Lacunar Stroke

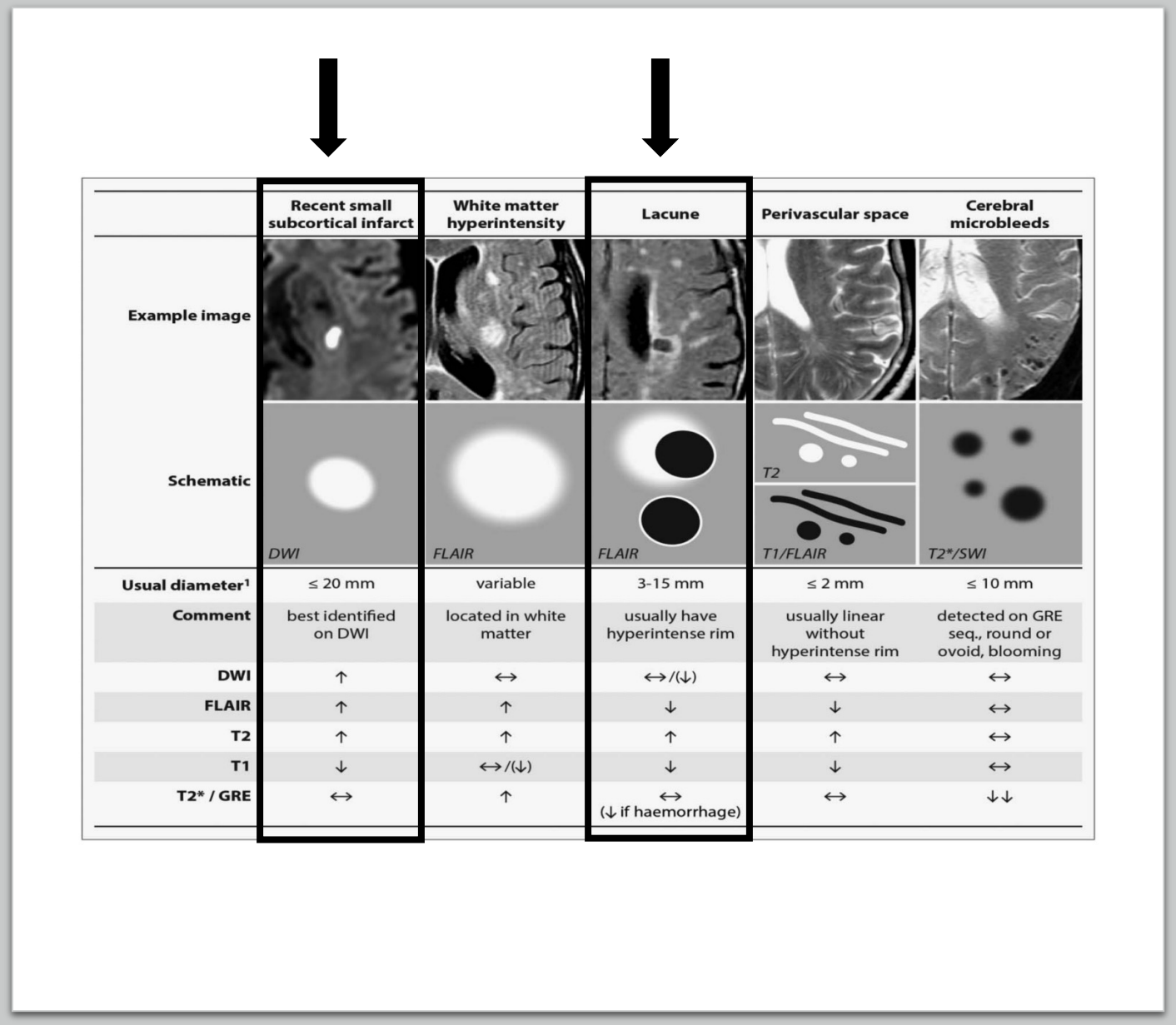
Outline

1. Definition
2. Pathology
3. Epidemiology
4. Clinical Syndromes
5. Diagnosis
6. Management Considerations
7. Prognosis

Cerebral Small Vessel Disease

- Various pathologies affecting small arteries, arterioles, capillaries, and venules
  - Arteriolosclerosis
  - Genetic, inflammatory / immune, other

- Small cortical arteries/arterioles + penetrating arteries

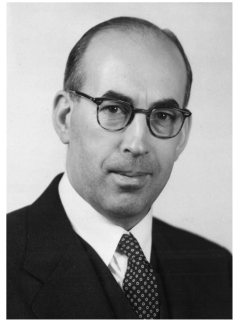


	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleeds
Example image					
Schematic	DWI	FLAIR	FLAIR	T2 / T1/FLAIR	T2*/SWI
Usual diameter[1]	≤ 20 mm	variable	3-15 mm	≤ 2 mm	≤ 10 mm
Comment	best identified on DWI	located in white matter	usually have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

Stroke Vasc Neurol. 2016 Oct 25;1(3):83-92.

History

- 1838: Lacune → lacuna (Latin: cavity)
  - *état criblé* → enlarged spaces in WM
- 1901: Pierre Marie & Ferrand → capsular, lenticular, and pontine infarction
- Mid-20th century: C. Miller Fisher → clinicopathologic characterization
  - Clinical syndromes
  - Lipohyalinosis



Gazette Médicale

DE PARIS.

SOMMAIRE.

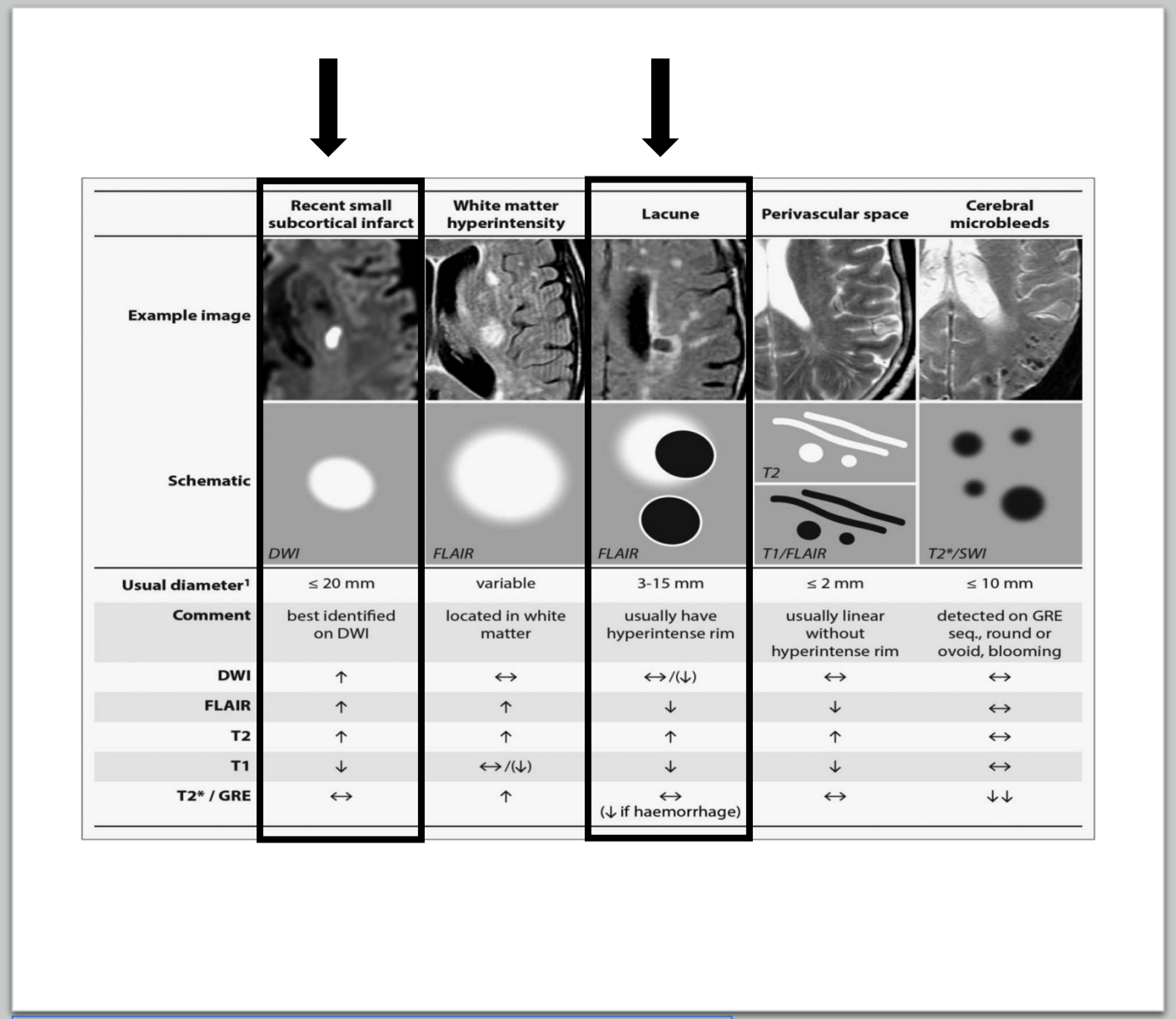
PATHOLOGIE INTERNE.

