Cerebral Small Vessel Diseases: How To Recognize and Treat

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UNLABELED/UNAPPROVED USES DISCLOSURE: none.

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- Carlos Camara, Hugh Markus.
- Research team.

CCNA
Canadian Consortium on Neurodegeneration in Aging

CCNV
Consortium canadien en neurodégénérescence associée au vieillissement

Fondation Brain Canada Foundation

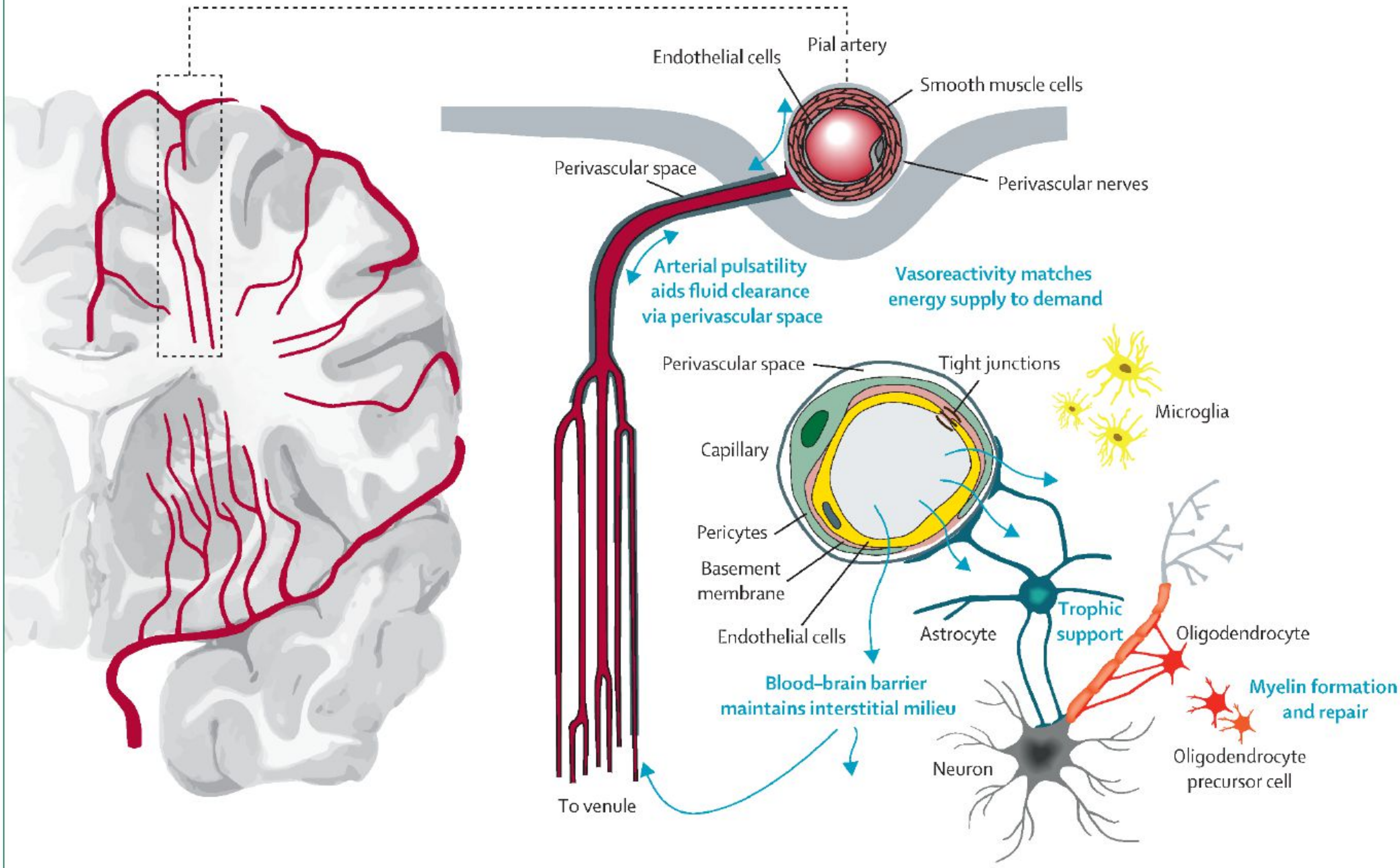
Société Alzheimer Society
CANADA

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Outline

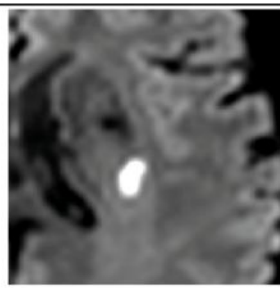
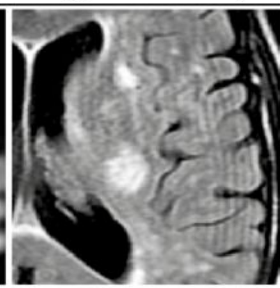
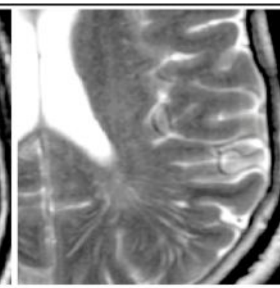
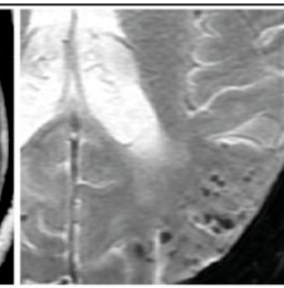
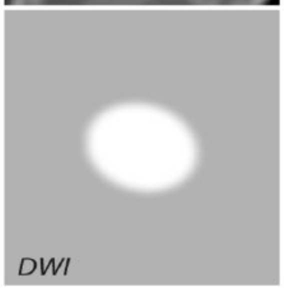
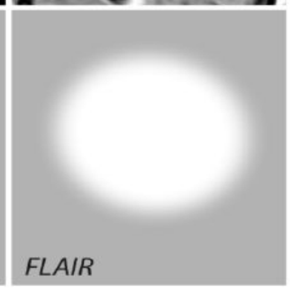
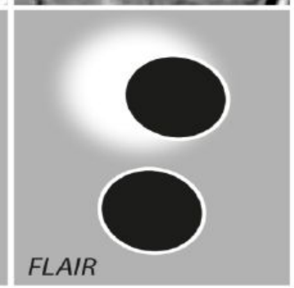
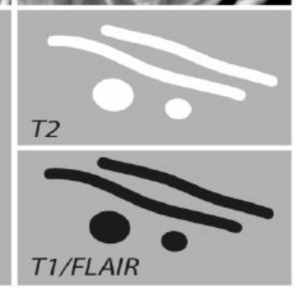
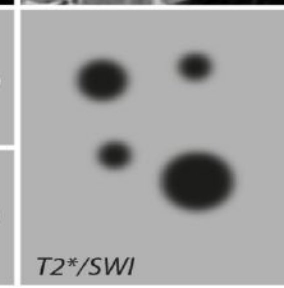
- Epidemiology.
- Vascular pathology.
- Clinical syndromes.
- Preventing stroke and dementia.
- Trial of remote ischemic conditioning.

Cerebral Small Vessel Disease (SVD)



Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 2019;18:684-696.

Radiological Manifestations of SVD

	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleeds
Example image					
Schematic					
Usual diameter[1]	≤ 20 mm	variable	3-15 mm	≤ 2 mm	≤ 10 mm
Comment	best identified on DWI	located in white matter	usually have hyperintense rim	usually linear without hyperintense rim	detected on GRE seq., round or ovoid, blooming
DWI	↑	↔	↔/(↓)	↔	↔
FLAIR	↑	↑	↓	↓	↔
T2	↑	↑	↑	↑	↔
T1	↓	↔/(↓)	↓	↓	↔
T2* / GRE	↔	↑	↔ (↓ if haemorrhage)	↔	↓↓

Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The Lancet Neurology 2013;12:822-838.

Prevalence of “Silent” SVD

TABLE 6-3 Prevalence of Cerebral Small Vessel Disease on Magnetic Resonance Imaging in the General Population Without Dementia[a]

Age Decade	Infarcts		Beginning Confluent or Confluent White Matter Hyperintensities on MRI[b]	Microbleeds[c]	
	≥1 infarct	≥2 infarcts		T2*-Weighted Gradient Recalled Echo (GRE)	Susceptibility-Weighted Imaging (SWI)/ High-Sensitivity Sequence
50–59	5–8%	1–2%	1%	3%	12%
60–69	7–12%	2–3%	1–4%	5–10%	15–17%
70–79	12–23%	3–6%	6–14%	8–16%	30–31%
80+	25–38%	6–9%	19%	18%	40%

MRI = magnetic resonance imaging.

[a] Data are aggregated from multiple population-based studies.

[b] As measured using the Fazekas scale.[13]

[c] As can be seen from the table, susceptibility-weighted imaging (SWI) and other newer, high-sensitivity MRI sequences detect about twice as many microbleeds as older T2*-weighted gradient recalled echo (GRE) sequences.

Smith EE. Vascular Cognitive Impairment. Continuum (Minneapolis, Minn) 2016;22:490-509.

Hazard of Future Clinical Events in Patients with MRI Markers of Vascular Brain Injury

Lesion	Stroke	Dementia	Mortality
Brain infarct	2.38 (1.87-3.04)	1.29 (1.02-1.65)	1.64 (1.40-1.91)
High WMH	2.45 (1.93-3.12)	1.84 (1.40-2.43)	2.00 (1.69-2.36)
Microbleeds	1.98 (1.55-2.53)	1.41 (0.90-2.21)	1.53 (1.31-1.80)

Meta-analysis of estimates adjusted for age, sex, and vascular risk factors.

Debette S, et al. Clinical significance of magnetic resonance imaging markers of vascular brain injury: A systematic review and meta-analysis. JAMA Neurol 2018;76:81-94.

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

Eric E. Smith, MD, MPH, FAHA, Chair; Gustavo Saposnik, MD, MSc, FAHA, Vice Chair; Geert Jan Biessels, MD, PhD; Fergus N. Doubal, PhD, FRCP; Myriam Fornage, MS, PhD, FAHA; Philip B. Gorelick, MD, MPH, FAHA; Steven M. Greenberg, MD, PhD, FAHA; Randall T. Higashida, MD, FAHA; Scott E. Kasner, MD, MS, FAHA; Sudha Seshadri, MD; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension

Stroke 2017;48:e44-e71.

- Recommendations for radiological diagnosis (STRIVE).
- Investigations.
- Risk stratification for ischemic stroke.
- Considerations for antithrombotic strategies in patient patients with microbleeds.

