Instituto de Salud Carlos III

GOBIERNO DE ESPAÑA · MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

Cofinanciado por la Unión Europea

RICORS - ICTUS

IV CONGRESO ANUAL DE ICTUS

PODEMOS USAR BIOMARCADORES SANGUÍNEOS EN EL MANEJO DE LA SVD ¿CUÁLES Y CUÁNDO?

Mar Castellanos
Servicio de Neurología
Complejo Hospitalario Universitario A Coruña
Instituto de Investigación Biomédica A Coruña

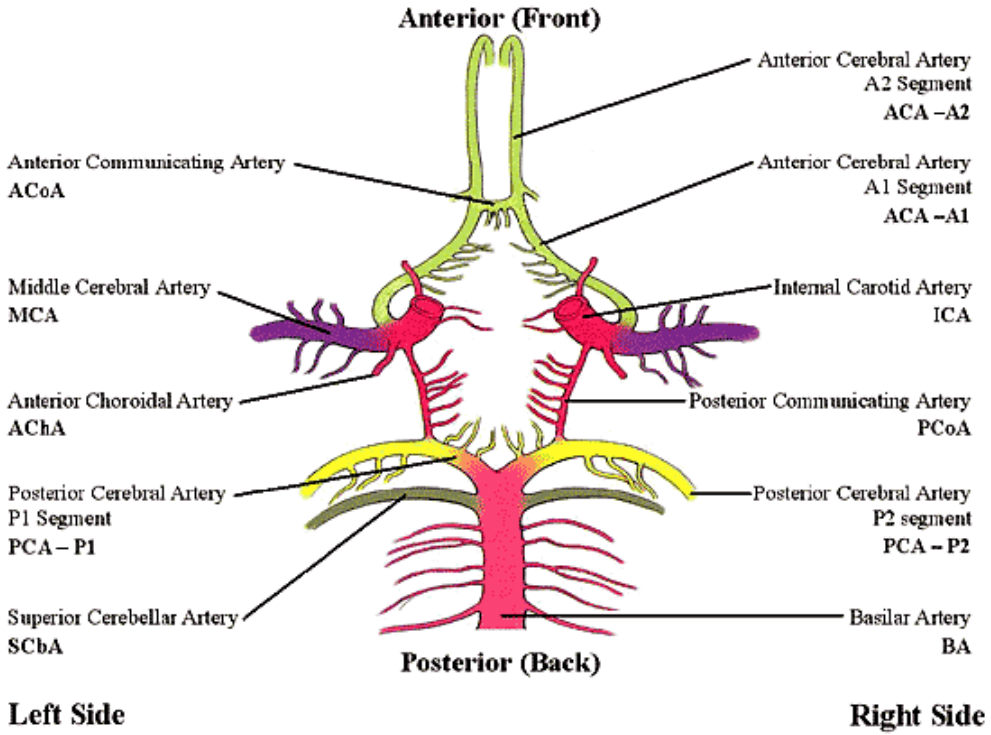
SERVIZO GALEGO de SAÚDE | Complexo Hospitalario Universitario A Coruña

