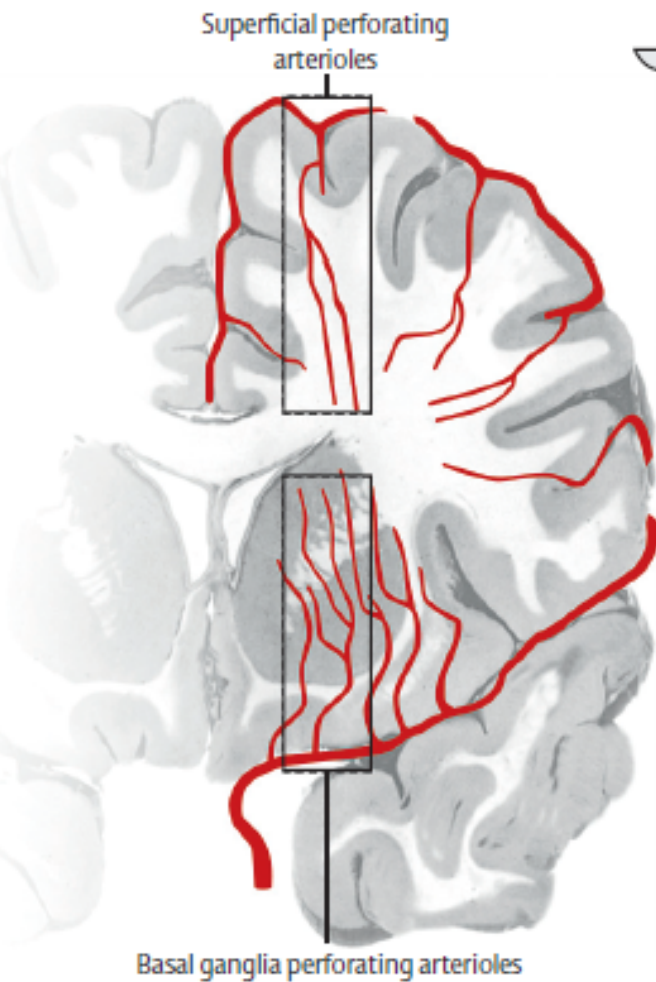
Maladie des petits vaisseaux au cours de l'infection par le VIH