WMH Reporting

MRI Fazekas White Matter Hyperintensity Scale Score

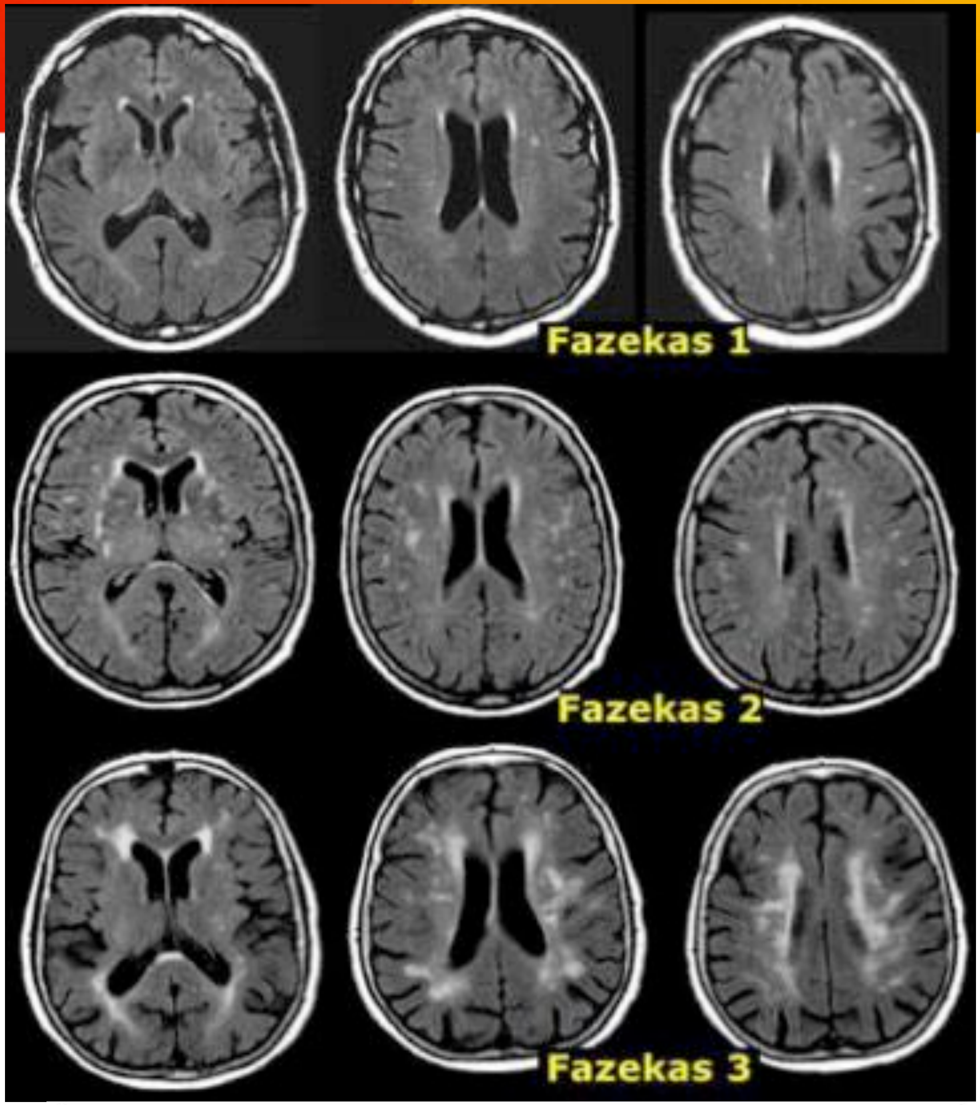
		Periventricular			Subcortical			
		0	1	2-3	0	1	2	3
Age	N	None	Caps/lining	Halo	None	Punctate	Early Confluence	Confluent
<55	440	72%	28%	0%	52%	45%	3%	0%
55-64	644	51%	47%	2%	27%	66%	5%	2%
65-74	563	34%	57%	9%	12%	60%	22%	6%
≥75	149	6%	74%	19%	3%	44%	30%	23%

Diagnosis by neuroimaging

WMHs of presumed vascular origin should be reported with the use of a validated visual rating scale such as the Fazekas scale for MRI.

Smith EE, et al. 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..

Fazekas Scale



Periventricular hyperintensity (PVH) was graded as:
0 = absence, 1 = “caps” or pencil-thin lining, 2 = smooth “halo,” 3 = irregular PVH extending into the deep white matter.

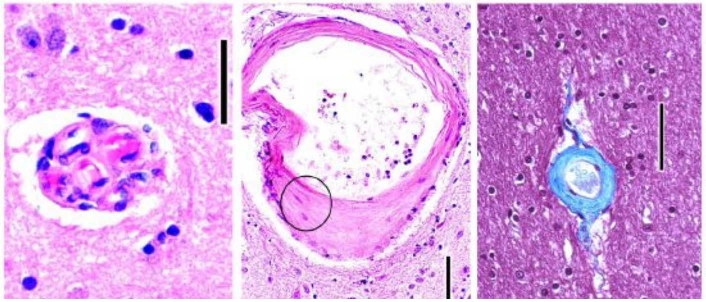
Separate deep white matter hyperintense signals (DWMH) were rated as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas.

Fazekas F, et al. AJR Am J Roentgenol 1987;149:351-356.

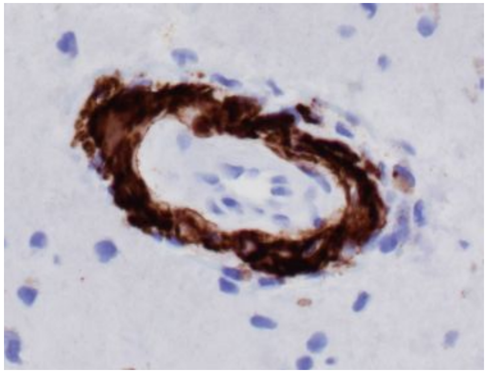
Cerebral Small Vessel Pathology

Two main pathologies:

1. **Arteriolosclerosis**: caused by aging, hypertension and conventional vascular risk factors.



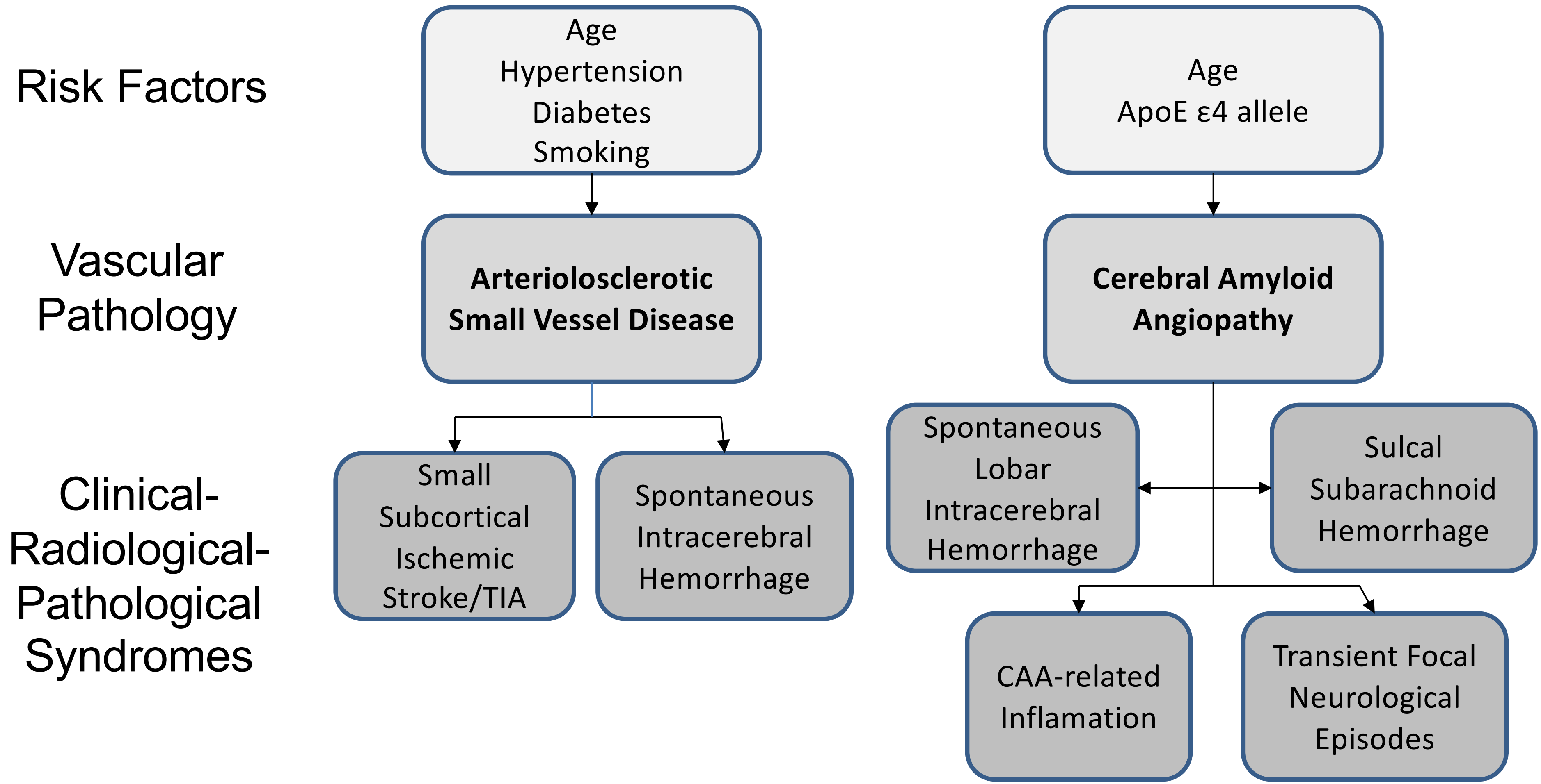
2. **Cerebral amyloid angiopathy**: caused by vascular beta-amyloid deposition.



3. **Others**
   - **Genetic:** CADASIL, CARASIL, others.
   - **Venous:** collagenosis.
   - **Arteritis**
   - **Embolism**
   - **Branch occlusive disease**