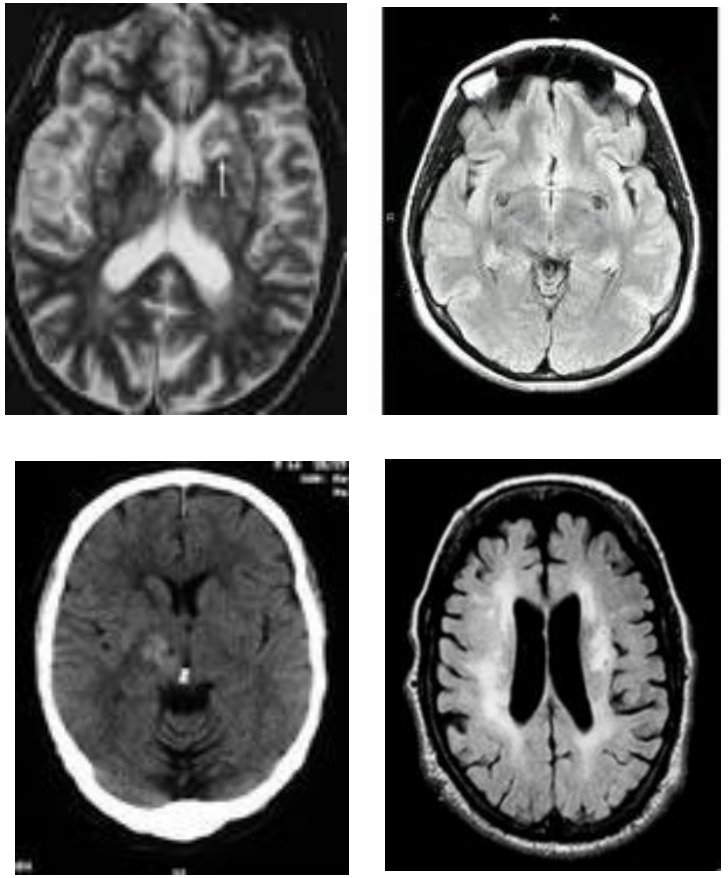
Madrid, 12 Junio 2025

inibic instituto de investigación biomédica de a coruña

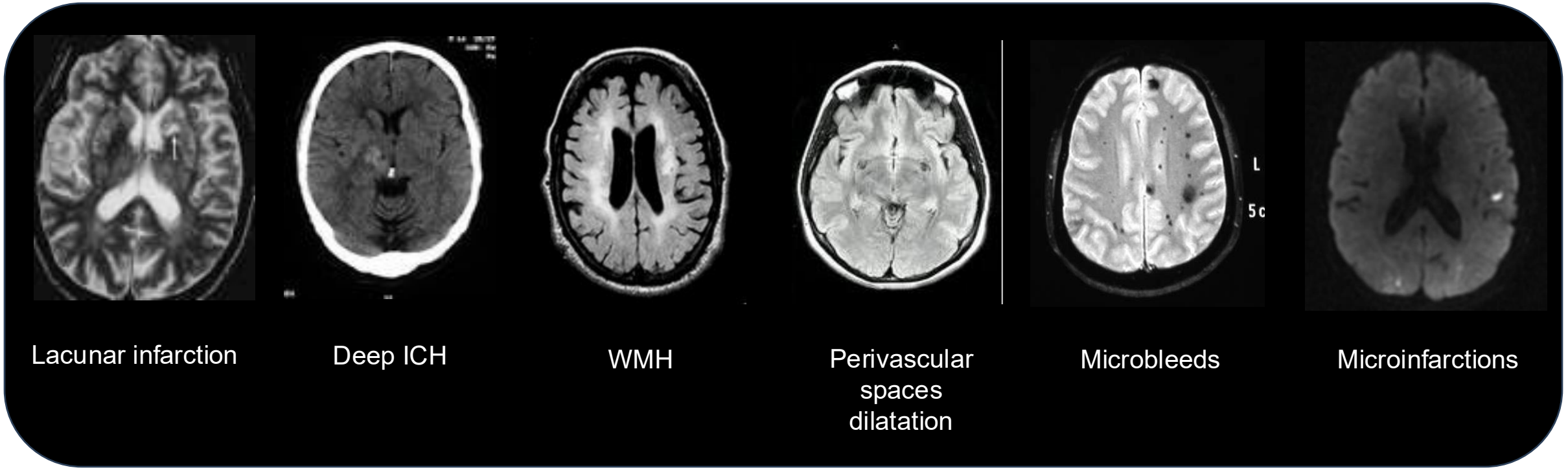
Smaill vessel disease concept

Set of clinical manifestations, and radiological and anatomo-pathological findings that appear as a consequence of different pathological alterations at the level of small caliber cerebral arteries and veins (small caliber arteries, arterioles, capillaries and small caliber veins).





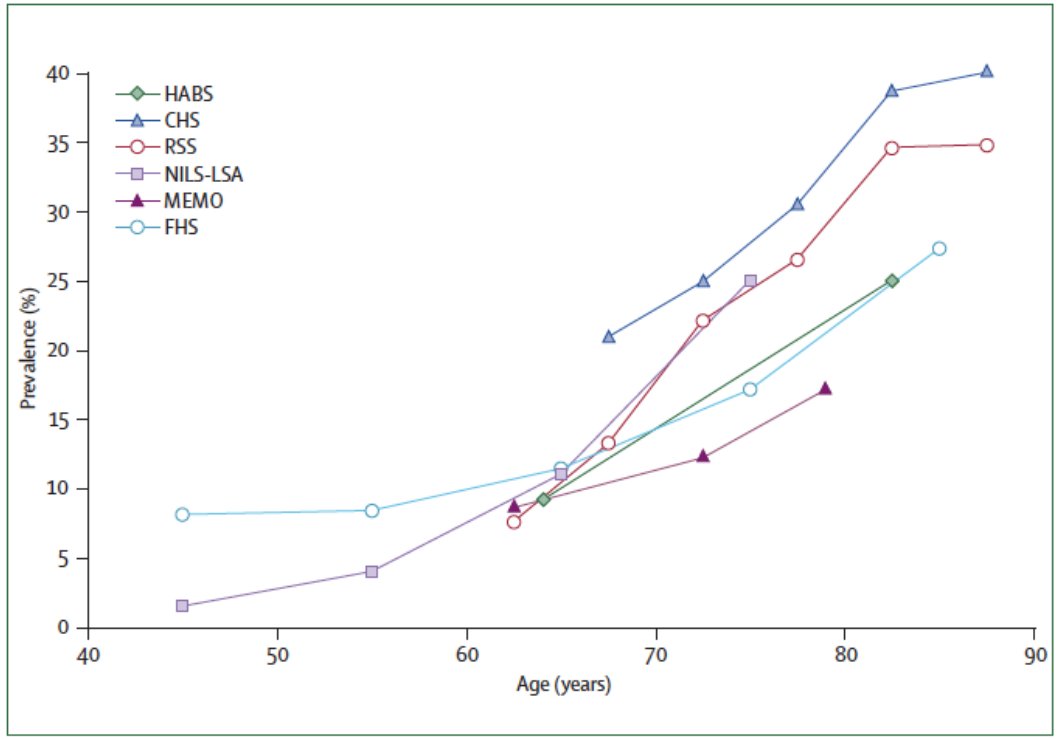
Radiological findings of SVD



ICH: Intracranial hemorrhage; WMH: White matter hyperintensities

Epidemiology of SVD

- 25% of all non-silent ischemic strokes
- MRI-defined silent brain infarcts detected in 20% of healthy elderly people and up to 50% of patients in selected series