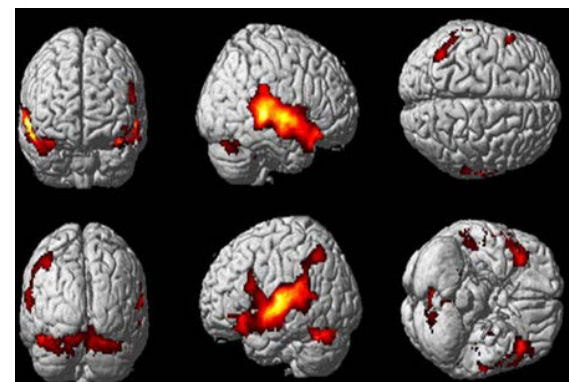
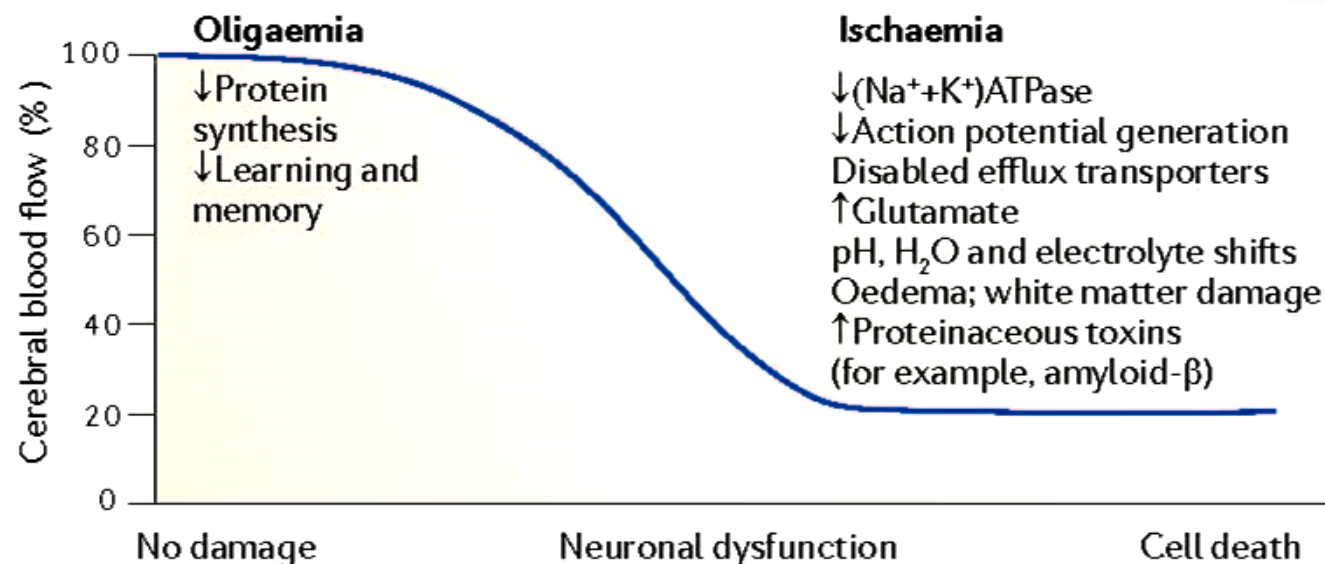
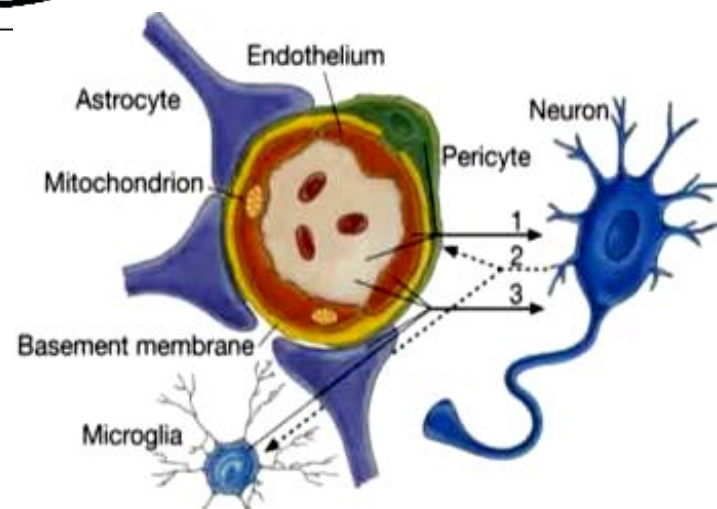
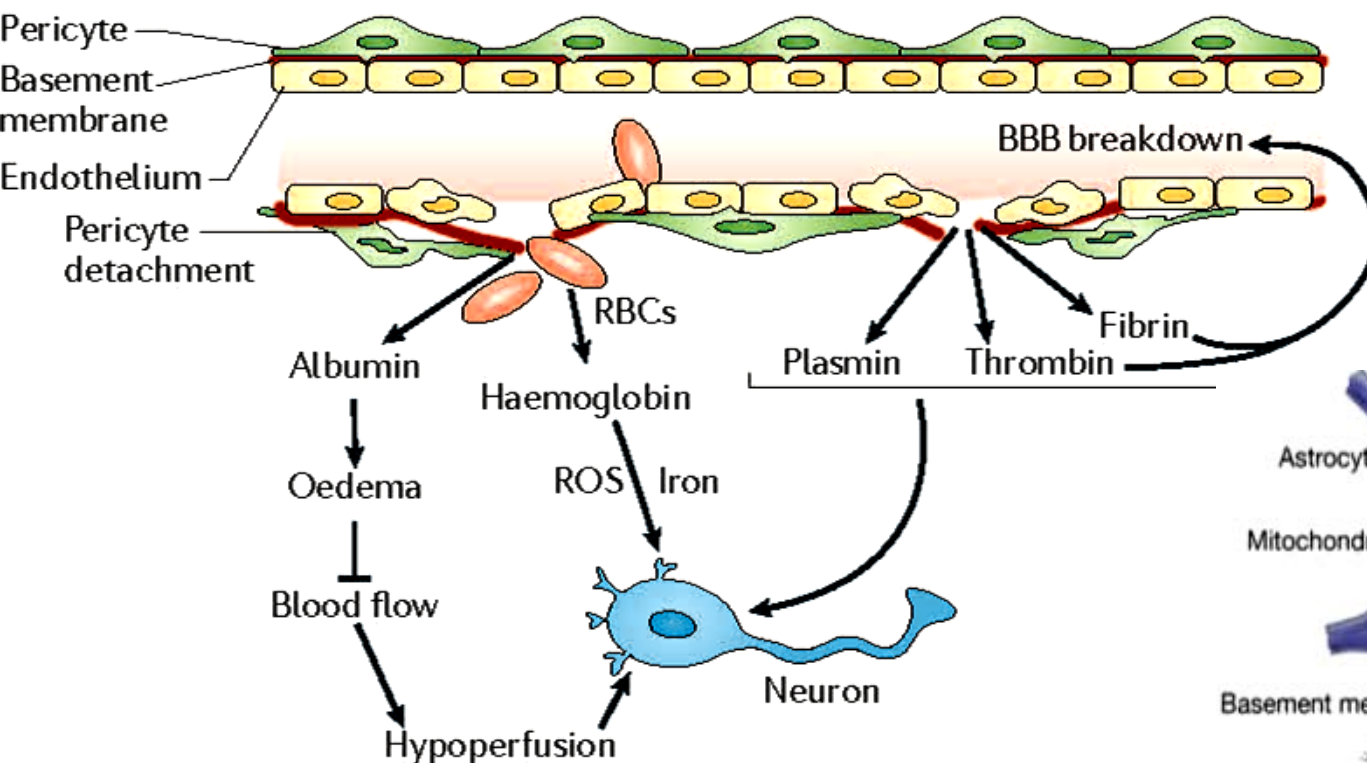
	Periventricular leukoaraiosis			Punctate white matter lesions		
	present	absent	p value	present	absent	p value
Number	48	9	n/a	17	40	n/a
Age, years	47.54 ± 9.59	43.64 ± 11.08	0.28	55.16 ± 5.93	43.42 ± 9.07	<0.001
Years of education	14.62 ± 2.43	13.56 ± 1.94	0.68	14.77 ± 2.68	13.48 ± 2.11	0.057
Systolic blood pressure, mm Hg	127.54 ± 17.19	125.00 ± 12.61	0.68	134.12 ± 19.01	124.18 ± 14.54	0.036