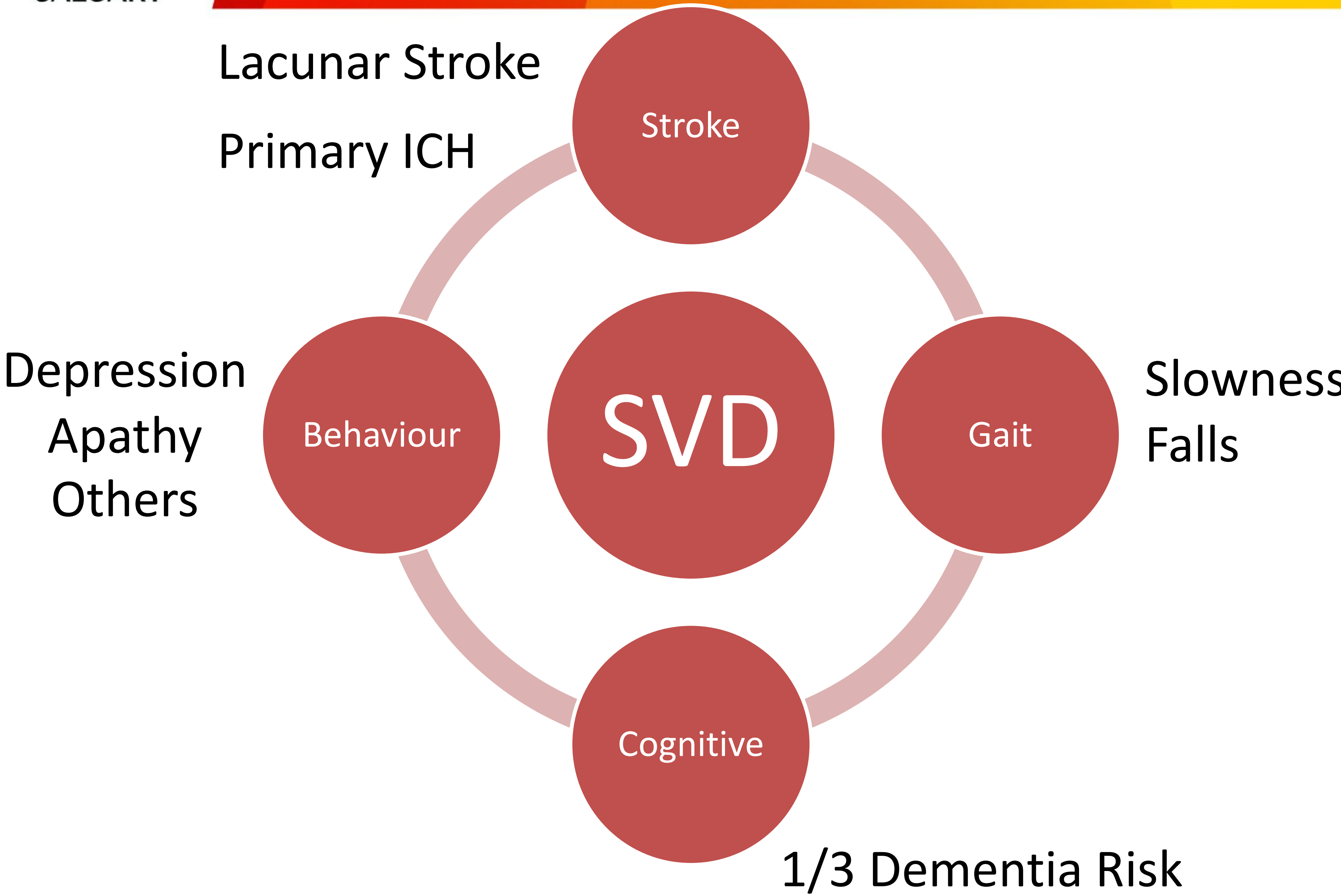
Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurology 2010;9:689-701.

Two Main Types of Cerebral Small Vessel Disease

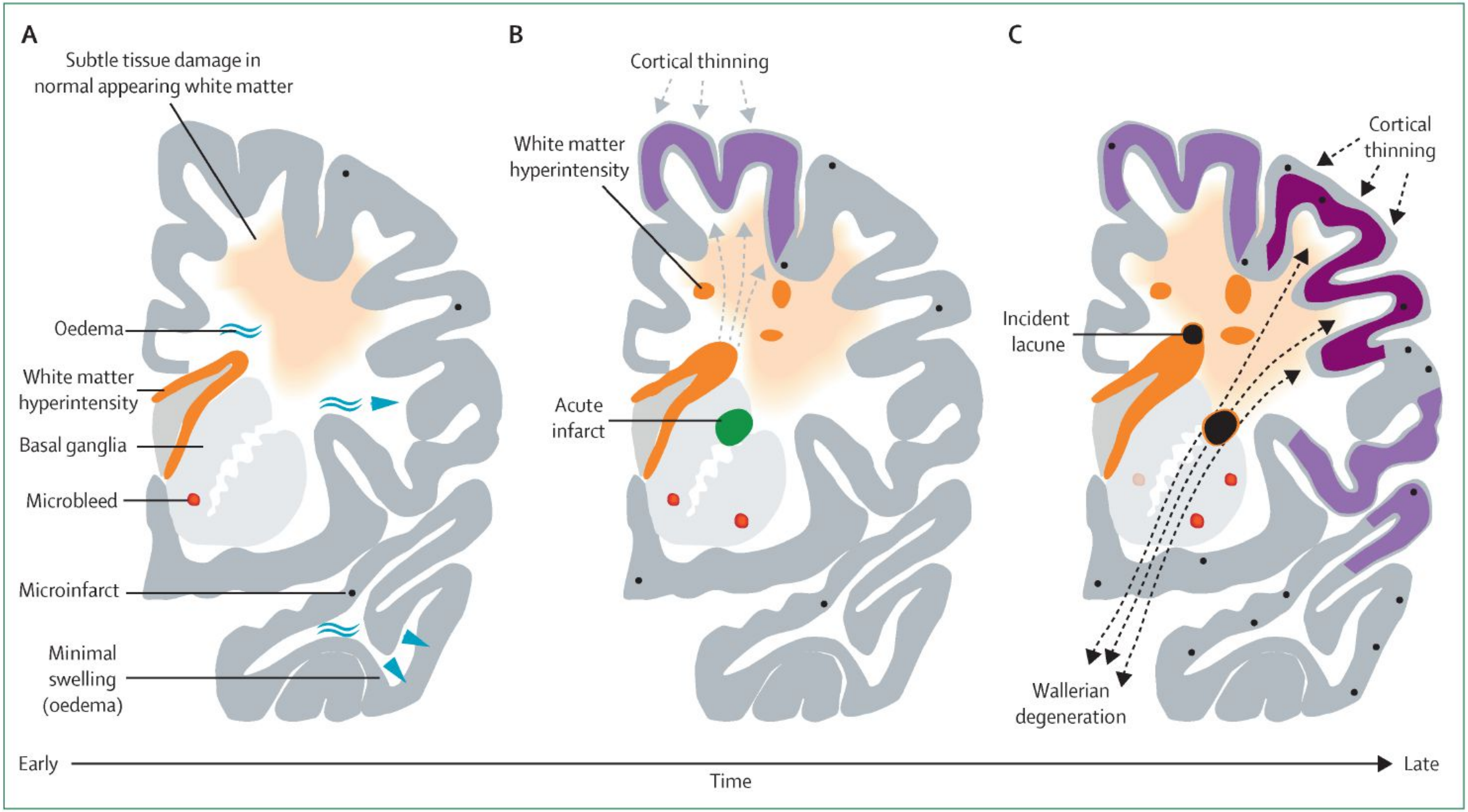


Smith EE. Prevention of cerebral small vessel disease. Seminars in Neurology 2017;37:316-325.

Many Manifestations



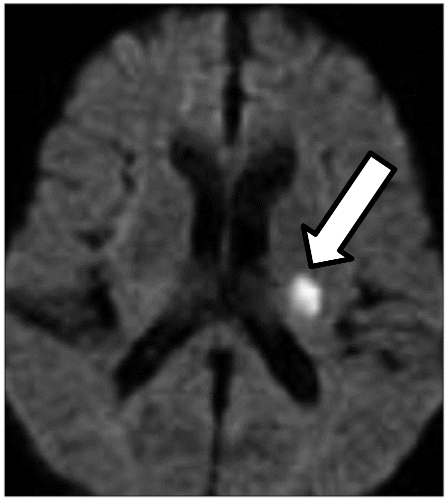
Pathophysiology of Small Vessel Disease

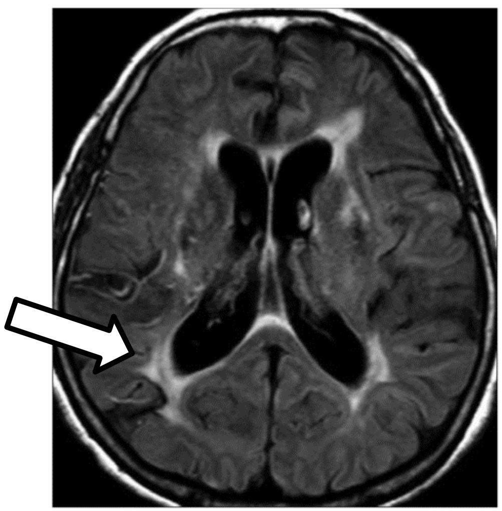


Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. The Lancet Neurology 2019;18:684-696.

LACUNAR STROKE

Diffuse SVD





Bang OY. Considerations When Subtyping Ischemic Stroke in Asian Patients. J Clin Neurol. 2016;12:129-136. PMID 26833987.

La

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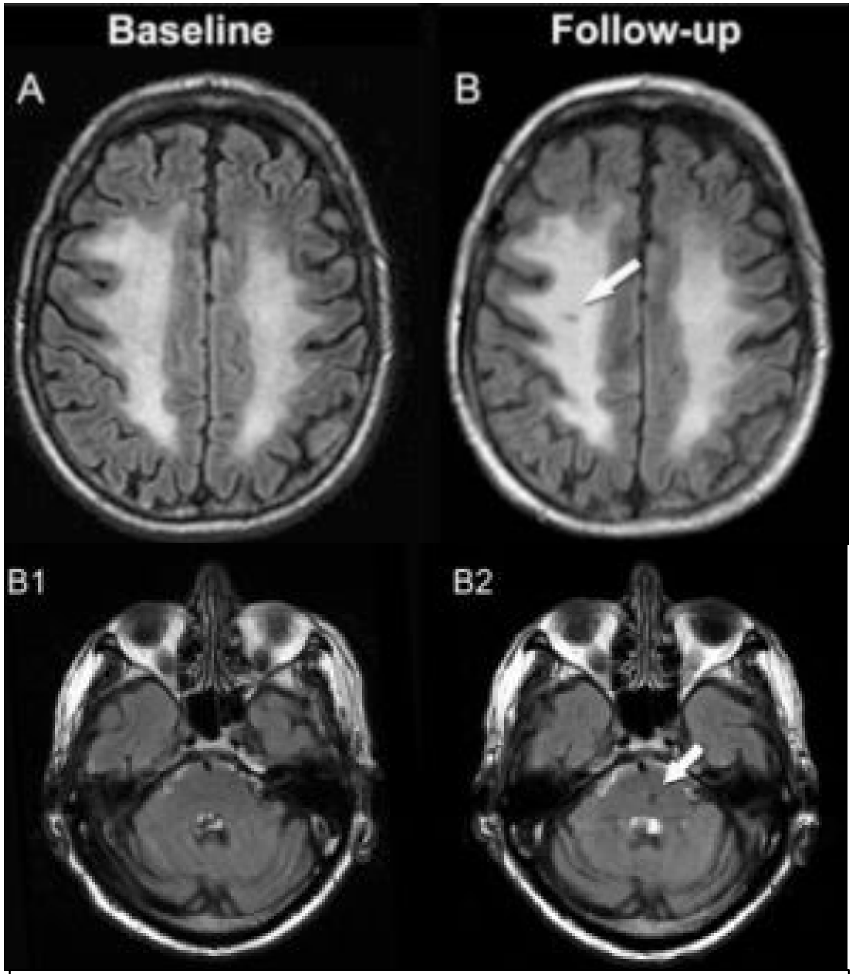
ter lacunes