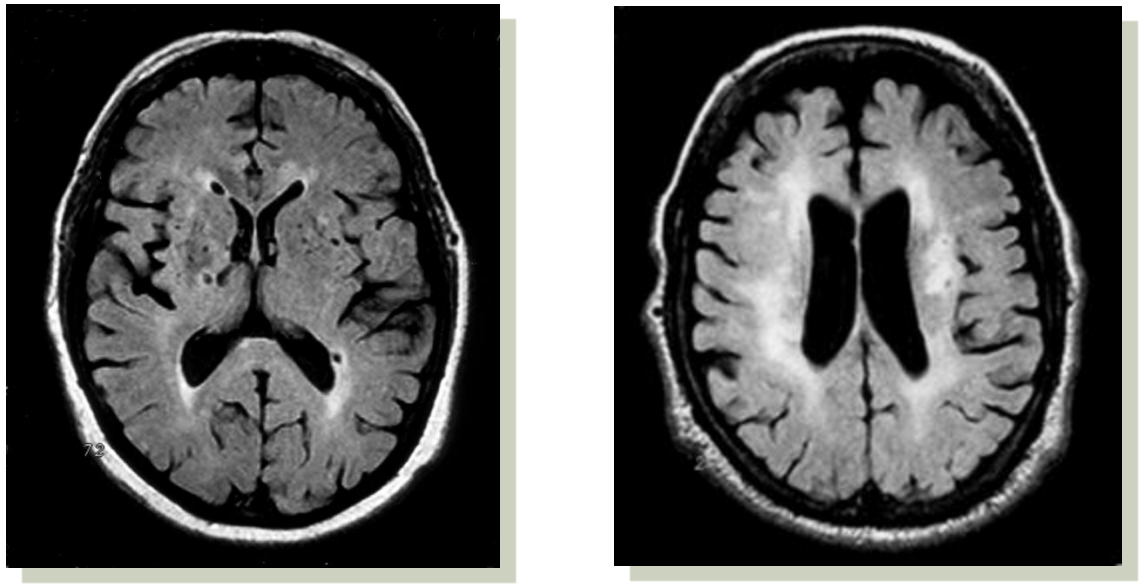


Overal prevalence of silent brain infarctions ranges from 8 to 28% (up to five fold higher than the prevalence of stroke) and clearly incresases with age.

Wermeer SE et al. Lancet Neurol 2007;6:611-619

Epidemiology of SVD

- 25% of all non-silent ischemic strokes
- MRI-defined silent brain infarcts detected in 20% of healthy elderly people and up to 50% of patients in selected series
- 45% to age related dementia
- Incidence of whitte matter hyperintensities in population older than 70 years old → 17%
  → Increase risk of stroke, dementia and death.



Debette S et al. BMJ 2010;341:c366
Sun Y et al. Aging Dis 2025;17(1). https://doi.org/10.14336/AD.2024.1515

Classification of SVD

Pathological subtypes of sporadic cerebral small vessel disease

Characteristic	Specification	**Amyloidal cSVD (cerebral amyloid angiopathy)**	**Non-amyloidal cSVD (hypertensive arteriopathy)**
Small vessel	Size of vessel	5 µm–2 mm (capillaries, arterioles, and arteries)	40–900 µm
	Pathology	Deposition of Aβ in cortical and leptomeningeal vessels	Arteriolosclerosis, fibrinoid necrosis, mural damage (different manifestation)
Clinical syndromes	ICH	Lobar	Often deep (basal ganglia, thalamus, pons, cerebellum)
	Stroke	Non-lacunar (not typically associated with lacunes)	Lacunar
	Other	Transient focal neurological episodes, cognitive impairment and dementia	Cognitive impairment and dementia
Imaging markers	Cerebral microbleeds	Lobar	Deep
	Cortical superficial siderosis	Most significant feature (marker of CAA)	Rare
	Perivascular spaces	Centrum semiovale	Basal ganglia
	White matter hyperintensities	Posterior predominance	Not specific to brain region