Diastolic blood pressure, mm Hg	79.60 ± 8.36	79.78 ± 9.28	0.96	83.83 ± 13.61	82.46 ± 10.66	0.82
Serum glucose, mg/dl	99.38 ± 27.95	96.89 ± 16.00	0.80	101.5 ± 38.22	97.98 ± 20.24	0.65
Serum cholesterol, mg/dl	183.91 ± 51.88	165.11 ± 31.17	0.30	186.50 ± 58.52	178.65 ± 45.91	0.60
Smoking, pack-years	14.17 ± 13.80	11.56 ± 9.29	0.59	17.69 ± 15.94	12.13 ± 11.64	0.16
Viral load, copies/μl	133.39 ± 316.30	266.50 ± 596.63	0.33	137.66 ± 294.55	161.52 ± 401.58	0.83
CD4 count at examination, cells/dl	327.96 ± 277.55	313.89 ± 206.23	0.89	254.71 ± 176.12	355.93 ± 292.81	0.19
CD4 nadir, cells/dl	131.11 ± 151.59	144.22 ± 155.89	0.81	115.13 ± 147.56	140.53 ± 153.53	0.59
Reported years since HIV diagnosis	10.49 ± 5.12	9.93 ± 6.85	0.78	11.65 ± 5.27	9.87 ± 5.37	0.25
Gender, male/female	41/7	8/1	0.78	15/2	34/6	0.75
Reported diagnosis of diabetes, yes/no	44/3	9/0	0.44	15/1	38/2	0.85
On HAART/not on HAART	13/35	4/5	0.29	8/9	9/31	0.064
Protease inhibitor/no protease inhibitor	24/19	4/4	0.76	10/5	18/18	0.28