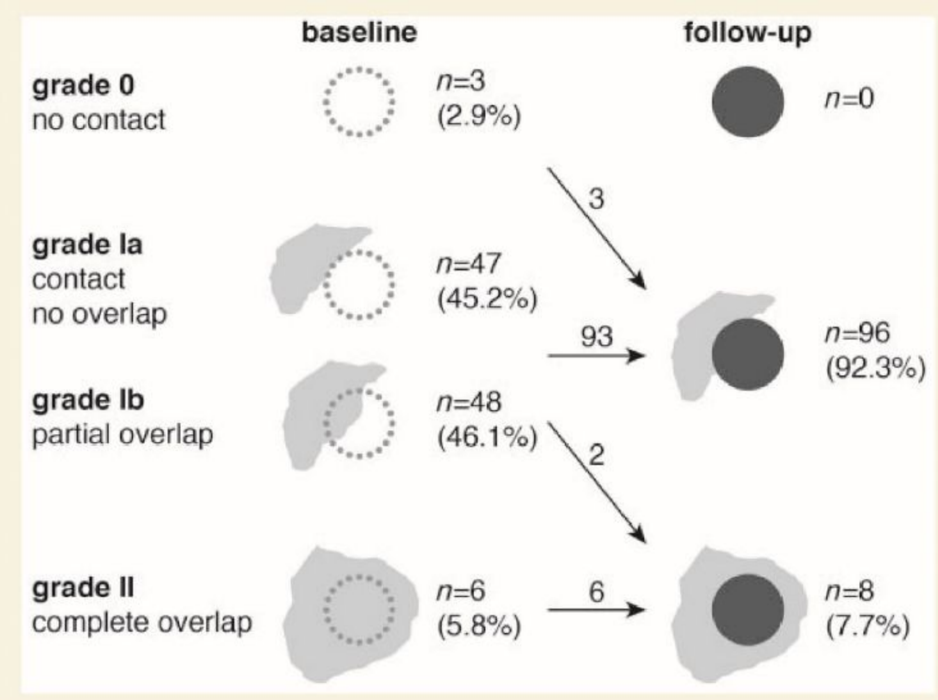
Branch Occlusive Disease

Ryoo S, Park JH, Kim SJ, et al. Branch occlusive disease: clinical and magnetic resonance angiography findings. Neurology 2012;78:888-896. Epub 2012 Mar 2017.

Cavitating Lacunes



Gouw AA et al. On the etiology of incident brain lacunes: longitudinal observations from the LADIS study. Stroke. 2008;39:3083-3085

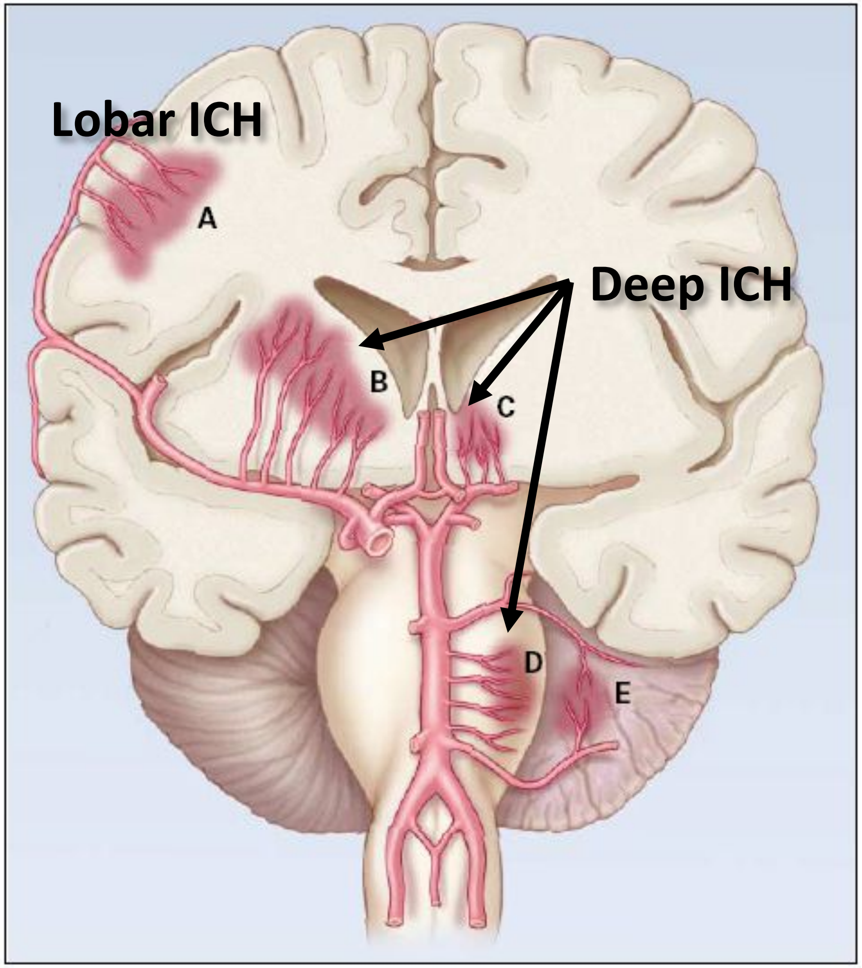


Duering M, et al. Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease. Brain. 2013;136:2717-2726

INTRACEREBRAL HEMORRHAGE AND CAA

Intracerebral Hemorrhage

- SVD causes primary ICH.
- Can be subtyped based o
  (basal ganglia, brainstem
  subcortical white matter)
  - Different risk factors.
  - Different path correlates.
  - Different outcomes.



N Engl J Med 2001;344:1450-1460.

Conventional Treatment

- Acute (<4.5 hours) small subcortical infarct: tPA.
- Prevent recurrent ischemic stroke:
  - Blood pressure control.
  - Antithrombotic.
  - Statin.
- Prevent recurrent primary ICH:
  - Blood pressure control.
- CAA: no disease-modifying treatments.

Smith EE. Prevention of cerebral small vessel disease. Seminars in Neurology 2017;37:316-325.

SPS3 Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

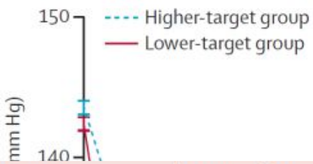
N Engl J Med 2012;367:817-825.

No benefit

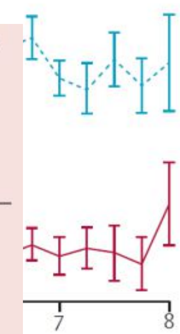
Blood-pressure targets in patients with recent lac the SPS3 randomised trial

Lancet 2013;382:507-515

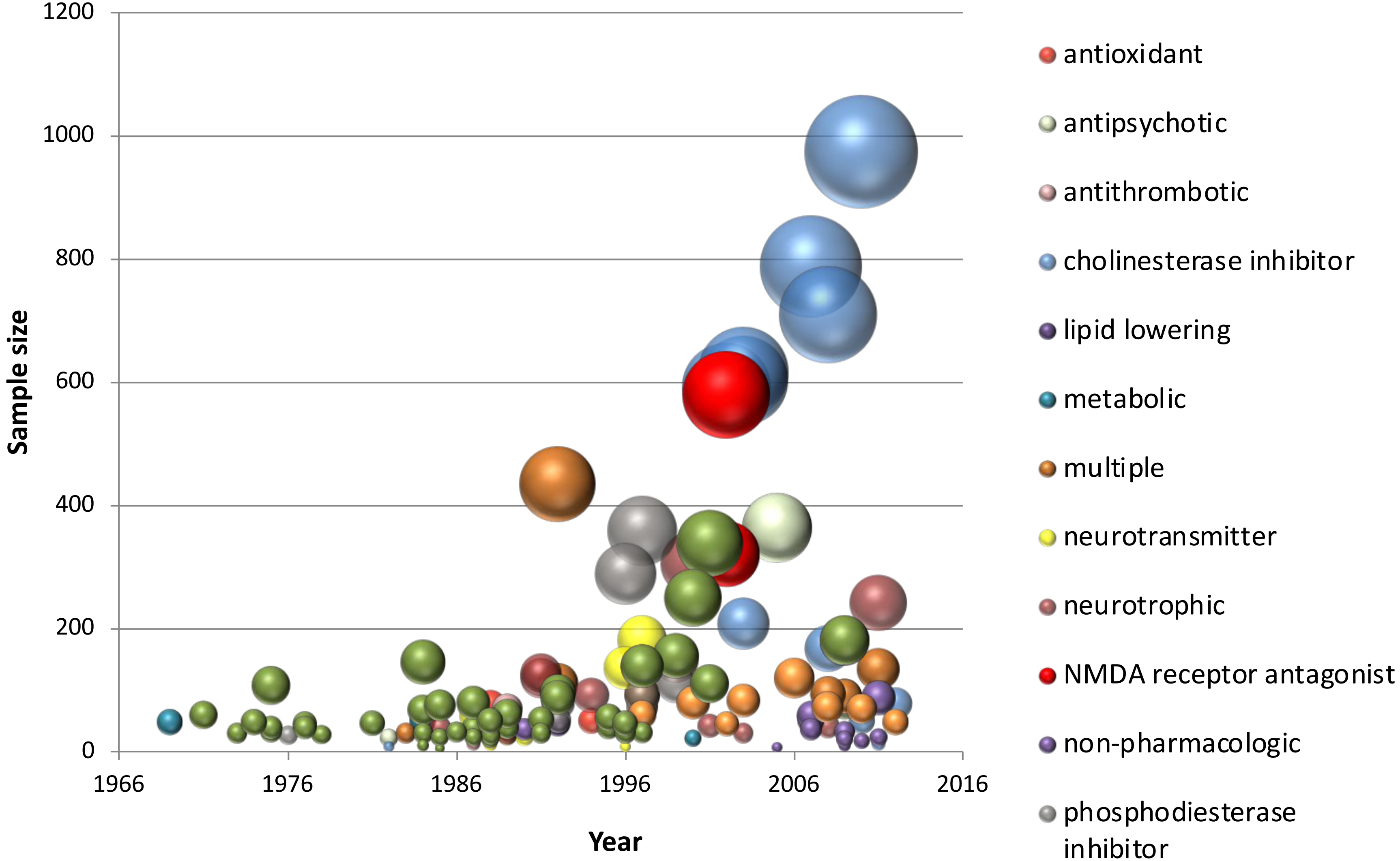
*The SPS3 Study Group**



	Higher-target group (n=1519)		Lower-target group (n=1501)		Hazard ratio (95% CI)	p value
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)		
Stroke						
All stroke	152	2·77%	125	2·25%	0·81 (0·64–1·03)	0·08
Ischaemic stroke or unknown	131	2·4%	112	2·0%	0·84 (0·66–1·09)	0·19
Intracranial haemorrhage						
All	21*	0·38%	13†	0·23%	0·61 (0·31–1·22)	0·16
Intracerebral	16	0·29%	6	0·11%	0·37	0·03