Cuadrado E et al. J Stroke 2018;20(3):302-320

Classification of SVD

Genetic types of cerebral small vessel disease

Type of disease	Age of presentation	Presence of accumulated material	Vessels involved	Known genetic alteration	Consequences due to genetic alteration	Possibly involved comorbidities (hypertension, diabetes)
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Adults	Granular osmiophilic material	Plasma membrane of vascular muscle (smooth muscle cell)	Missense mutation in the N3ECD	Alters the number of cysteine residues in the N3ECD, leading to accumulation and deposition of Notch3ECD	Ischemic attacks or strokes, migraine with aura, psychiatric manifestations such as depression and apathy, and impaired memory
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)	Adults	Deposition of hyaline material in the wall	Splitting of the internal elastic membrane	Homozygous mutations in HTRA1 gene	Interferes the enzymatic property of the protease	Early-onset lacunar stroke, progressive memory dysfunction, gait disturbance, and low back pain
Incontinentia pigmenti	Infant	None	Loss of brain endothelial cells (string vessel)	Mutations in the NEMO gene	Inactivate NEMO which is an essential subunit of the IκB kinase complex	Neurological symptoms may precede or follow skin lesions
Collagen IV related cSVD	Adults	-	Impaired synthesis of the basement membrane and blood vessel fragility	Mutations in COL4A1 and COL4A2 genes	Impairing in the formation of the resulting collagen molecule	Early-onset lacunar stroke, progressive memory dysfunction, gait disturbance, and low back pain
Retinal vasculopathy with cerebral leukodystrophy	Adults	Accumulation of genetic material in the cells	Vessel wall degeneration	Frameshift mutations in TREX1 which encodes a 3'-5' exonuclease	Impairment of this enzyme trigger immune system reactions	Vision loss, lacunar strokes and ultimately dementia, HERNS
Fabry disease	> 55 years	Accumulation of glycolipids	Walls of small blood vessels, nerves, glomerular and tubular epithelial cells, and cardiomyocytes	Mutation in lysosomal GLA gene	Absent or deficient lysosomal GLA activity	Various stroke mechanisms

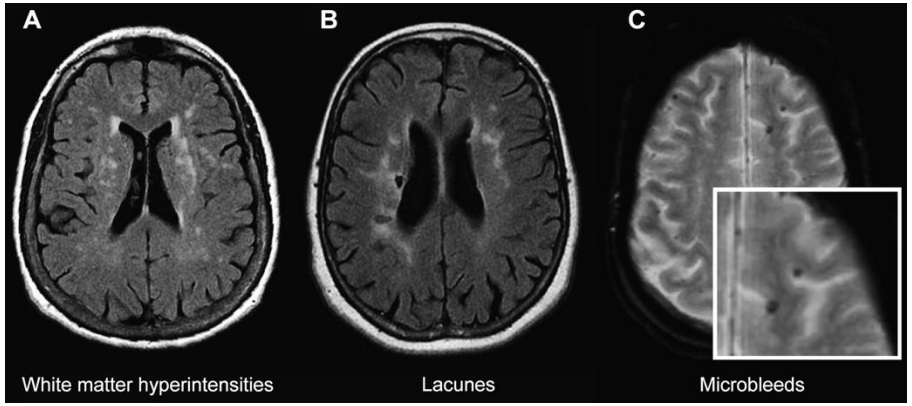
N3ECD, extracellular domain of NOTCH3; HTRA1, high-temperature requirement a serine peptidase 1; NEMO, nuclear factor κB (NF-κB) essential modulator; cSVD, cerebral small vessel disease; COL4A1, collagen type IV alpha 1 chain; COL4A2, collagen type IV alpha 2 chain; HANAC, hereditary angiopathy with nephropathy, aneurysms, and muscle cramps; TREX1, three prime repair exonuclease 1; HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; GLA, α-galactosidase A.

Cuadrado E et al. J Stroke 2018;20(3):302-320

Blood biomarkers of SVD

A biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”