84% d'HSSB

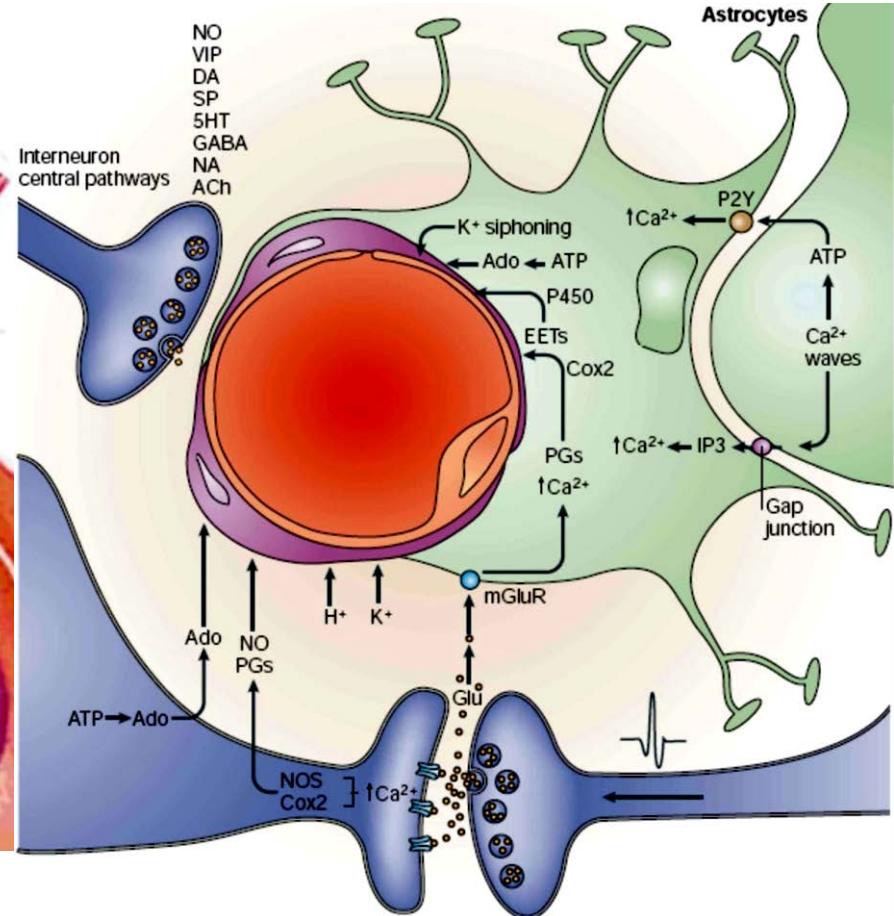
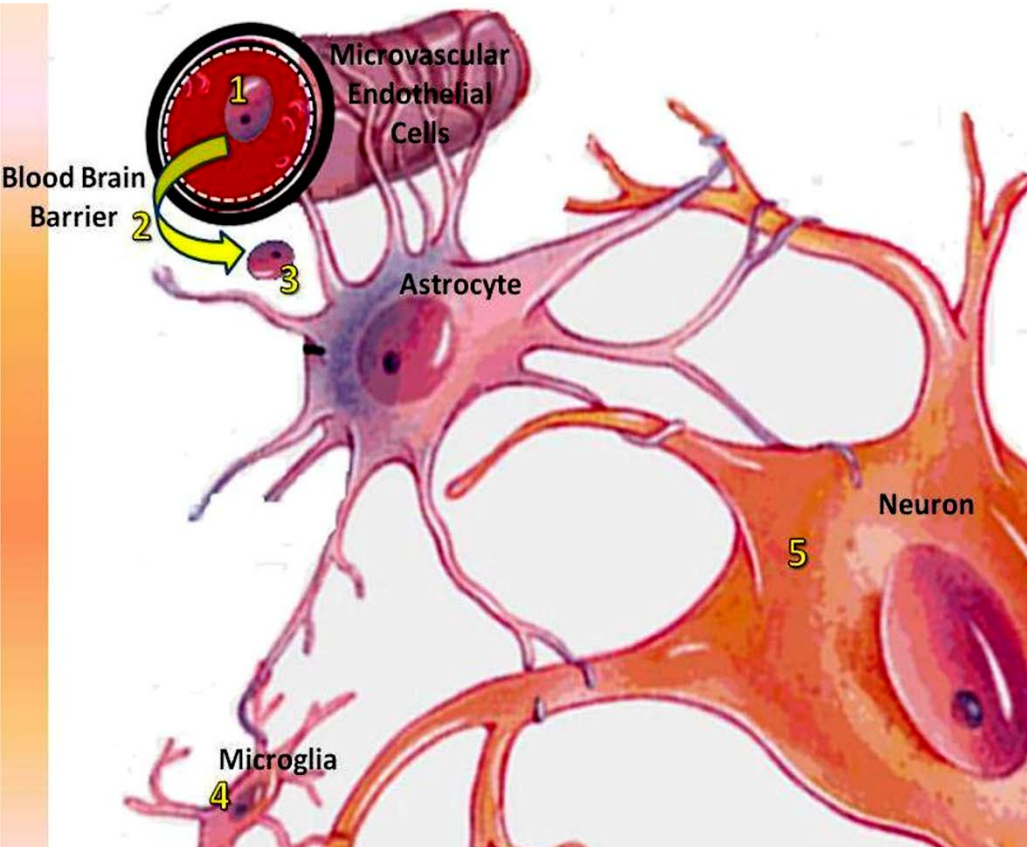
30% d'état lacunaire