MÉMOIRE SUR LA CURABILITÉ DU RAMOLLISSEMENT CÉRÉBRAL; par A. Decharme, ancien interne à la Salpêtrière.

Neurology Jan 1986, 36 (1) 85.
J Stroke Cerebrovasc Dis. 2019 Aug;28(8):2079-2097.
Neurology. 1965 Aug;15:774-84.

Evolution of the Definition

- Lacune (neuropathologic term: cavitation from small deep brain infarct) → lacunar infarct (precavitary phase)
- Lacunar stroke (clinical entity) & lacunar syndrome (neurologic features)
- **ST**andards for **R**eport**I**ng **V**ascular changes on n**E**uroimaging (STRIVE)



	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleeds
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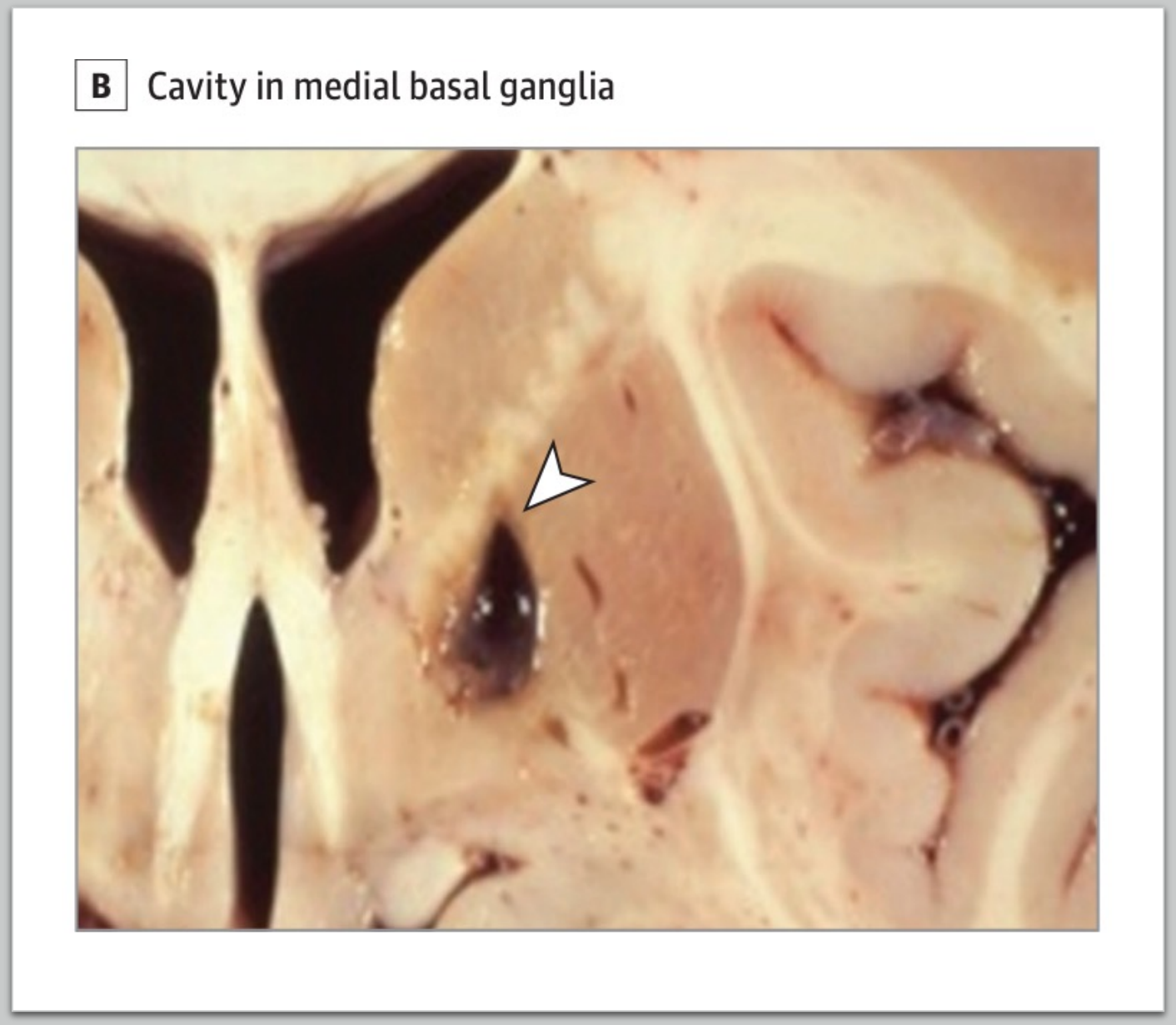
FLAIR	↑	↑	↓	↓	↔
T2	↑	↑	↑	↑	↔
T1	↓	↔/(↓)	↓	↓	↔
T2* / GRE	↔	↑	↔ (↓ if haemorrhage)	↔	↓↓

Cerebrovasc Dis 1991;1:311–320.
Lancet Neurol. 2013 Aug;12(8):822-38.

Location

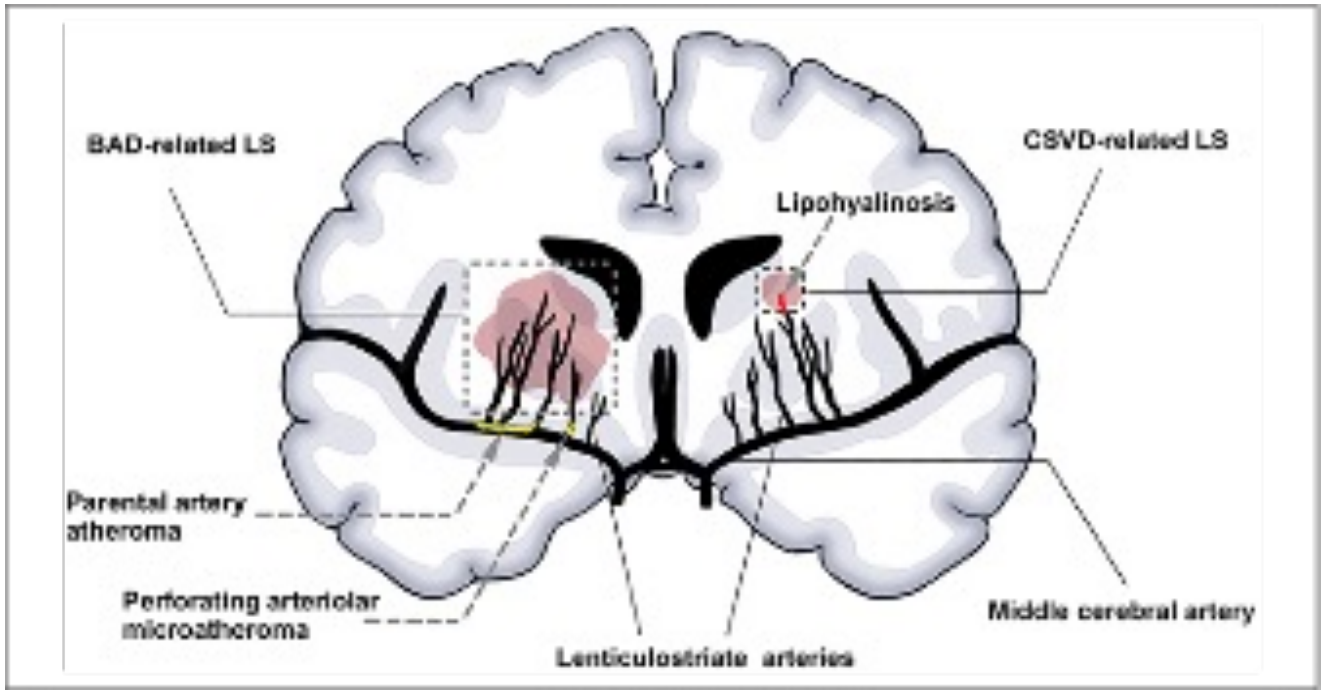
- Basal ganglia (putamen), thalamus, WM – IC, pons
  - WM of cerebral gyri
- Lenticulostriate, thalamoperforating, paramedian branches
  - Small size (diameter 40 - 900 μm)
  - Proximal origin
  - Lack of collateral circulation



JAMA Neurol. 2018 Oct 1;75(10):1273-1281.