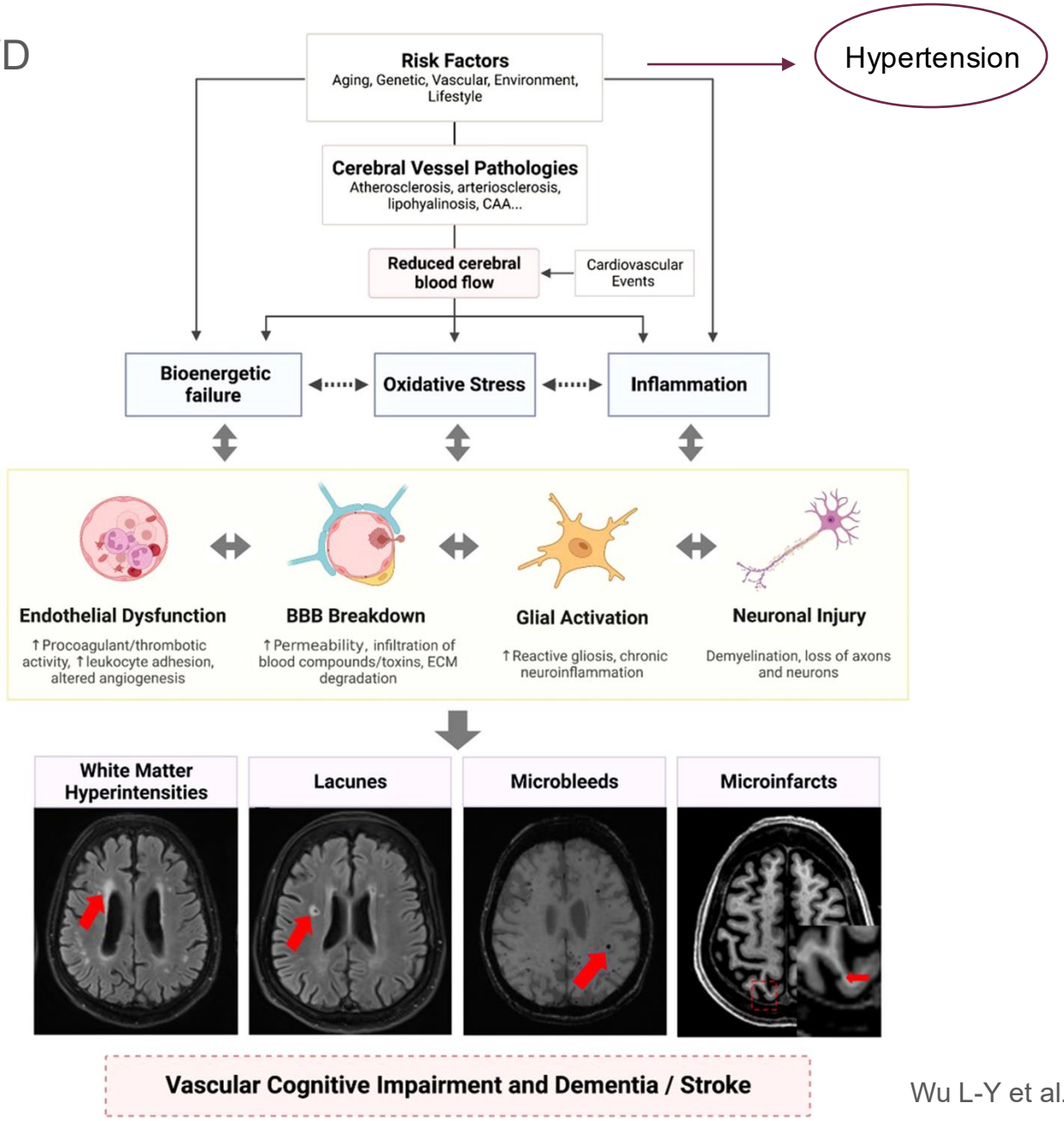
The “overall expectation of a biomarker is <u>to enhance the ability of the clinican to optimally manage the patient”</u>



Discover pathophysiology of cerebral disease to blood/urine/salive…

Biomarkers Definitions Working Group. *Bethesda, Md.* Clin Pharmacol Ther 2001;69:89-95

Pathophysiology of SVD



Wu L-Y et al. Aging Res Rev 2024;95:102247

Blood biomarkers and SVD

Vascular neurotoxic/ Metabolic factors

Biomarker	MRI findings			
	WMH	Lacunes	CMB	CMI
Homocysteine	↑	↑	-	NA
ADMA	↑ / -	↑	NA	NA

ADMA: asymmetric dimethilarginine

↑: positive association; ↓: negative association; NA: Not assessed; (-): no association.

WMH: White matter hyperintensities; CMB: Cerebral microbleeds; CMI: Cerebral microinfarcts

Wu L-Y et al. Aging Res Rev 2024;95:102247
Liu X et al. Front Neurol 2022;13:969185

Blood biomarkers and SVD

Cardiovascular dysfunction

Biomarker	MRI findings			
	WMH	Lacunes	CMB	CMI
NT-proBNP	↑	↑ / -	↑	NA
hs-CTnT	↑	↑	NA	↑
MR-proANP	↑	↑	NA	NA
GDF-15	↑	-	NA	NA
Cystatin C	↑	↑	NA	NA

NT.-proBNP: N-terminal pro-brain natriuretic peptide; hs-CTNT: high sensitivity cardiac troponin T; MR-proANP, mid-regional pro-atrial natriuretic peptide; GDF: Growth differentiation factor

↑: positive association; ↓: negative association; NA: Not assessed; (-): no association.

Wu L-Y et al. Aging Res Rev 2024;95:102247
Liu X et al. Front Neurol 2022;13:969185

Blood biomarkers and SVD

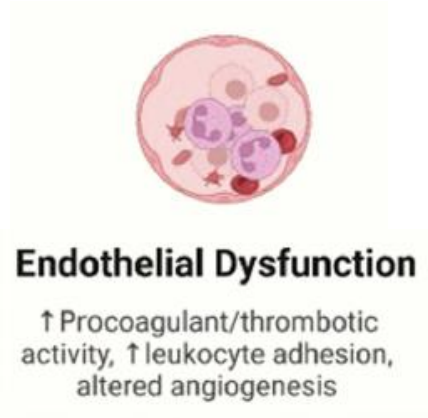
Biomarker	MRI findings			
	WMH	Lacunes	CMB	CMI
8-Isoprostane	↑	NA	-	NA
LPH	↑	NA	-	NA
4-HNE	-	NA	↑	NA
24-OHC	↑	↑	NA	NA
MPO	↑ / ↓	↓	↑	NA
Ergothioneine	↓	-	NA	NA

LPH, lipid hydroperoxides; 4-HNE, 4-hydroy-2-nonenal; 24-OHC, 24S-hydroxycholesterol; MPO, myeloperoxidase

↑: positive association; ↓: negative association; NA: Not assessed; (-): no association.