Physiopath





L'unité vasculo-gliale



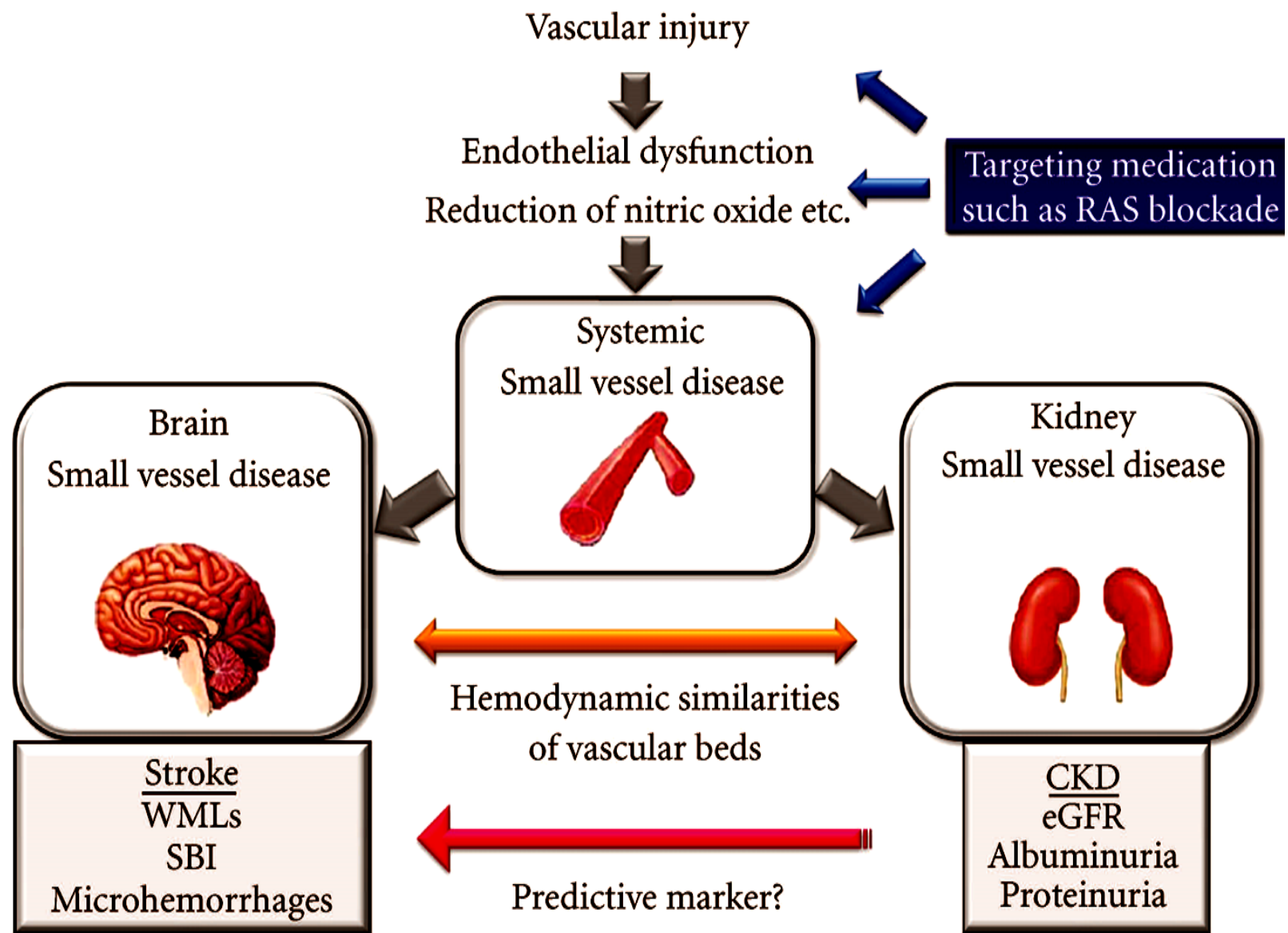
Mais le cerveau, c'est dur à évaluer

Confère problématique de mesure / TNC

L'IRM est un outil cher et contraignant

La ponction lombaire reste invasive

etc



Rein, cerveau et endothelium

- Microalbuminurie (MA) et thrombomoduline (TM) sont associées à la présence d'infarctus lacunaires

OR (95% CI) for the presence of lacunar infarcts in elderly subjects

Models	OR-unadjusted	OR-adjusted ^a
MA	1.64 (1.12–2.40) *	1.53 (1.02–2.30) *
TM	1.38 (0.97–1.96)	1.14 (0.78–1.66)
MA+TM	2.52 (1.49–4.26) **	2.07 (1.19–3.60) **

N=470, age 68 ans, 28% d'infarctus lacunaires

Reno-cerebrovascular disease: linking the nephron and neuron

Expert Rev. Neurother. 11(2), 241–249 (2011)

A Prospective Study of Albuminuria and Cognitive Function in Older Adults

Simerjot K. Jassal*, Donna Kritz-Silverstein, and Elizabeth Barrett-Connor

Invited Commentary: Albuminuria and Microvascular Disease of the Brain—A Shared Pathophysiology