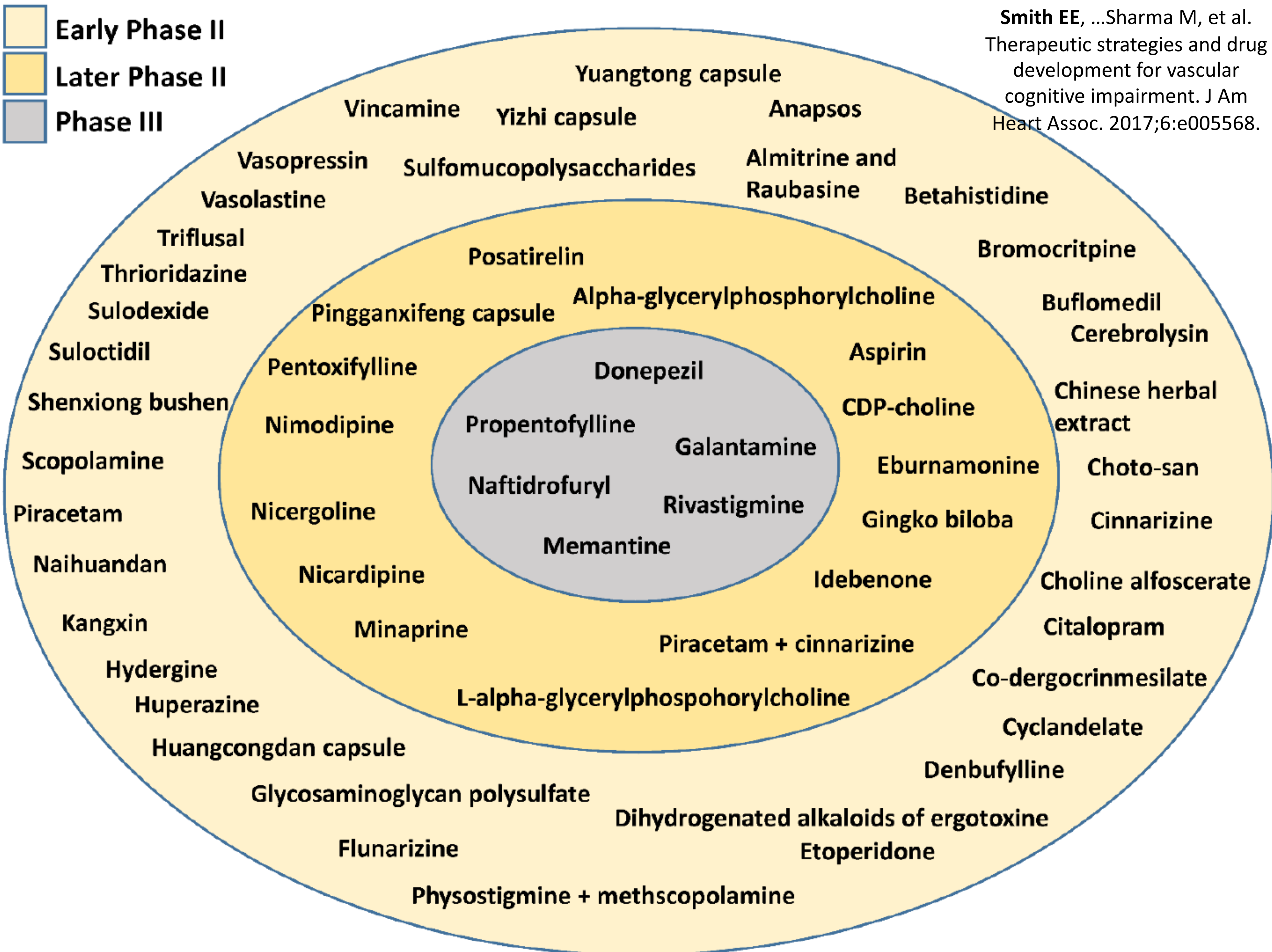


Past Failures in Vascular Cognitive Impairment



Smith EE, …Sharma M, et al. Therapeutic strategies and drug development for vascular cognitive impairment. J Am Heart Assoc. 2017;6:e005568.

Smith EE, …Sharma M, et al. Therapeutic strategies and drug development for vascular cognitive impairment. J Am Heart Assoc. 2017;6:e005568.



Trials for Cerebral Small Vessel Disease

- Systematic review of Pubmed and Clinicaltrials.gov identified 1 additional phase 3 and 23 phase 2 trials targeting SVD progression or lacunar infarct prevention; 17 still ongoing.
- Interventions:
  - Vasodilators: cilostazol, isosorbide dinitrate.
  - Antihypertensives: telmisartan, tadalafil, amlodipine, losartan, atenolol.
  - Other drugs: allopurinol, DL-3-n-butylphthalide.
  - Systolic blood pressure lowering.
  - Aerobic exercise, resistance training, dancing.
  - Remote ischemic conditioning.

Smith EE, Markus HS. New Treatment Approaches to Modify the Course of Cerebral Small Vessel Diseases. Stroke 2019: in press.

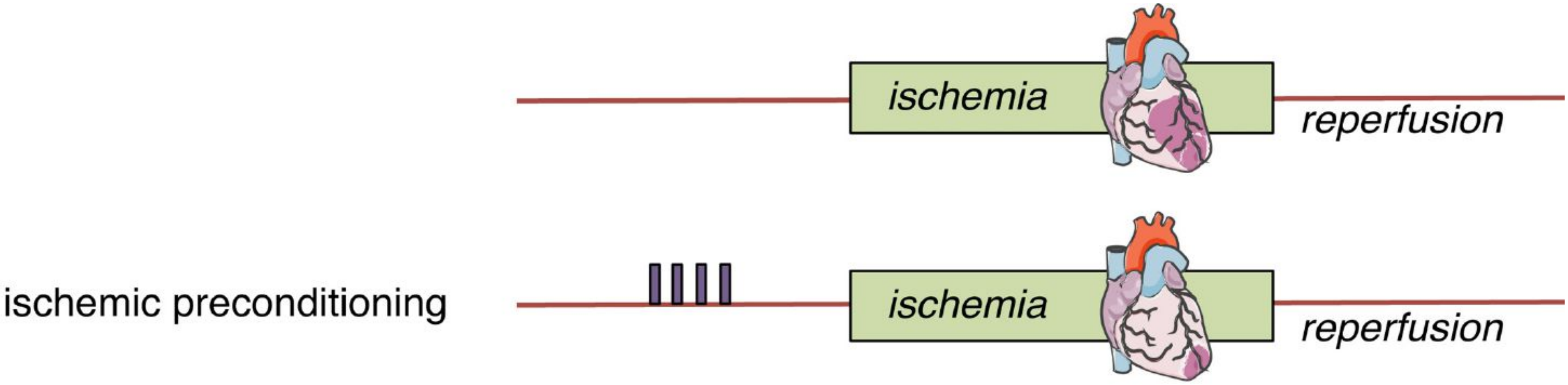
UNIVERSITY OF CALGARY

Trial of Remote Ischemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI)

Clinicaltrials.gov NCT 04109963

Ischemic Preconditioning

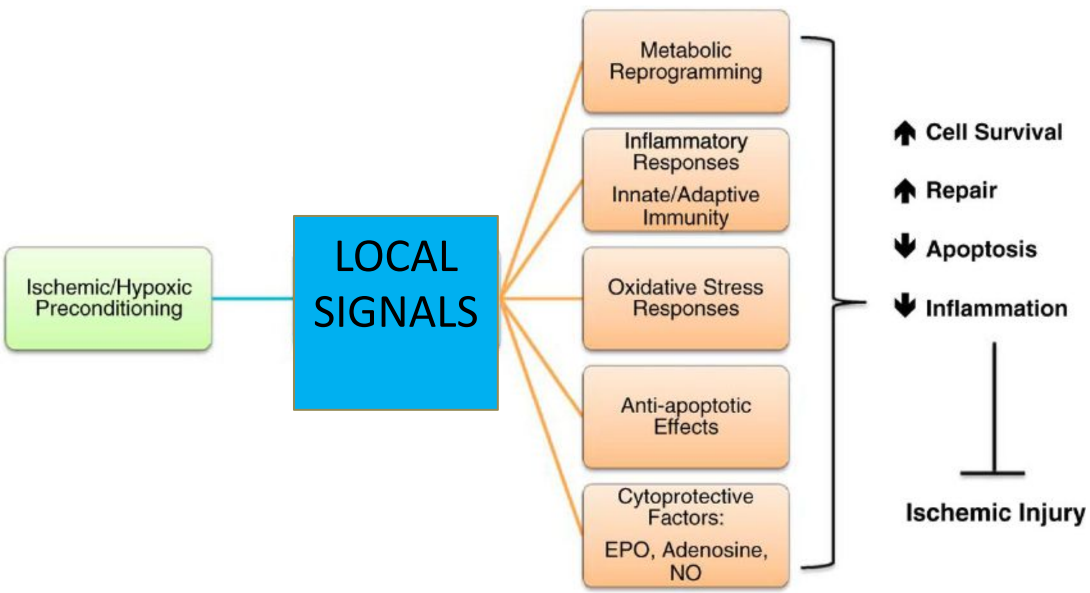
Over 3 decades ago, investigators found that experimentally inducing short-lasting IR (for periods that do not result in tissue injury) before an actual injurious event, reduces the subsequent injury. This is known as Ischemic Preconditioning (IP).

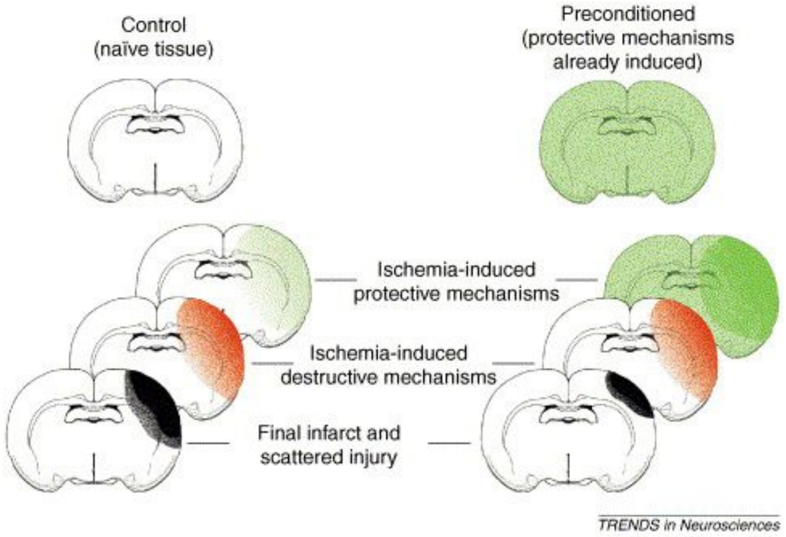


Stokfisz et al. Adv Med Sci. 2017 Sep;62(2):307-316.

Protective Mechanisms

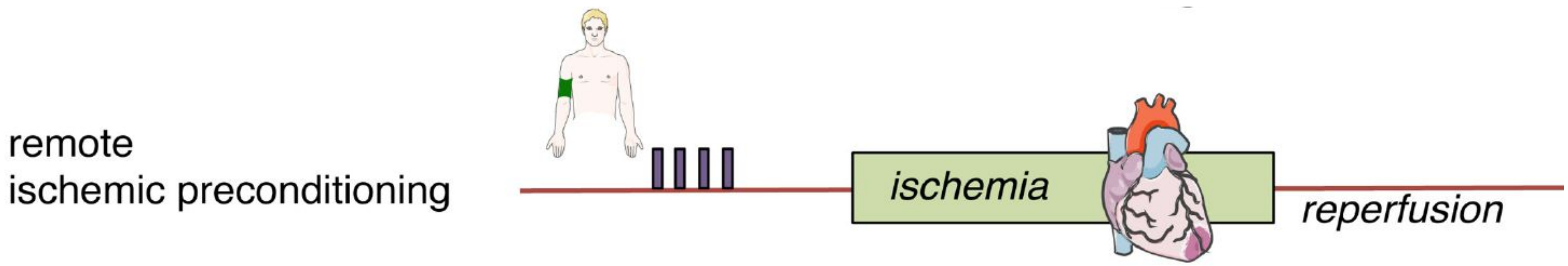
The rationale is that these short periods of IR induce an **endogenous protective environment**, consisting of humoral and neuronal-mediated responses.