Wu L-Y et al. Aging Res Rev 2024;95:102247
Liu X et al. Front Neurol 2022;13:969185

Blood biomarkers and SVD



Biomarker	MRI findings			
	WMH	Lacunes	CMB	CMI
ICAM-1	↑ / -	↑	NA	NA
VCAM-1	↑	↑	NA	NA
P-selectin	↑		NA	NA
E-selectin	-	-	↑	NA
vWF	↑	↑	NA	NA
PAI-1	↑	↑	NA	NA
Fibrinogen	↑	↑ / -	NA	NA
TM	↑	↑	NA	NA
tPA	↑	-	-	NA
Lp-PLA2	↑	↑	NA	NA
F1+2	↑	↑	NA	NA
D-Dimer	↑		NA	NA
VEGF-A	-	NA	↑	NA
PlGF	↑	NA	NA	NA
Ang2	↑	-	-	NA
Tie2	↑	NA	NA	NA
HGF	↑	↑	↑	↑
Albuminuria	↑	↑	↑	NA

↑: positive association; ↓: negative association;
NA: Not assessed; (-): no association.

ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; vWF, von Willebrand factor; PAI-1:plasminogen activator inhibitor type 1; TM, thrombomodulin; tPA_ tissu plasminogen activator; Lp-PLA2, lipoprotein-associated phospholipase A2; F1+2, prothrombin fragment 1+2; VEGF: vascular endothelial growth factor; PlGF, placental growth factor: Ang2, angiopoietin 2; HGF, hepatocyte growth factor

Blood biomarkers and SVD

BBB Breakdown

↑Permeability, infiltration of blood compounds/toxins, ECM degradation

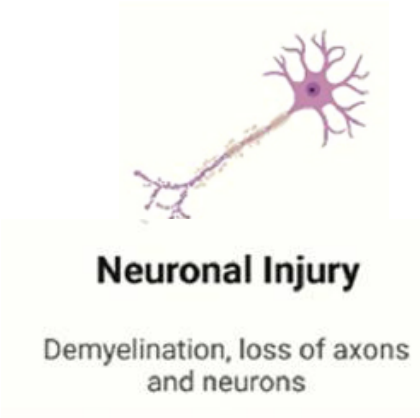
Biomarker	MRI findings			
	WMH	Lacunes	CMB	CMI
Protein S100B	-	NA	NA	NA
NSE	↑	NA	NA	NA
MMP-9	↑	-	NA	NA
MMP-2	-	-	NA	NA
TIMP-1	↑	-	NA	NA

NSE, neuron-specific enolase; MMP, matrix metalloproteinase; TIMP-1, tissue inhibitor of metalloproteinase 1.

↑: positive association; ↓: negative association; NA: Not assessed; (-): no association.

Wu L-Y et al. Aging Res Rev 2024;95:102247
Liu X et al. Front Neurol 2022;13:969185

Blood biomarkers and SVD



Biomarker	MRI findings			
	WMH	Lacunes	CMB	CMI
Aβ40	↑ / -	↑ / -	↑	NA
Aβ42	↑ / -	↑ / -	↑ / -	NA
Aβ38	↑ / -	↑ / -	↑ / -	NA
T-tau	-	-	↑	NA
NfL	↑	↑ / -	↑ / -	NA

NfL, neurofilament light chain

↑: positive association; ↓: negative association; NA: Not assessed; (-): no association.

Wu L-Y et al. Aging Res Rev 2024;95:102247
Liu X et al. Front Neurol 2022;13:969185

Biomarkers related with SVD progression

Biomarker	SVD progresssion
WMH progresssion	ICAM-1, tPA, ET-1, PF-4, MR-proADM, ACT, CRP, Aβ40,NfL, **Total Homocysteine level at the highest quintile (≥16.2 mmol/L)** **Highest NT-proBNP quartile (>119.1 pg./mL)** **High serum Cystatin C levels (≥1.00 mg/ L).**
Progression of lacunes	NfL
Progression of lacunes and microbleeds	ET-1
Progression pf SBI	ICAM-1. CRP
Decline of memory	NT-proBNP, hs-cTnT, and GDF- 15

CRP: C reactive protein; ICAM: intercellular adhesion molecule; ; tPA: tissue plasminogen activator; PF-4, platelet factor-4; MR-proADM, mid-regional pro-adrenomedullin; NT-proBNP, N-terminal pro-brain natriuretic peptide; NfL, neurofilament light chain; ET: endothelin; hs-cTnT, high sensitivity cardiac troponin T; GDF-15, growth differentiation factor 15; SBI: Silent brain infarct