David S. Knopman*

American Journal of Epidemiology

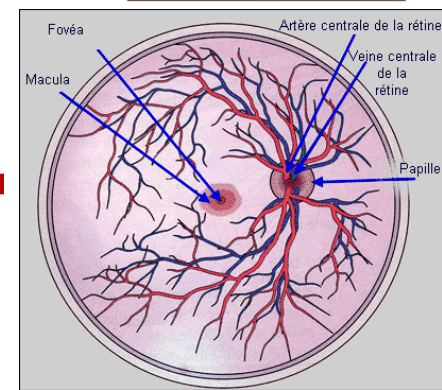
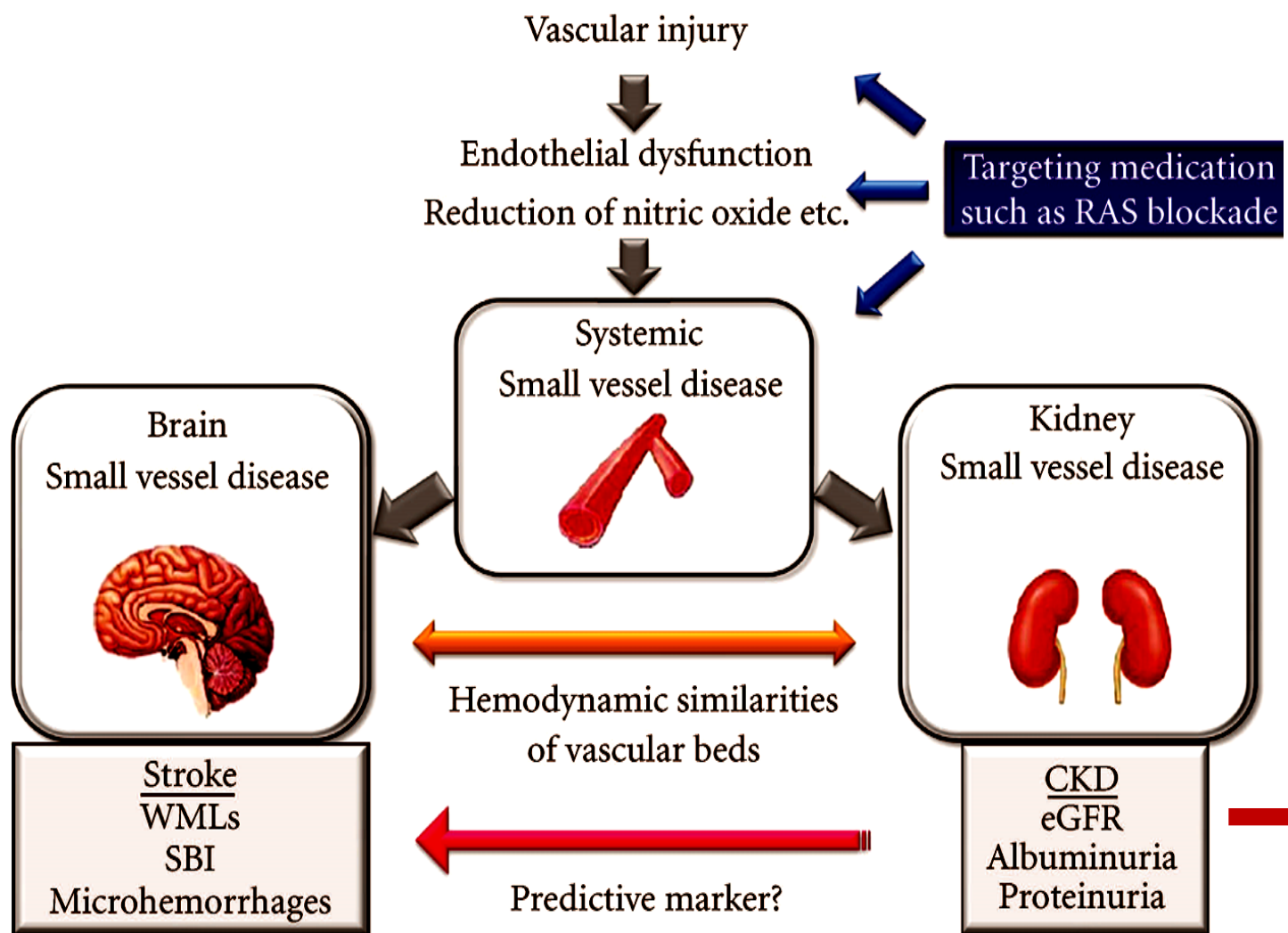
NEUROLOGY 2006;67:196–198



Reno-cerebrovascular disease?

The *incognito* kidney in cognition and stroke

Rebeca D. Monk, MD; and David A. Bennett, MD



PEC MPAC

- Qui mesure la TA des patients en cs?
- Qui mesure correctement la TA des patients? *Nagay 2013*
- Intérêt d'outils prédictifs (FO, microalbU)
- Le traitement optimal de la TA a un effet positif (progression des HSSB) *Dufouil C et al, Circulation, 2005*
- Approche globale
- Le « bien vieillir » vs «vieillissement anticipé»

**Take home
message**

Conclusion

- La MPAC // âge, FdR CV +/- inflammation
- Prévalence dans le VIH inconnue
- « *little stroke, big trouble* »,
- « *la menace « silencieuse* » »
- La MPAC a un impact cognitif majeur
- Approche // celle de la population générale
- Réflexion de PEC globale
- Mieux vaut prévenir que « guérir »
- Intérêt d'outils diagnostiques voire prédictifs