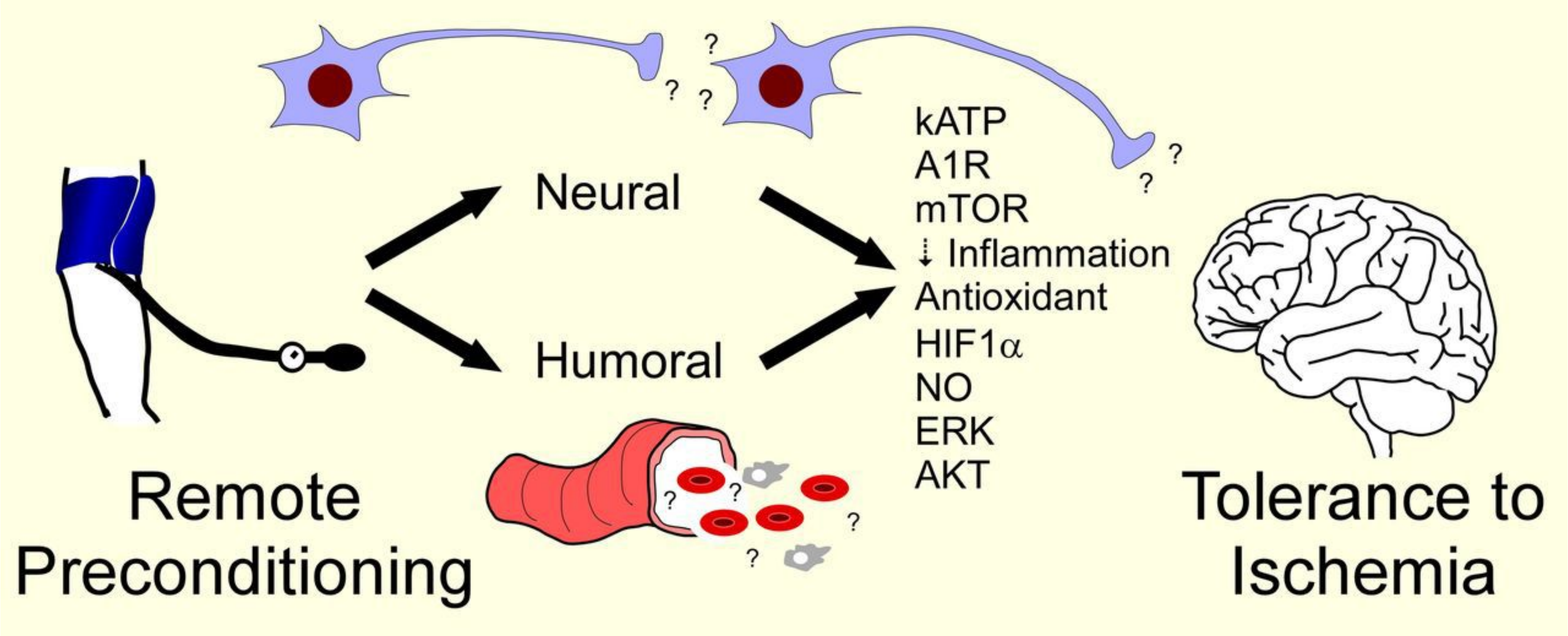




Pan et al. Rev Neurosci. 2016 Jul 1;27(5):501-10.

Systemic, Remote, Effects





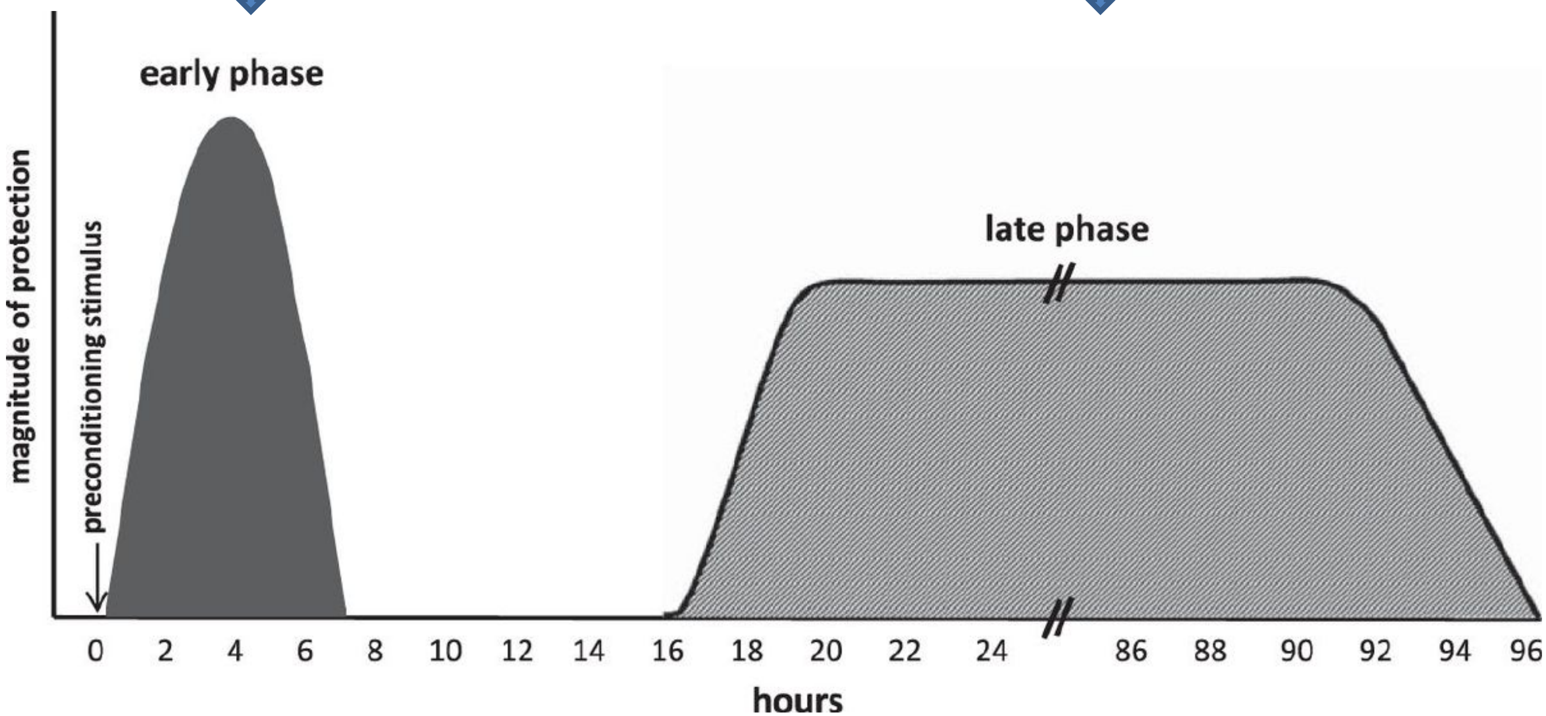
Stokfisz et al. Adv Med Sci. 2017 Sep;62(2):307-316.

Early and Late Changes

In addition to early phase effects, there are longer term effects resulting from changes in gene expression and protein synthesis.

- Metabolic
- Energy
- Blood-flow

- Inflammatory
- Oxidative
- Genes



J Appl Physiol (1985). 2015;119:1143-51.

Human Trials

Pre-procedural

Cardiac surgery

PCI/CABG

AAA repair

Carotid stent

Peri-event

MI

Stroke

Protection against recurrent event

TIA/stroke due to intracranial atherosclerosis

Cerebral small vessel disease and MCI

Recent systematic reviews:

- Zhao W, Zhang J, Sadowsky MG, Meng R, Ding Y, Ji X. Remote ischaemic conditioning for preventing and treating ischaemic stroke (Review). Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD012503. DOI: 10.1002/14651858.CD012503.pub2
- McLeod SL, Iansavichene A, Cheskes S. Remote ischemic perconditioning to reduce reperfusion injury during acute ST-segment-elevation myocardial infarction: A systematic review and meta-analysis. *J Am Heart Assoc* 2017; **6**(5).
- Blusztein DI, Brooks MJ, Andrews DT. A systematic review and meta-analysis evaluating ischemic conditioning during percutaneous coronary intervention. *Future Cardiol* 2017; **13**(6): 579-92.

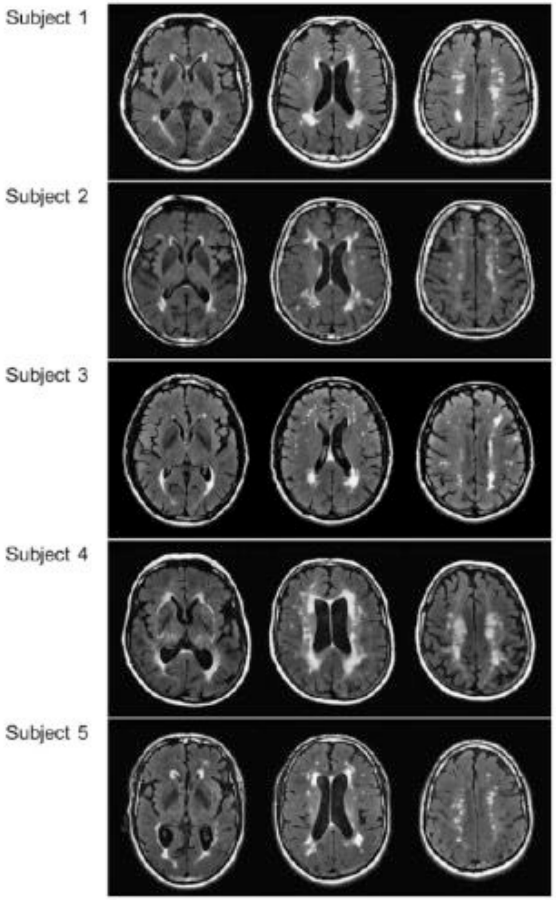
Safety and Tolerability

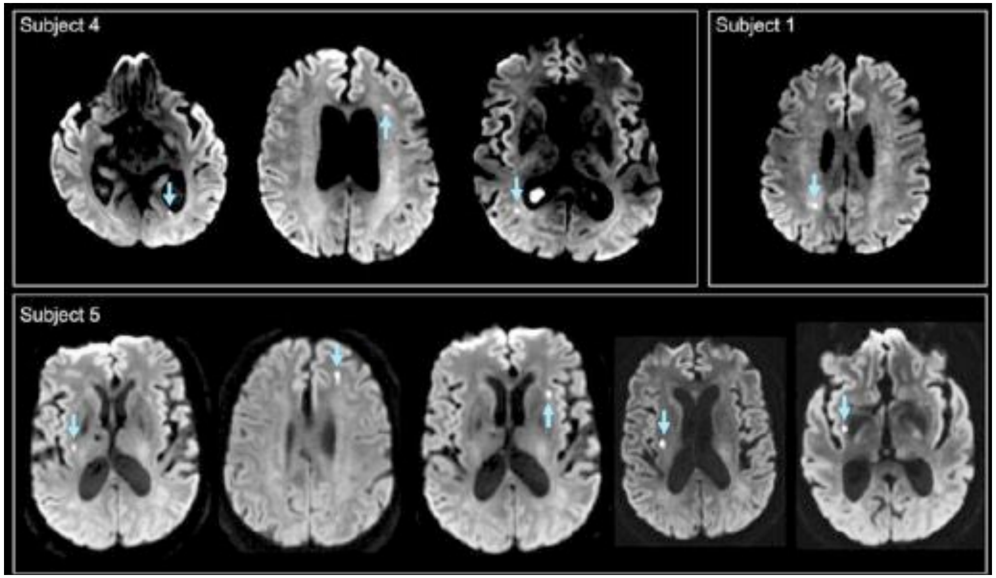
- Thousands of patients have undergone RIC
- No major AE have been reported.
- Populations have included severely ill patients (transplant recipients, major vascular surgery…).
- Frequently used exclusions: Prior history of vascular, soft tissue or orthopedic injury; history of peripheral vascular disease involving the arms.
- Patients on anticoagulants often excluded.