Wu L-Y et al. Aging Res Rev 2024;95:102247
García Danieta J et al. Alzheimer's Dement. 2025;21:e70152
;

Biomarkers related with prognosis in patients with lacunar infarction

Biomarker	SVD progresssion
Neurological deterioration (first 24 h of evolution)	**TNF-** α levels > 14 pg/mL I**CAM-1** levels > 208 pg/mL **Glutamate levels >** 200 mmol/L **GABA** levels ,240 nmol/L
Funciontal prognosis	**TNF-** α levels > 14 pg/mL I**CAM-1** levels > 208 pg/mL

ICAM: intercellular adhesion molecule; ; TNF: tumor necrosis factor

Serena J et al. Stroke 2001;32:1154-1161
Castellanos M et al. Stroke 2002;33:982-987

What we know (that we must solve)

- ✓ The majority of studies have involved single-centre, small-sized cohorts → limited statistical power and increased likelihood of both false positive and false negative associations.

- ✓ Considerable variability between studies:

  - ✓ Differences in cohort profiles (e.g., age, geographical region, type and stage of disease, and diagnostic evaluations)
  - ✓ Sample preparation
  - ✓ imaging protocols
  - ✓ Assay reliability
  - ✓ Follow-up duration, etc

- ✓ The majority of studies performed do not report sensitivity/specificity of the analized blood biomarkers which are necessary to evaluate the performance of a biomarker.

- ✓ The pathophysiological complexity of SVD with multiple factors involved and with many different clinical and radiological expression, suggests that a single blood biomarker will not be useful, nor for the diagnosis neither for the progression of this disease → Clusters de biomarkers

  - ✓ Large sample size --> Consortiums
  - ✓ Large-scale multidimensional blood-based “Omics” data, integrated with information obtained from clinical, demographic as well as state-of-the-art neuroimaging modalities