Vascular Pathology

- Microangiopathy – arterial media thickening
  - Arteriolosclerosis (40-150 µm)
  - Lipohyalinosis / fibrinoid necrosis (40-200 µm)
- Branch atheromatous disease (200-800 µm)
  - Parent large artery
  - Ostium or proximal segment of penetrator



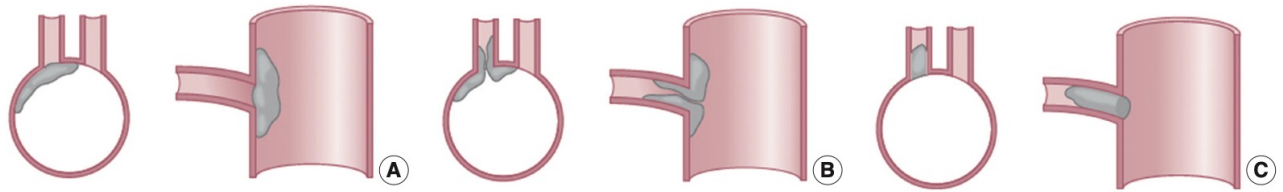
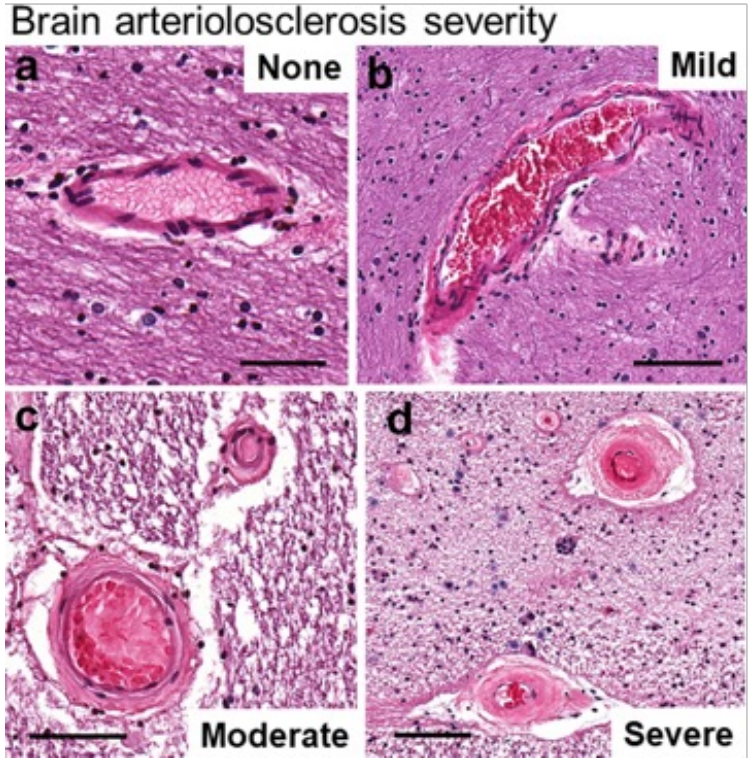
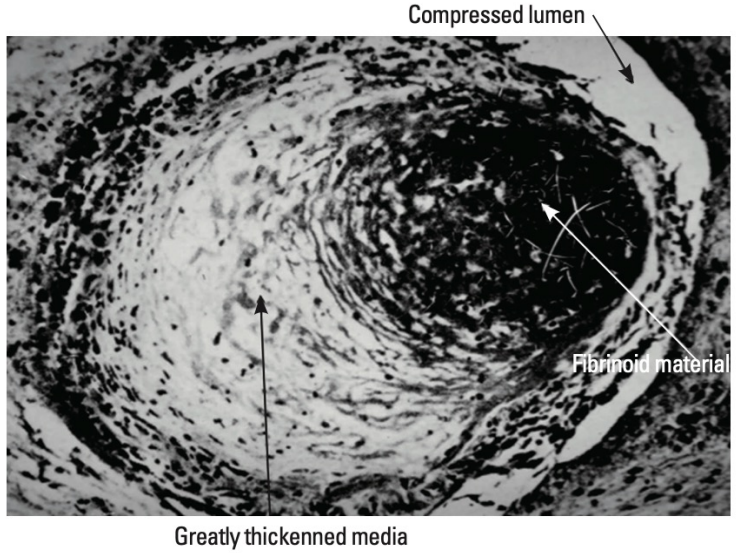


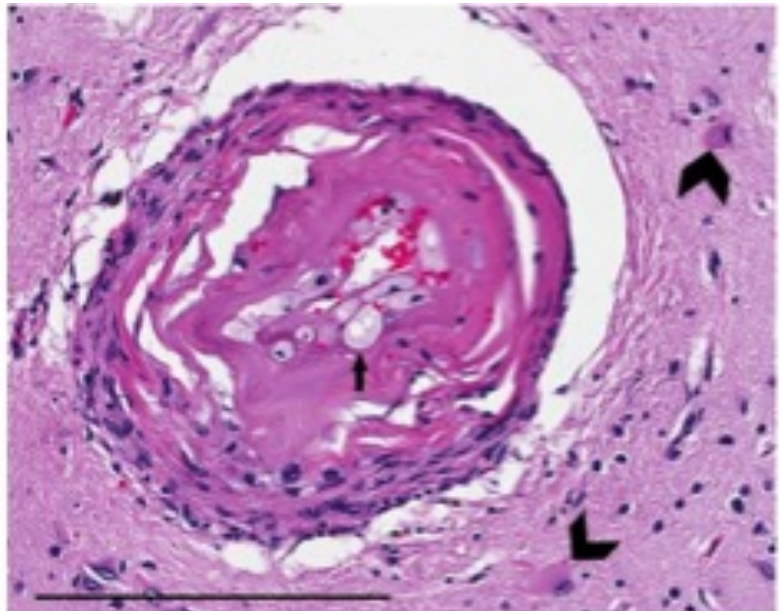
Figure 3. Drawing showing the arterial pathology in atheromatous branch disease: (A) plaque in parent artery obstructing a branch, (B) junctional plaque extending into the branch, (C) microatheroma formed at the orifice of a branch.

Cerebrovasc Dis. 2021;50(5):588-596.
Stroke. 2015 Jan;17(1):2-6.

Arteriolosclerosis & Lipohyalinosis







Acta Neuropathol. 2021 Jan;141(1):1-24.
Neuropathol Appl Neurobiol. 2018 Apr;44(3):247-266.