Safety

Adverse effect	Range	n/N (Pooled), % of patients (95% CI)
Local petechiae	0 to 9.5%	11/201, 5.5% (2.3-8.6%) Meng 2012, Meng 2015, Nicholson 2015, Zhao 2017, Zhao 2018
Intolerable discomfort	0 to 7.7%	1/337, 0.3% (0-0.9%) Botker 2010, England 2017, Hougaard 2014, Meng 2012
Thrombophlebitis or DVT	0%	0/533 Botker 2010, Hougaard 2014, England 2017, Gonzalez 2014, Lin 2014, Meng 2012, Meng 2015, Nicholson 2015, Zhao 2017, Zhao 2018
Limb ischemia	0%	0/533 Botker 2010, Hougaard 2014, England 2017, Gonzalez 2014, Lin 2014, Meng 2012, Meng 2015, Nicholson 2015, Zhao 2017, Zhao 2018

Rationale for Cerebral Small Vessel Disease





3/5 subjects with MRI every week for 16 weeks had new small infarcts.

Conklin, J., et al. (2014). "Are acute infarcts the cause of leukoaraiosis? Brain mapping for 16 consecutive weeks." Ann Neurol 76(6): 899-904.

RIC in Vascular Dementia Model

Transl. Stroke Res.
DOI 10.1007/s12975-017-0555-1

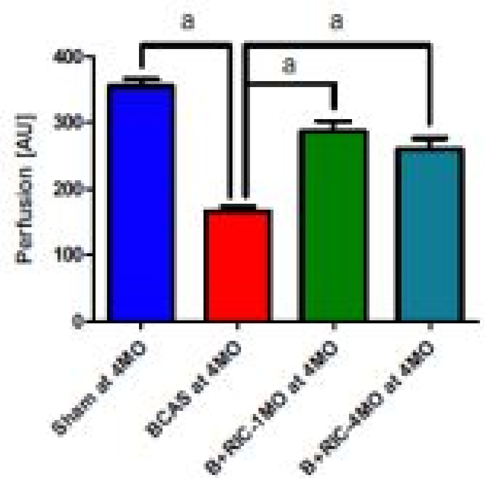
ORIGINAL ARTICLE

Chronic Remote Ischemic Conditioning Is Cerebroprotective and Induces Vascular Remodeling in a VCID Model

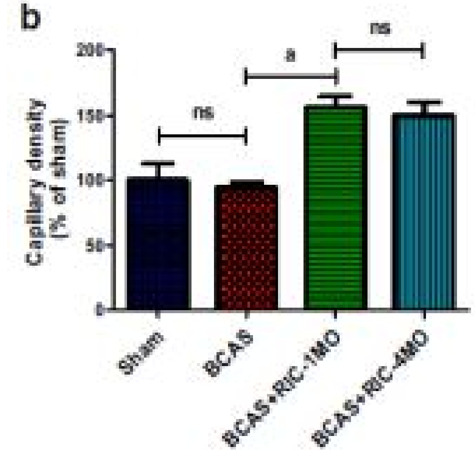
Mohammad Badruzzaman Khan[1] · Sherif Hafez[1] · Md. Nasrul Hoda[2] · Babak Baban[3] · Jesse Wagner[1] · Mohamed E. Awad[3] · Hasith Sangabathula[1] · Stephen Haigh[4] · Mohammed Elsalanty[3] · Jennifer L. Waller[5] · David C. Hess[1]

- Bilateral carotid occlusion model (BCAS)
- Bilateral hind limb RIC once daily for 1 month or 4 months
- Results:
  - Increased CBF
  - Increased angiogenesis
  - Decreased white matter damage

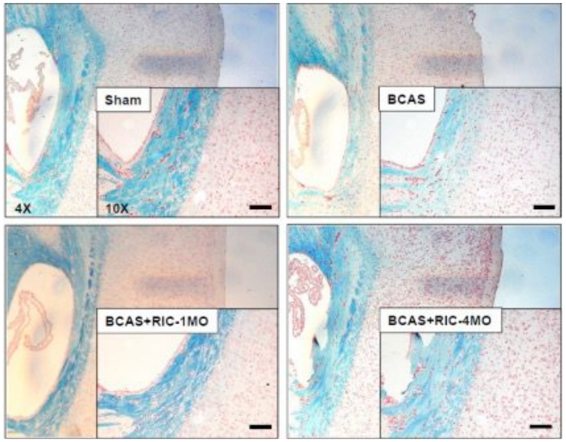
Increased CBF



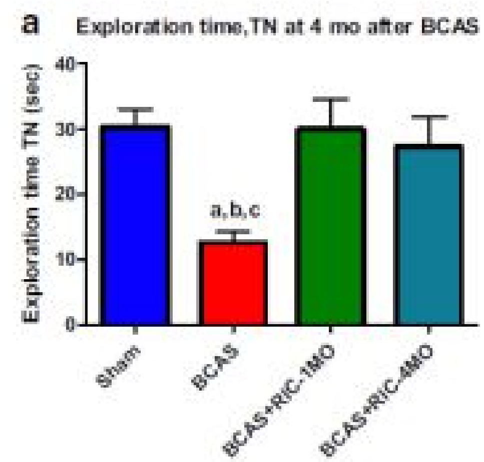
Increased Capillary Density



Increased Myelin



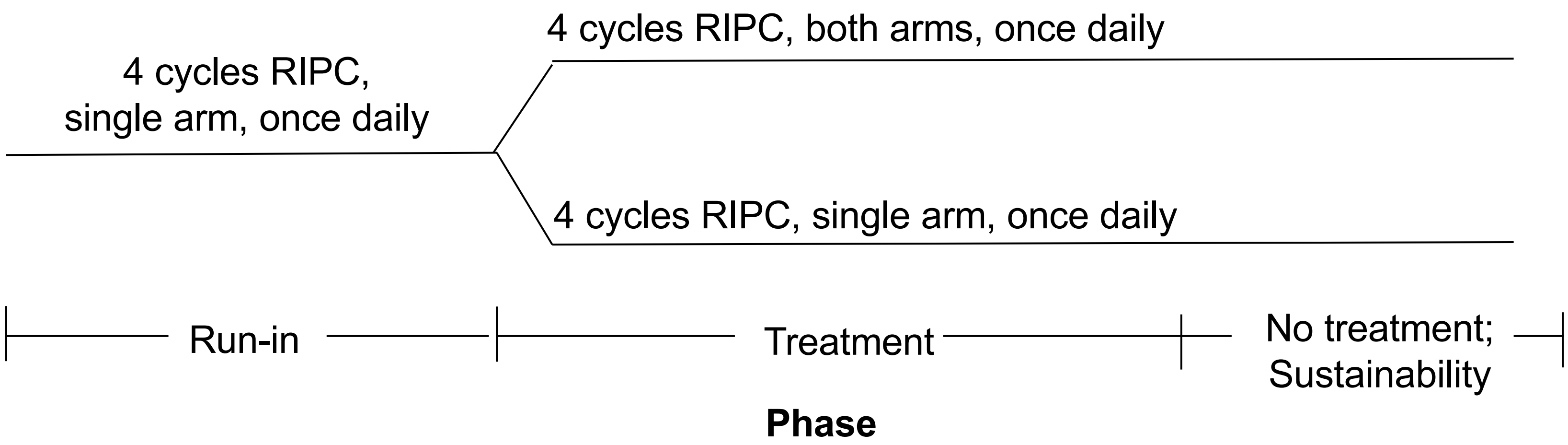
Increased Exploration Time



Khan MB, et al. Transl Stroke Res 2018;9:51-63.

TRIC-VCI Protocol

Visit	Screening	Random-ization	Phone	Phone	End Treatment	End
Time	-14	0	2±1	15±2	30±2	90±2
Measurements	Eligibility	Feasibility Safety/tolerability Efficacy			Feasibility Safety/tolerability Efficacy	Efficacy



Key Inclusion Criteria

Inclusion Criteria		Operationalized as:
	1. Evidence of cerebral small vessel disease on CT or MRI	Evidence of either: 1. Beginning confluent WMH (ARWMC grade 2) on any slice on CT or MRI OR 2. Two or more supratentorial subcortical infarcts
	2. Objective evidence of cognitive impairment	MoCA score ≤24
	3. Concern on the part of the patient, caregiver, or clinician that there has been a decline from previous level of cognitive functioning,	AD8 questionnaire (administered to informant) with 2 or more positive responses, or clinical judgement based on self report of participant or observations by examiner
	4. Independent with basic daily activities of living	Bristol Activities of Daily Living Scale response a) for questions 2, 4, 5, 6, 7, 8, 9, and 14.