Can we analyze blood biomarkers of SVD? Yes, at least some of them

Can be anbalyzed in clinical practice

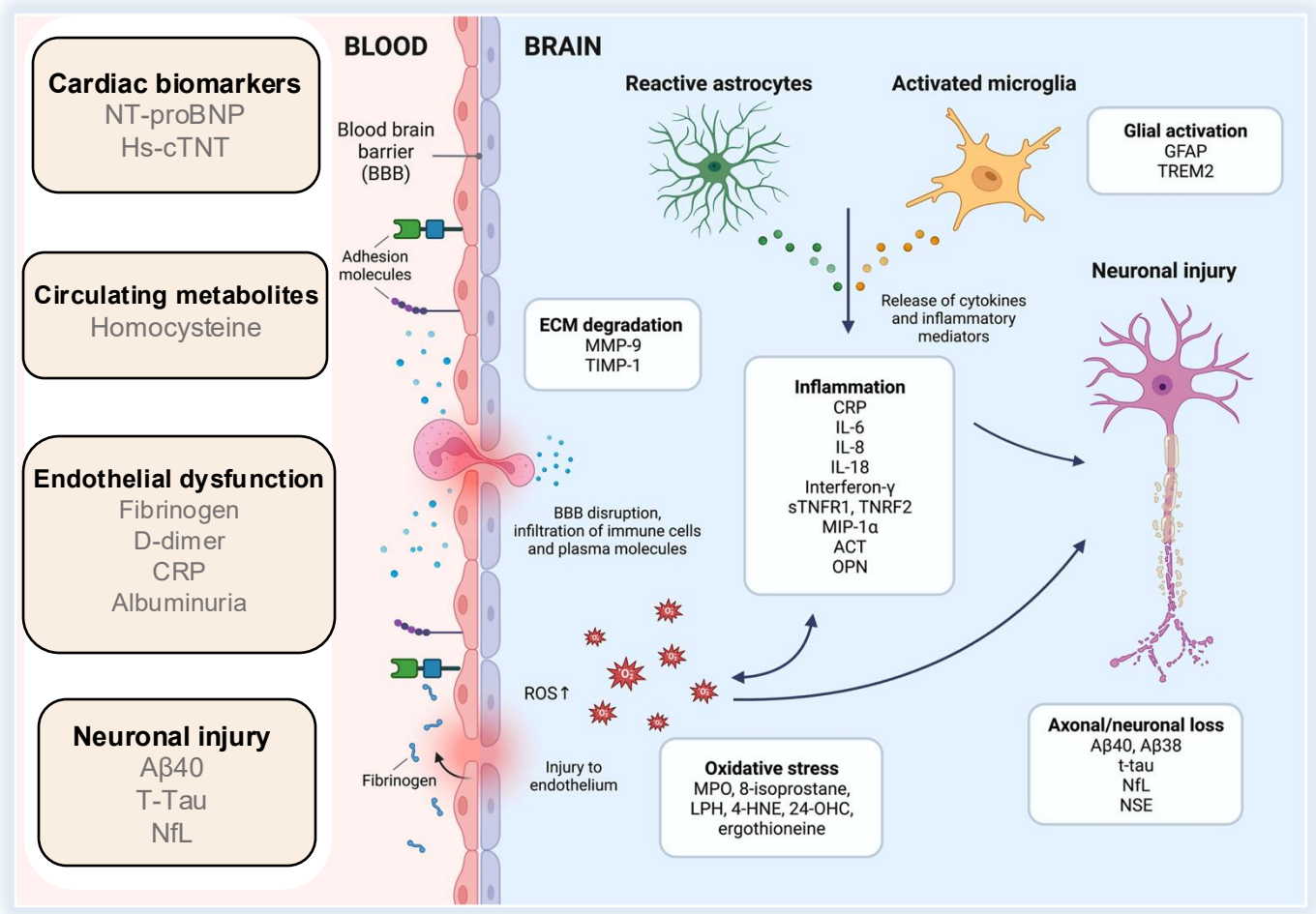


Image partifally modified from: Wu L-Y et al. Aging Res Rev 2024;95:102247

When should we analyze blood biomarkers of SVD? Not established yet

Include patients in clinical studies in you have the possibility!!

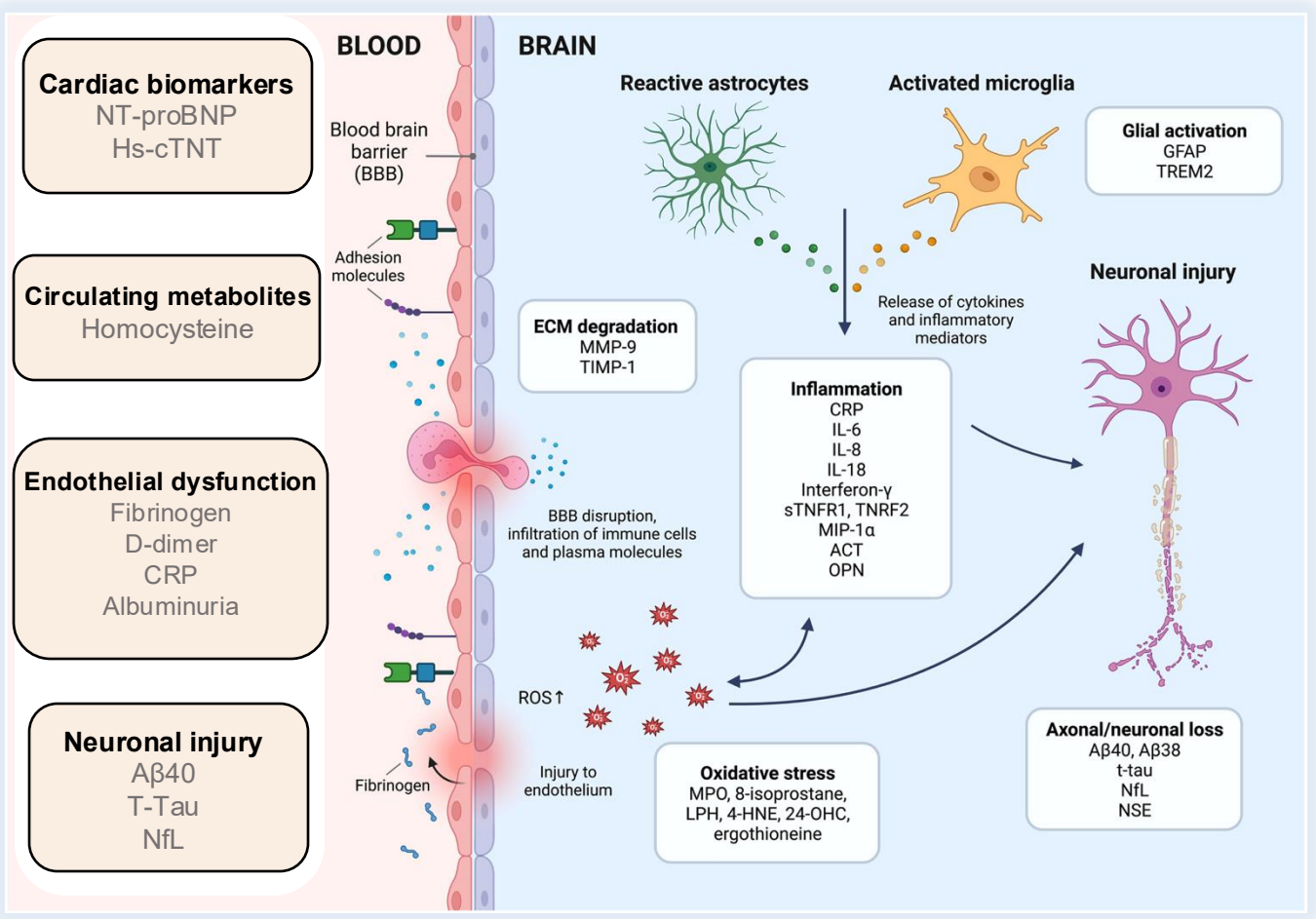


Image partifally modified from: Wu L-Y et al. Aging Res Rev 2024;95:102247


HOSPITAL PÚBLICO
NOVO HOSPITAL PÚBLICO DA CORUÑA