Branch Atheromatous Disease

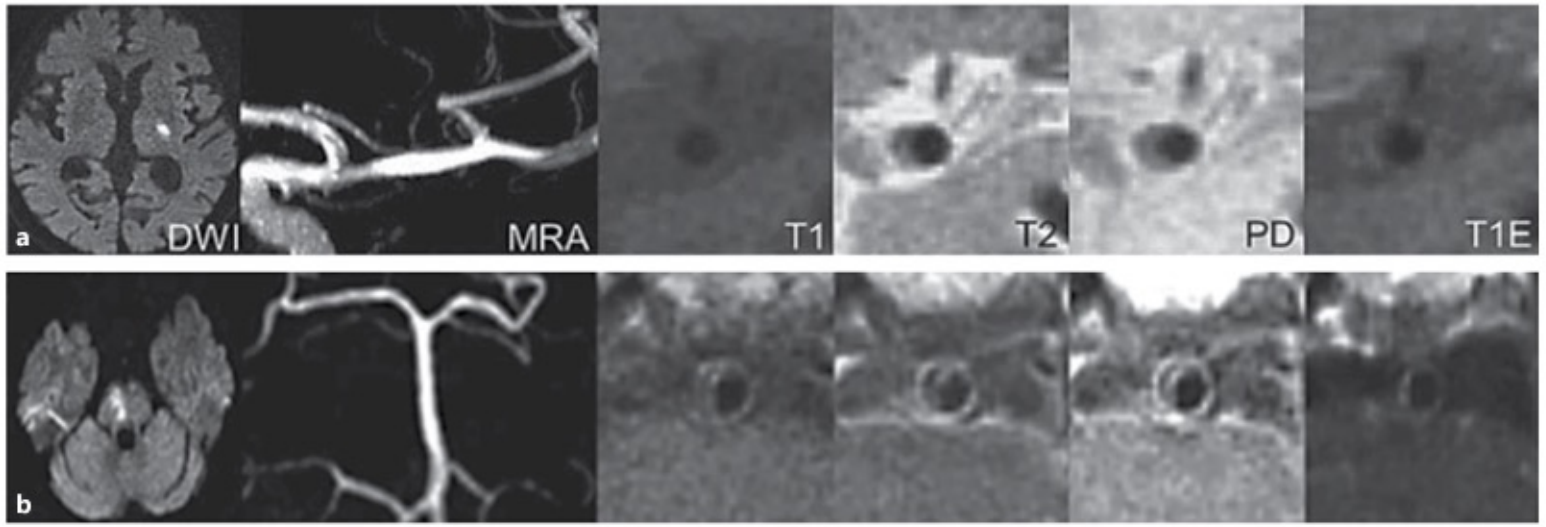
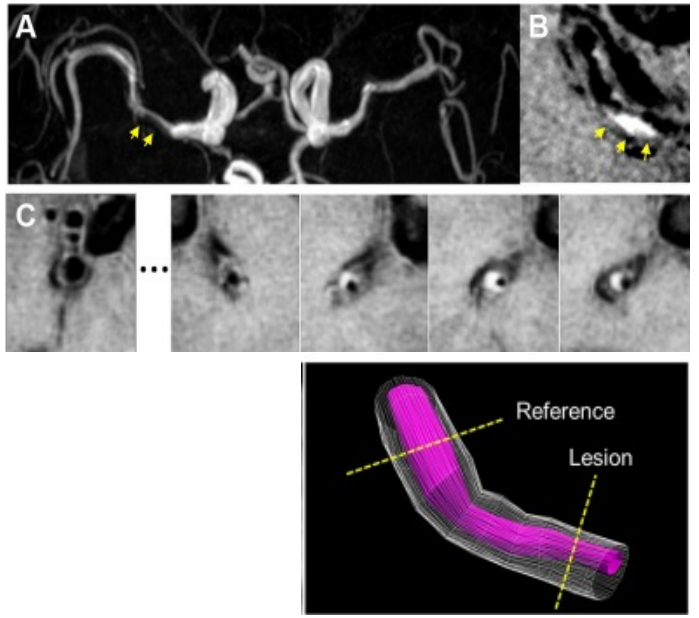
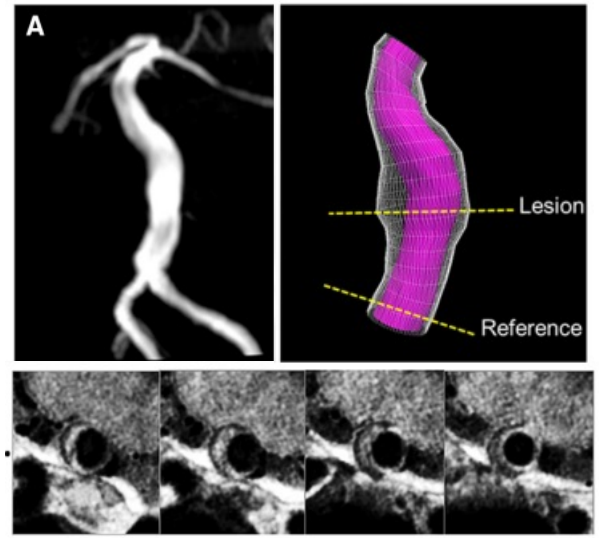


Fig. 3. HR MRI findings of BAD-related infarct and branch atheromatous plaque in the middle cerebral artery (**a**) and in the basilar artery (**b**).





Cerebrovasc Dis. 2016;41(1-2):87-95.
Hypertension. 2021 Jan;77(1):135-146.

Embolism

- Embolism
  - Causal relationship unclear
- Carotid stenosis & cardiac sources of embolism
  - Lacunar infarction < cortical infarction

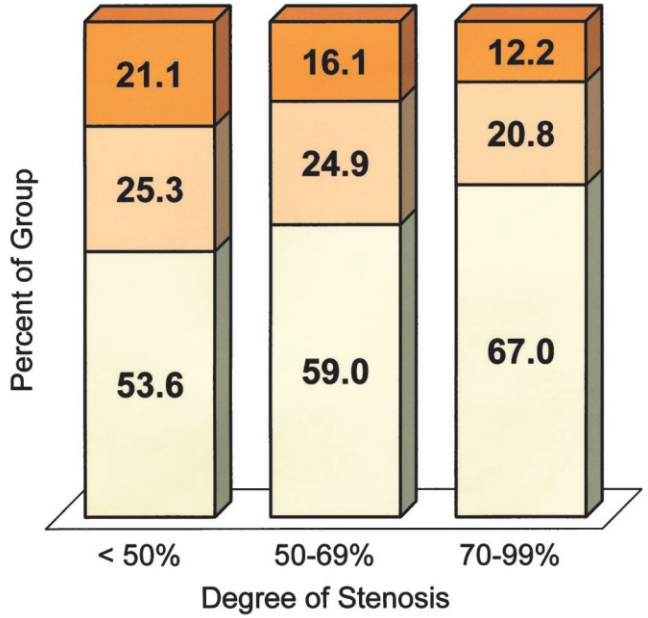


Figure 2. Relationship between category of stroke and degree of internal carotid artery (ICA) stenosis. Lacunar stroke was more likely to occur in patients with milder degrees of ICA stenosis than with severe (70 to 99%) stenosis. Probable lacunar (top)— possible lacunar (middle)—non-lacunar (bottom).

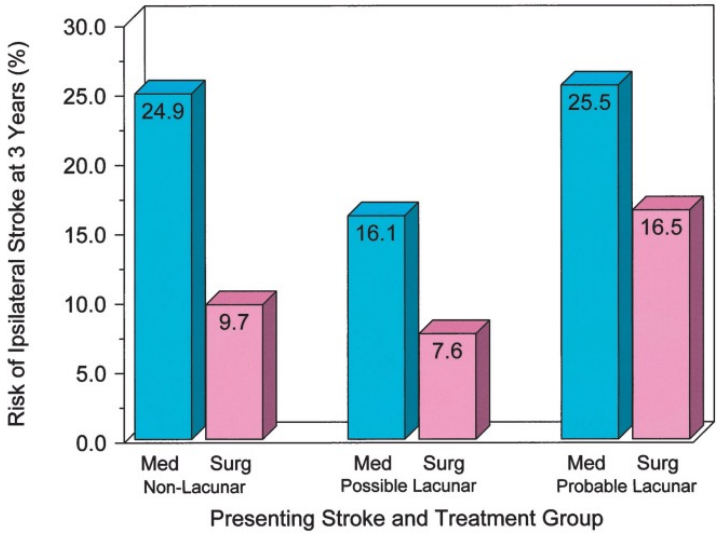
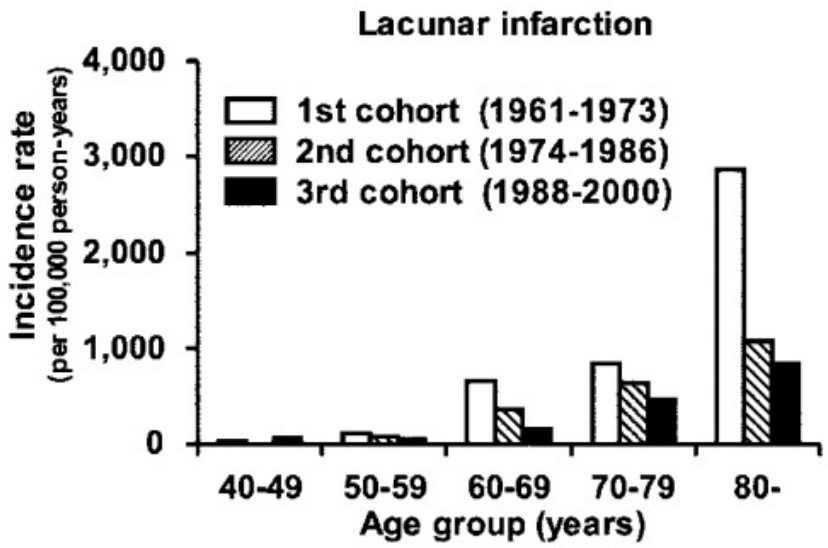