Device

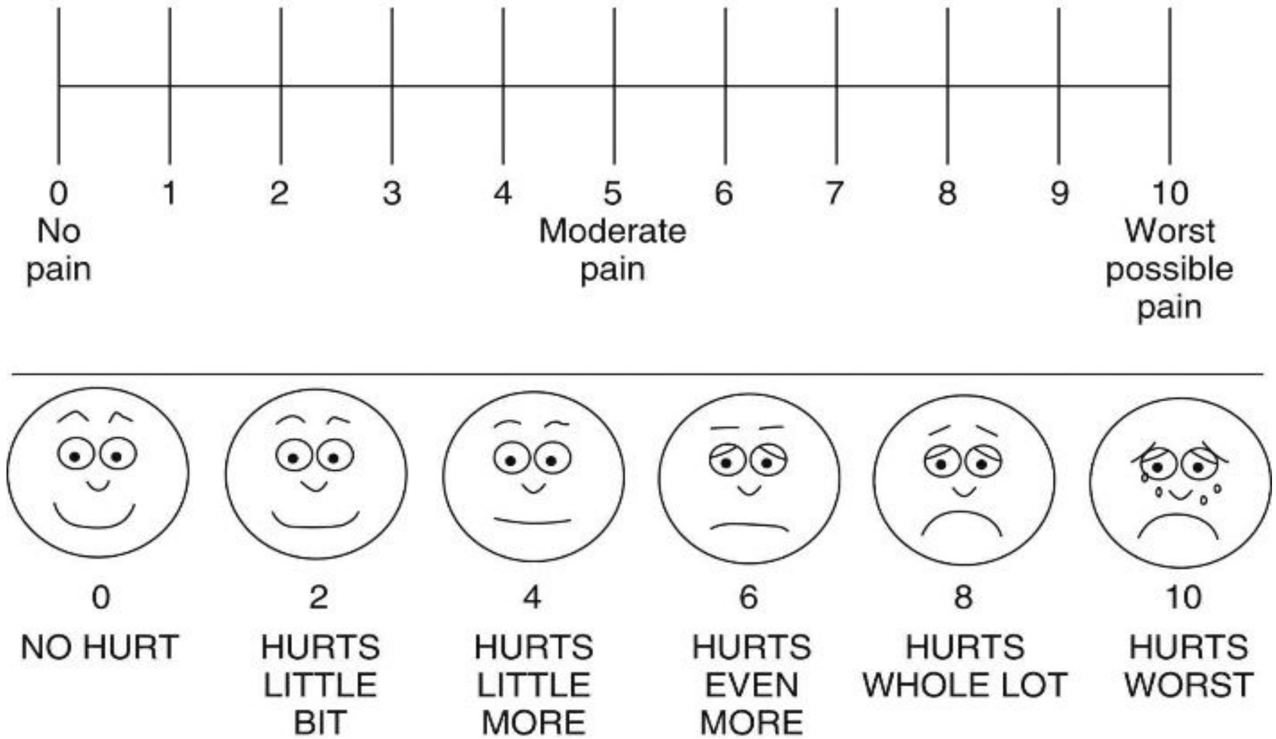
- Non-commercial device sold by Seagull Company, Denmark.
- Blood pressure measurement, programmable to apply cycles of cuff inflation and deflation.
- Plan: 4 cycles of 5 minutes cuff inflation to 35 mmHg above systolic BP followed by 5 minutes deflation.

Primary Outcome

- Proportion completing ≥80% of the assigned sessions.

Safety and Tolerability Outcomes

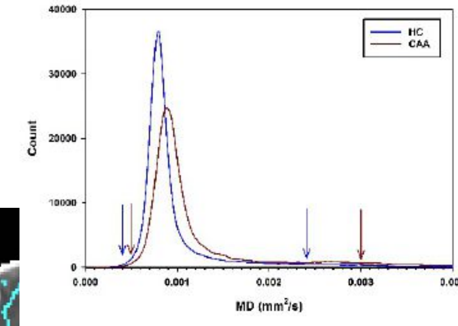
Outcome	
Tolerability	Drop out rate
	Compliance
Safety	Arm injury
	Pain (visual analog scale)

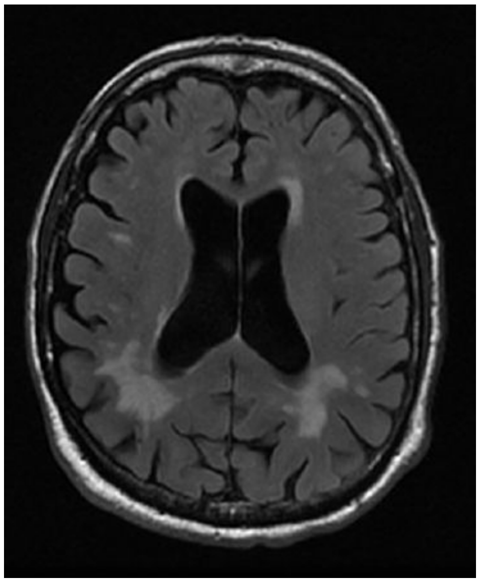


Secondary Efficacy Outcomes

Outcome
Change in cerebral blood flow (ASL MRI)
Change in MRI WMH volume
Change in MRI DTI PSMD
Change in Montreal Cognitive Assessment
Change in Trail Making A and B
Change in Neuropsychiatric symptoms (Mild Behavioural Impairment Tracking Tool)
Change in activities of daily living (Bristol scale)

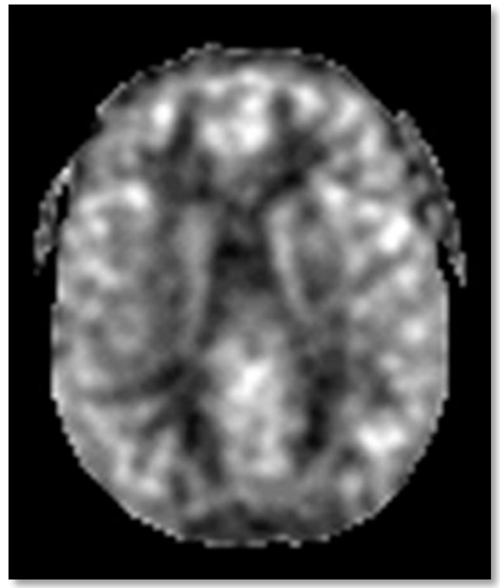
MRI Biomarkers





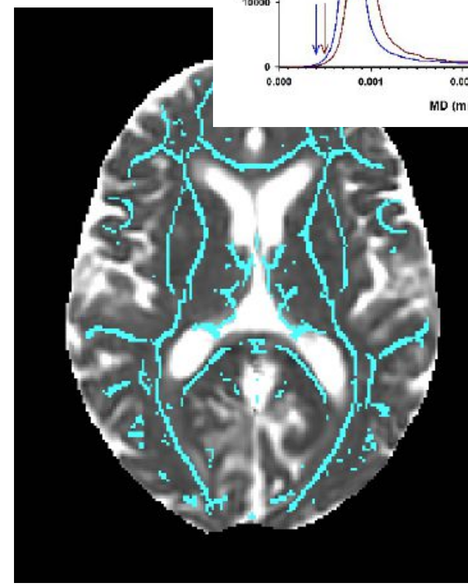
WMH Growth

FLAIR



Cerebral blood flow

ASL MRI

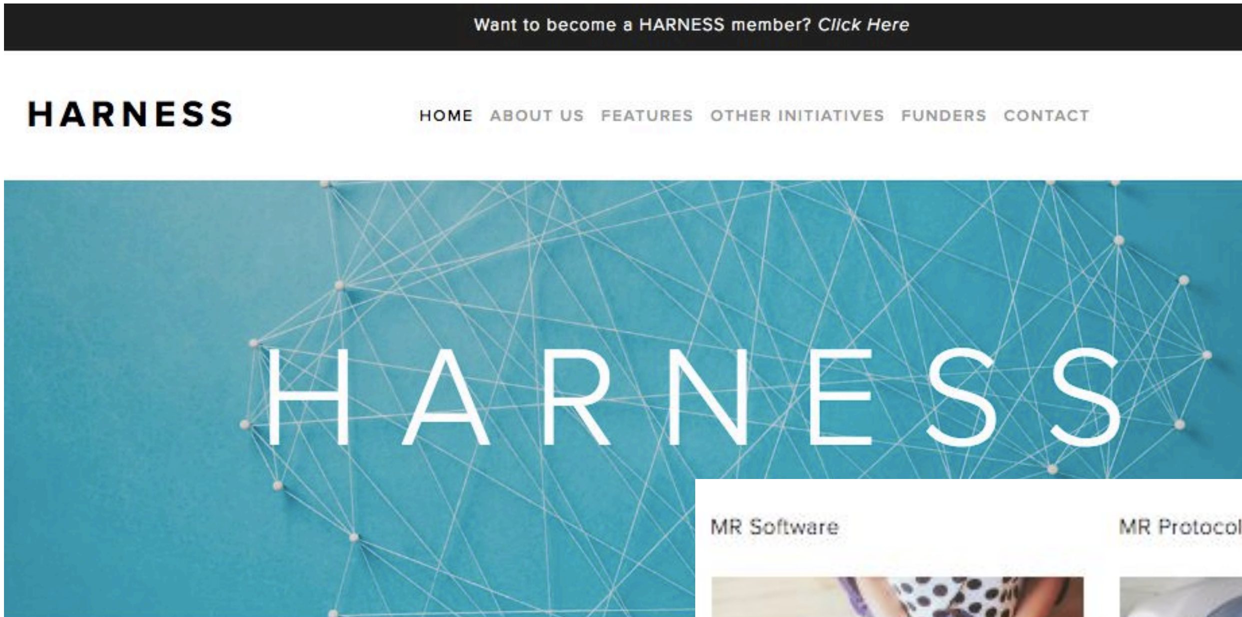


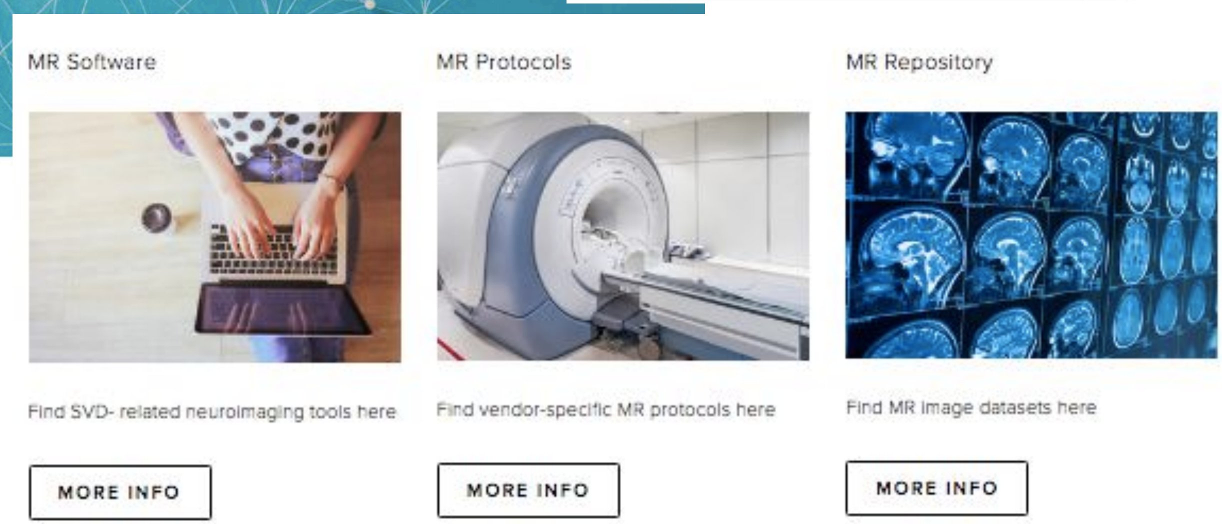
White Matter Disruption

DTI Peak Skeletonized

Mean Diffusivity

Harmonizing MRI Methods





JPND research
EU Joint Programme – Neurodegenerative Disease Research

www.harness-neuroimaging.org

Smith EE, et al. Harmonizing brain magnetic resonance imaging methods for vascular contributions to neurodegeneration. Alzheimer's & Dementia: DADM 2019;11:191-204.

Thank You

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