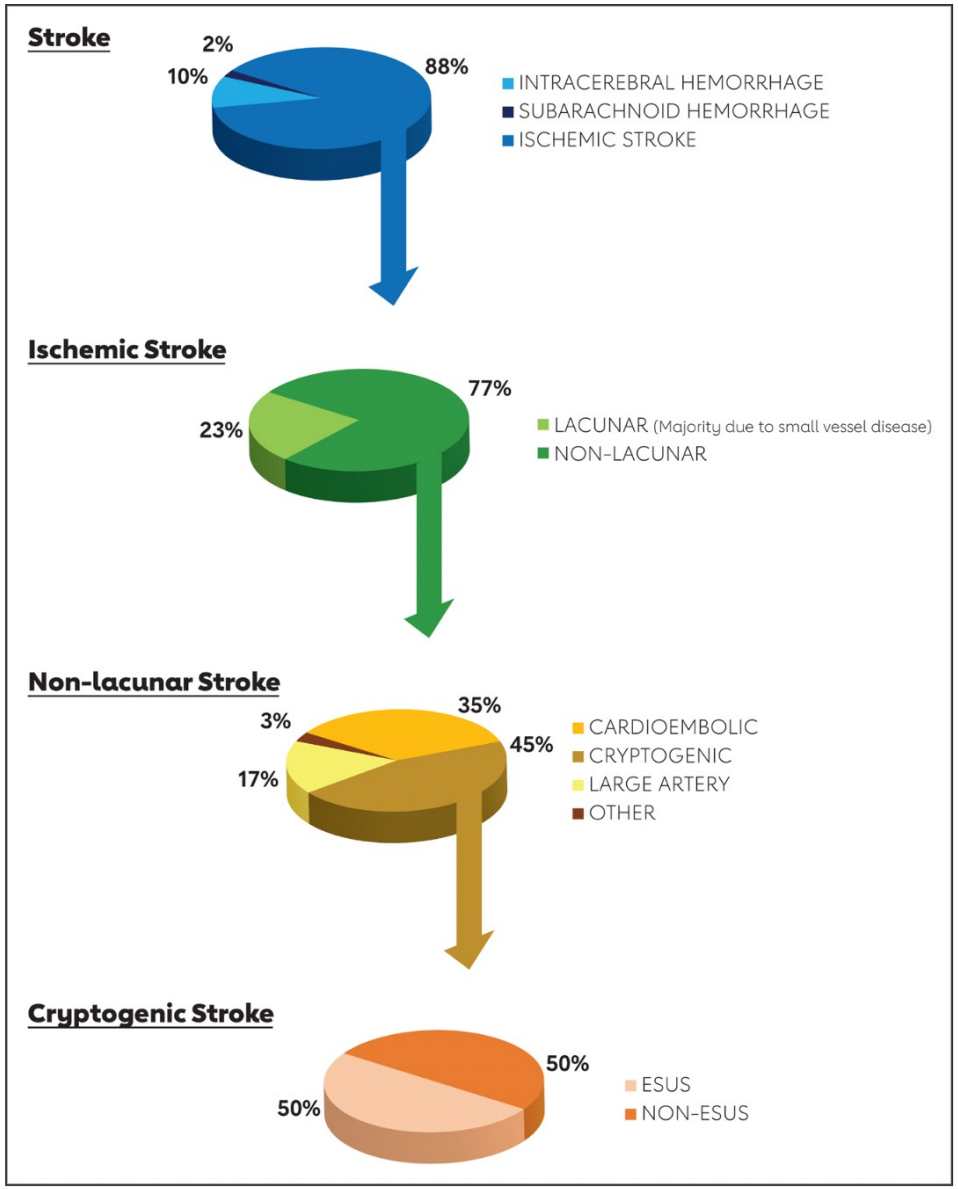
Figure 4. Risk of ipsilateral stroke at 3 years by presenting stroke category and treatment group for patients with 50 to 99% internal carotid artery stenosis. The numbers of patients represented in each bar, from left to right, are 172, 160, 57, 69, 41, and 38. Med = medically treated; Surg = surgically treated.

Stroke. 1991 Oct;22(10):1236-41.
Stroke. 1991 Feb;22(2):175-81.
Neurology. 2000 Feb 8;54(3):660-6.

Epidemiology

- ~ ¼ of ischemic stroke
- GCNKSS: incidence ↑ in Black Americans





Stroke. 2021 Jul;52(7):e364-e467.
Stroke. 1999 Dec;30(12):2517-22.
Neurology. 2006 May 23;66(10):1539-44.

Risk Factors

- Shared with other IS subtypes
- Age, Hypertension, Diabetes, Tobacco use
  - LDL-C, hyperhomocystinemia

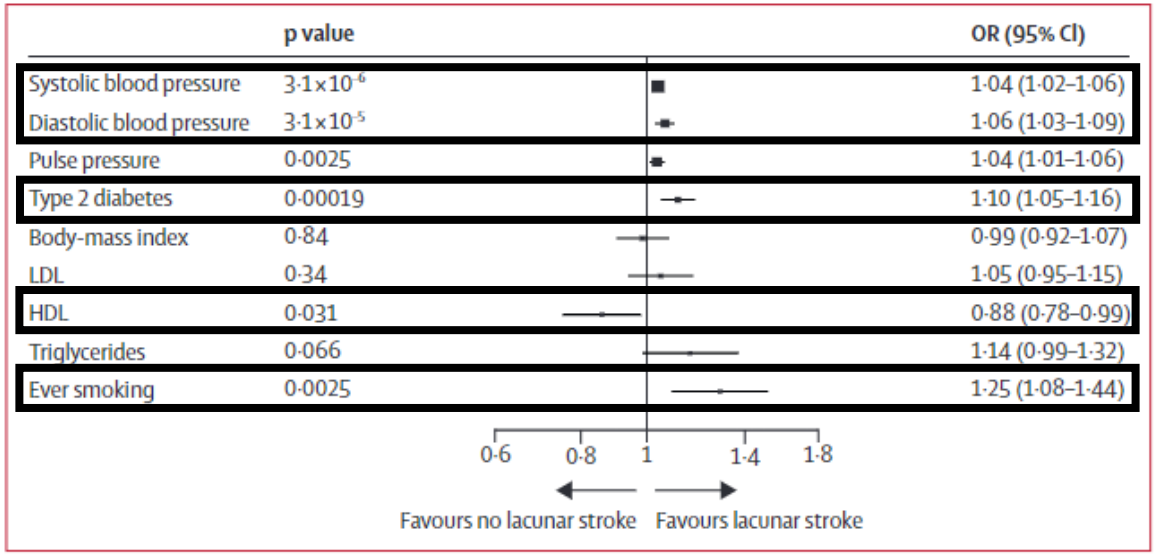


Figure 4: **Associations between genetically proxied cardiovascular risk factors and lacunar stroke from mendelian randomisation analysis using the inverse variance weighted method**
Estimates are presented as ORs per genetically proxied increase in each risk factor (original scale). OR=odds ratio.

Stroke. 2005 Apr;36(4):891-901.
Lancet Neurol. 2021 May;20(5):351-361.

Genetics

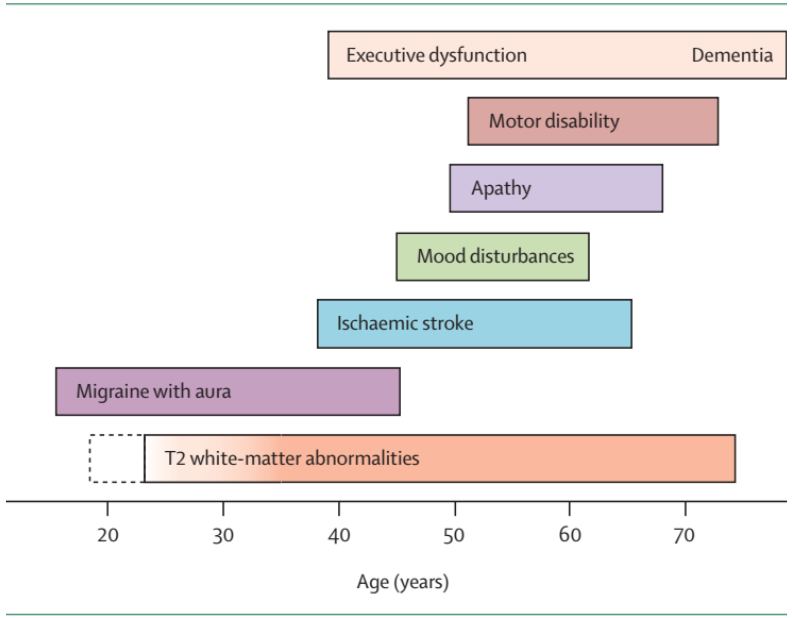
	Chromosome	Base position*	Genomic context	Identifier	RA/OA	RAF	Lacunar stroke (European: 6030 cases, 219 389 controls)			Lacunar stroke (transethnic: 7338 cases, 225 258 controls)	
							OR (SE)	p value	Studies	OR (SE)	p value
Genome-wide significance for lacunar stroke											
ICA1L-WDR12-CARF-NBEAL1†	2	203 968 973	Intronic	rs72934535	T/C	0·89	1·25 (0·04)	$3·7 \times 10^{-9}$	12	1·22 (0·04)	$5·2 \times 10^{-8}$
ULK4†	3	41 839 370	Intronic	rs4621303	T/A	0·83	1·15 (0·03)	$1·7 \times 10^{-7}$	14	1·16 (0·03)	$6·4 \times 10^{-9}$
SPI1-SLC39A13-PSMC3-RAPSN	11	47 434 986	Exonic	rs2293576	G/A	0·67	1·14 (0·02)	$7·2 \times 10^{-10}$	14	1·14 (0·02)	$6·0 \times 10^{-10}$
ZCCHC14	16	87 575 332	Intergenic	rs12445022	A/G	0·34	1·13 (0·02)	$2·5 \times 10^{-8}$	13	1·12 (0·02)	$9·0 \times 10^{-8}$
ZBTB14-EPB41L3	18	5 389 832	Intergenic	rs9958650	G/A	0·10	1·18 (0·03)	$9·9 \times 10^{-7}$	12	1·19 (0·03)	$2·4 \times 10^{-8}$
Genome-wide significance in multi-trait analysis											
SLC25A44-PMF1-BGLAP†	1	156 197 380	Intronic	rs2984613	C/T	0·64	1·10 (0·02)	$2·5 \times 10^{-5}$	13	1·09 (0·02)	$1·4 \times 10^{-5}$
LOX-ZNF474-LOC100505841	5	121 518 378	Downstream	rs2303655	T/C	0·81	1·14 (0·03)	$3·6 \times 10^{-5}$	11	1·12 (0·03)	0·00014
FOXF2-FOXQ1	6	1 366 718	Intergenic	rs7766042	C/T	0·11	1·17 (0·03)	$3·7 \times 10^{-6}$	11	1·18 (0·03)	$1·2 \times 10^{-6}$
VTA1-GPR126	6	142 562 417	Intergenic	rs225744	C/T	0·77	1·11 (0·03)	$3·5 \times 10^{-5}$	12	1·09 (0·02)	0·00050
SH3PXD2A	10	105 447 838	Intronic	rs61000833	T/C	0·60	1·10 (0·02)	$1·7 \times 10^{-5}$	12	1·07 (0·02)	0·0024
HTRA1-ARMS2	10	124 233 181	Intronic	rs79043147	T/C	0·07	1·21 (0·04)	$3·2 \times 10^{-6}$	11	1·22 (0·04)	$1·1 \times 10^{-6}$
COL4A2	13	111 040 681	Intronic	rs11838776	A/G	0·29	1·11 (0·02)	$4·3 \times 10^{-6}$	12	1·11 (0·02)	$1·6 \times 10^{-6}$

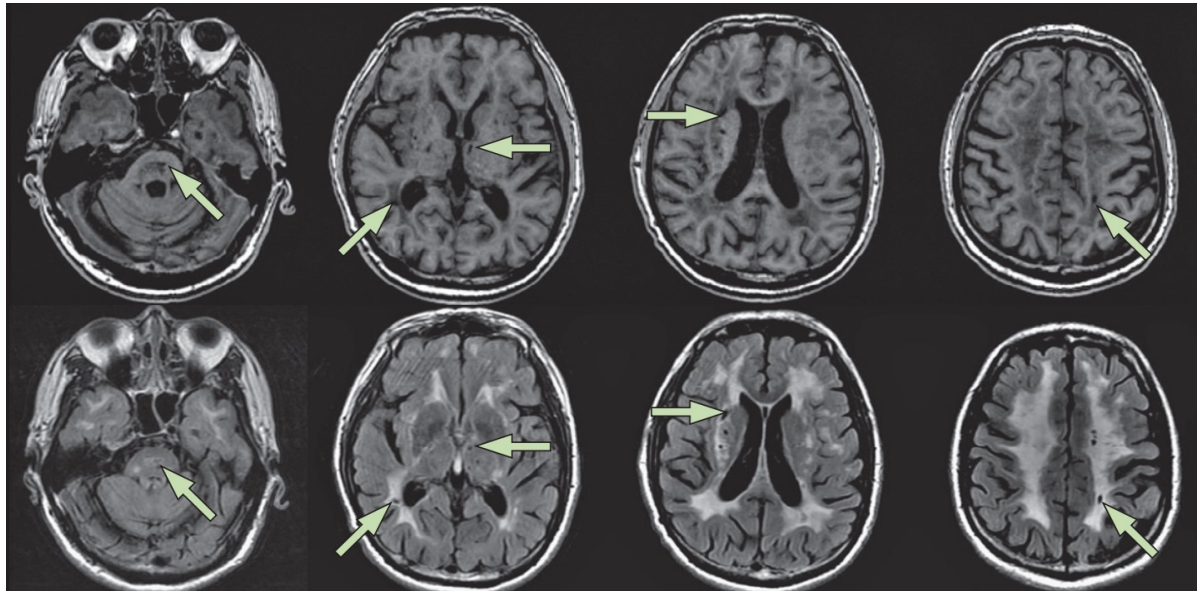
- ECM disruption, pericyte differentiation, TGF-β signaling, myelination
- Overlap with WMH
- Monogenic small vessel stroke
  - HTRA1
  - COL4A2

Stroke. 2015 Sep;46(9):2407-12.
Lancet Neurol. 2021 May;20(5):351-361.

Monogeneic Disorders

- CADASIL (cerebral AD arteriopathy w/ subcortical infarcts & leukoencephalopathy)
  - NOTCH3
- CARASIL
  - HTRA1
  - alopecia, spondylosis
- RVCL-S (retinal vasculopathy w/ cerebral leukodystrophy & systemic manifestations)
  - TREX1
  - Raynaud's, cirrhosis, renal dysfunction, osteonecrosis





BMC Med. 2017 Feb 24;15(1):41.

Clinical Syndromes

- Pure motor hemiparesis
- Pure sensory syndrome
- Sensorimotor syndrome
- Dysarthria-clumsy hand syndrome
- Ataxic hemiparesis

- Lack cortical findings

* Moderate-High PPV for radiological lacunar infarct

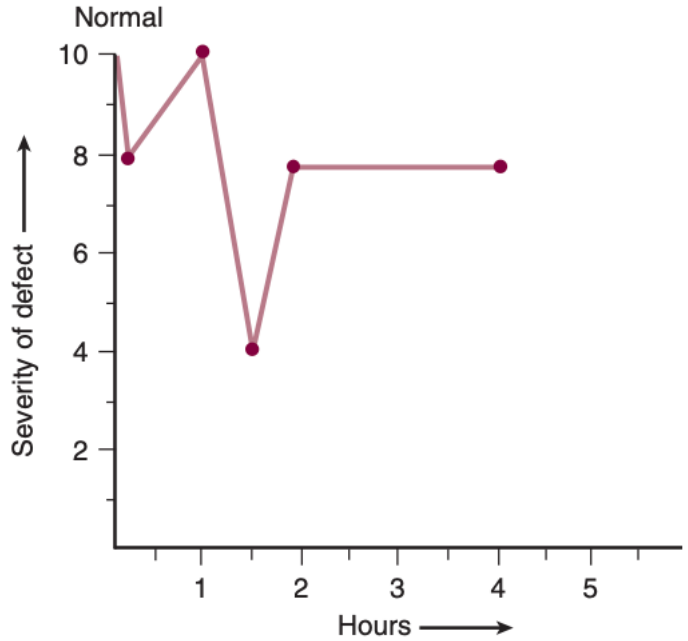
Modified pure motor hemiparesis with motor aphasia
Pure motor hemiparesis sparing face
Mesencephalo-thalamic syndrome
Thalamic dementia
Pure motor hemiparesis with horizontal gaze palsy
Pure motor hemiparesis with crossed third-nerve palsy (Weber syndrome)
Pure motor hemiparesis with crossed sixth-nerve palsy
Pure motor hemiparesis with confusion
Cerebellar ataxia with crossed third-nerve palsy (Claude syndrome)
Hemiballismus
Lower basilar branch syndrome -- dizziness, diplopia, gaze palsy, dysarthria, cerebellar ataxia, trigeminal numbness
Lateral medullary syndrome
Lateral pontomedullary syndrome
Locked-in syndrome (bilateral pure motor hemiparesis)
Pure dysarthria
Acute dystonia of thalamic origin
Lacunar state

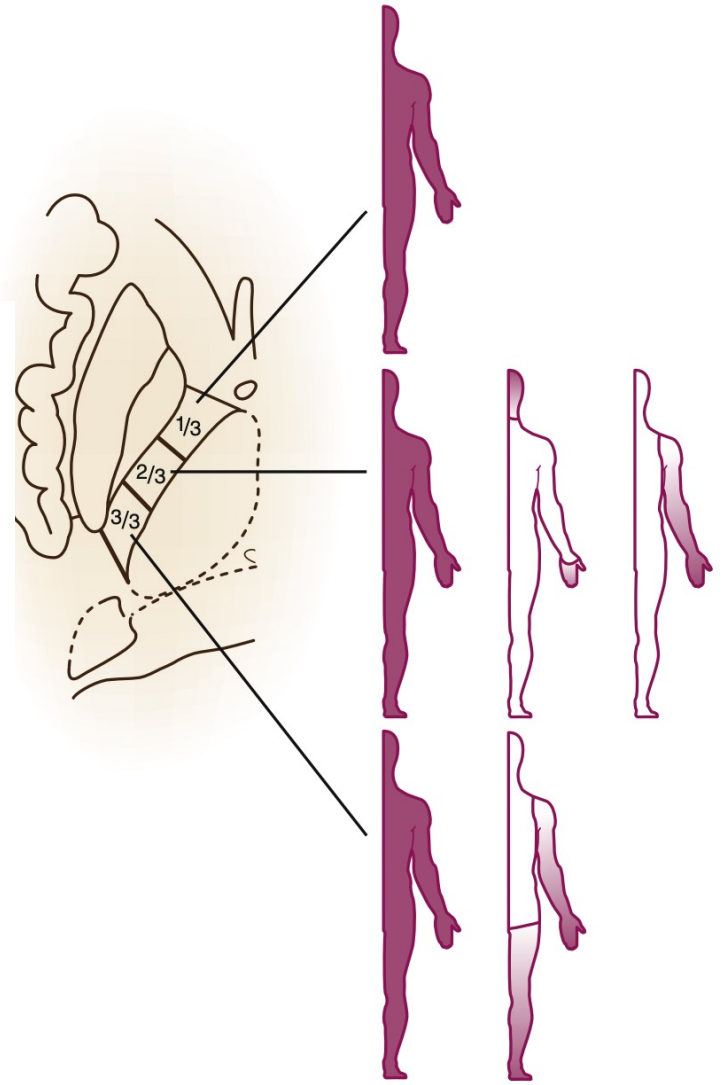
Neurology. 1982 Aug;32(8):871-6.
Neurology. 1997 May;48(5):1204-11.
Stroke. 2004 Jun;35(6):1430-5.

Pure Motor Hemiparesis

- Face / Arm / Leg
- Internal capsule, pons > corona radiata, medullary pyramid
- PPV: 52-85%

* Preceding TIA: “capsular warning syndrome”





Stroke: Pathophysiology, Diagnosis, and Management, 7th Edition
Caplan’s Stroke, 5th Edition
Stroke. 1991;22:175–181.

Pure Sensory Syndrome

- Face / Arm / Leg
- Thalamus > pons, corona radiata
- PPV: 95-100%

* Midline extension

* Cheiro-oral, cheiro-oral-pedal syndrome

* Central post-stroke pain

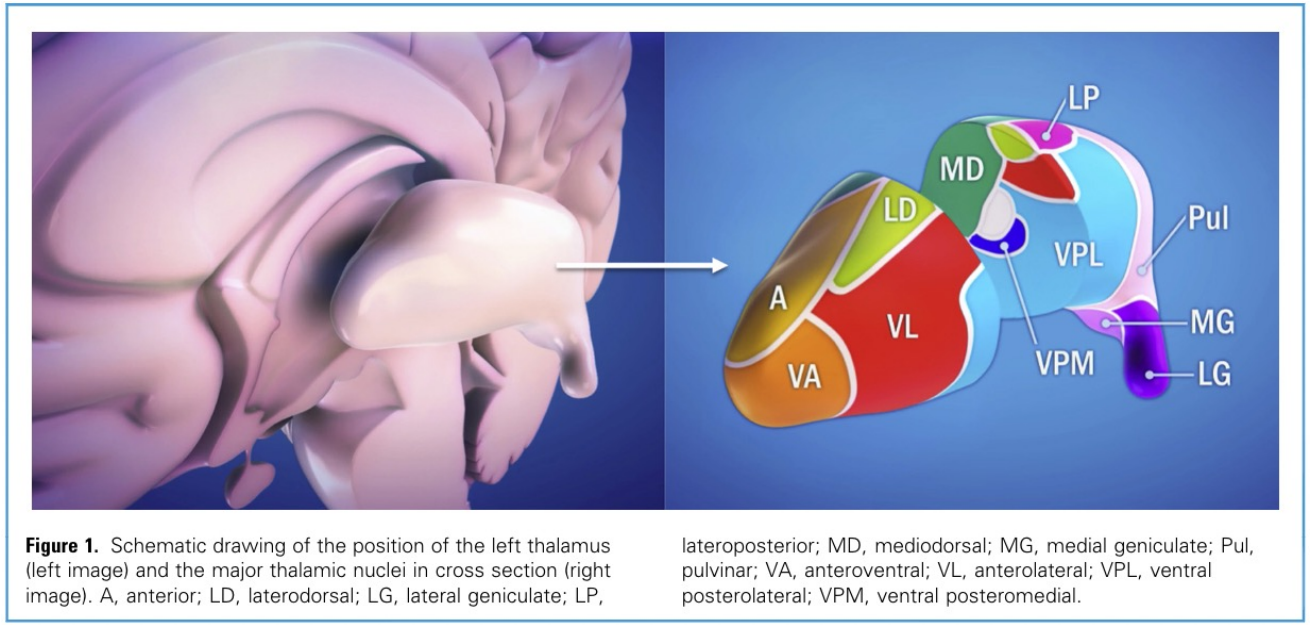
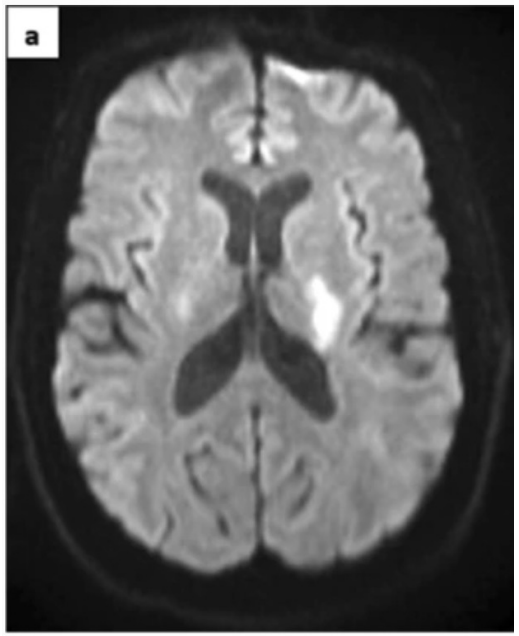


Figure 1. Schematic drawing of the position of the left thalamus (left image) and the major thalamic nuclei in cross section (right image). A, anterior; LD, laterodorsal; LG, lateral geniculate; LP, lateroposterior; MD, mediodorsal; MG, medial geniculate; Pul, pulvinar; VA, anteroventral; VL, anterolateral; VPL, ventral posterolateral; VPM, ventral posteromedial.

Neurosurg. 2020 May;137:310-318.

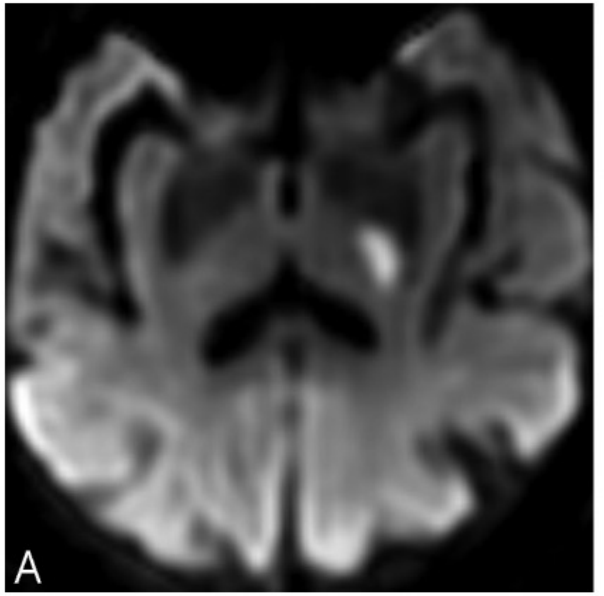
Sensorimotor Syndrome

- Face / Arm / Leg
- Thalamocapsular > pons, medulla
- PPV: 51-87%



Dysarthria-Clumsy Hand Syndrome

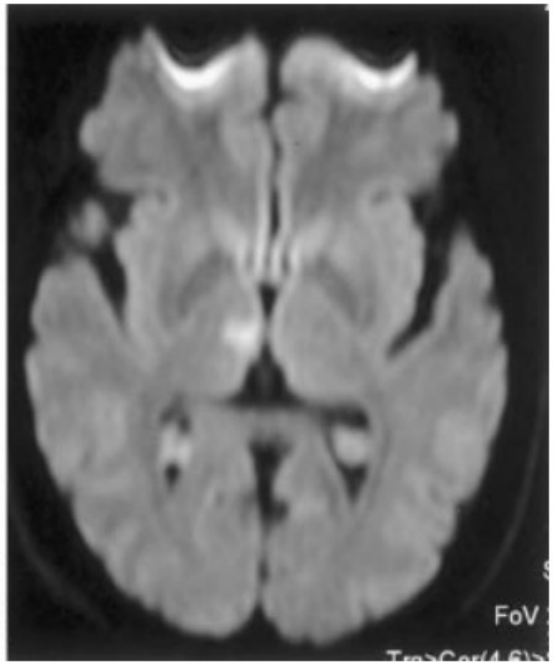
- Dysarthria, Hand Ataxia / Paresis + Ipsilateral Facial Paresis, Dysphagia
- Internal capsule > basal pons, corona radiata
- PPV: 96%



Emerg Radiol. 2021 Oct;28(5):985-992.
AJNR Am J Neuroradiol. 2010 Aug;31(7):1266-7.

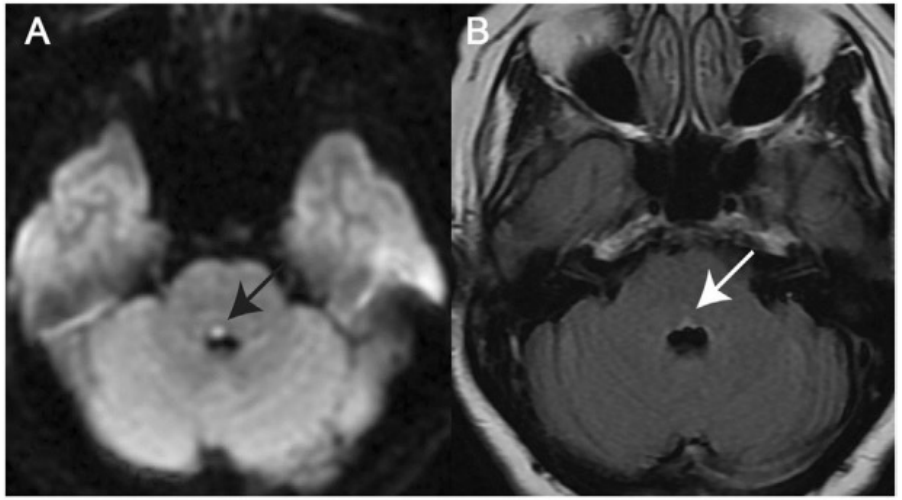
Ataxic Hemiparesis

- Ipsilateral limb ataxia > paresis
- Internal capsule, pons > corona radiata, thalamus
- PPV: 59-95%



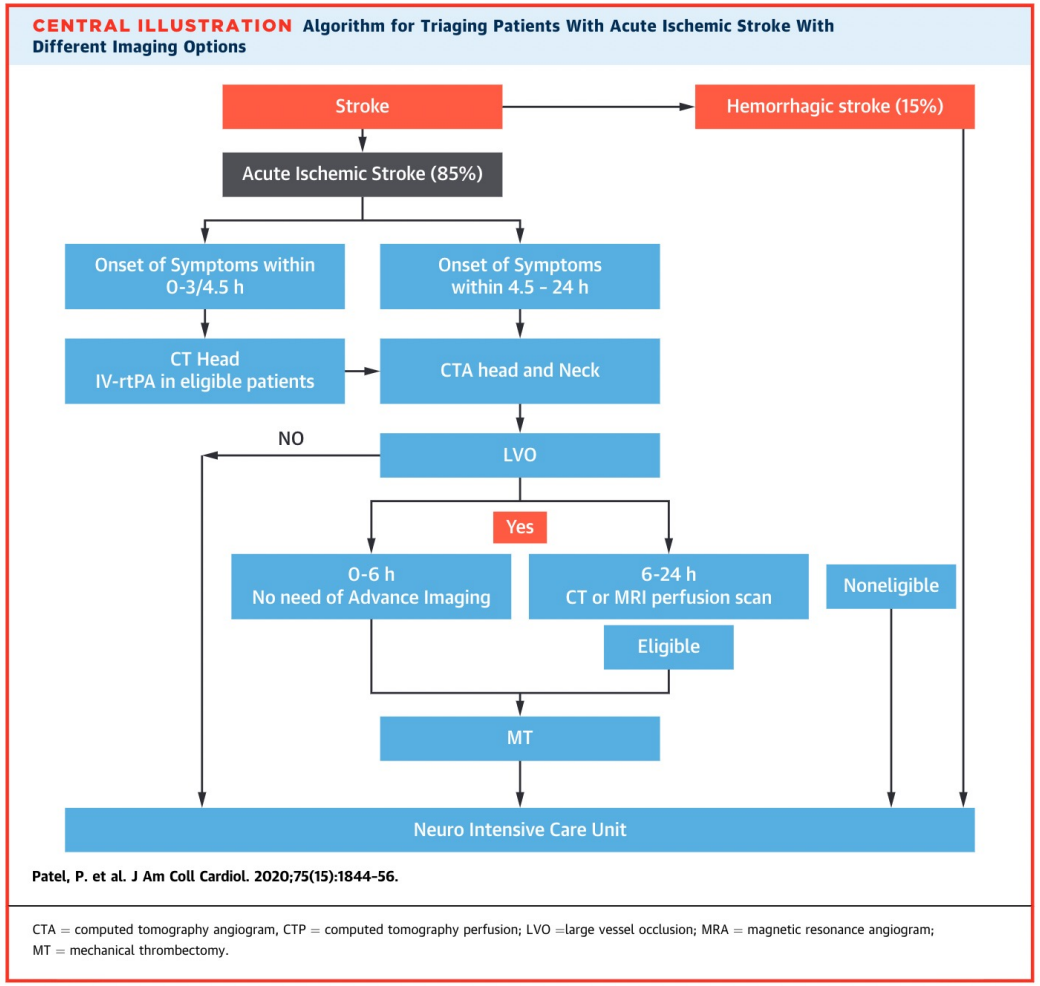
Other Syndromes

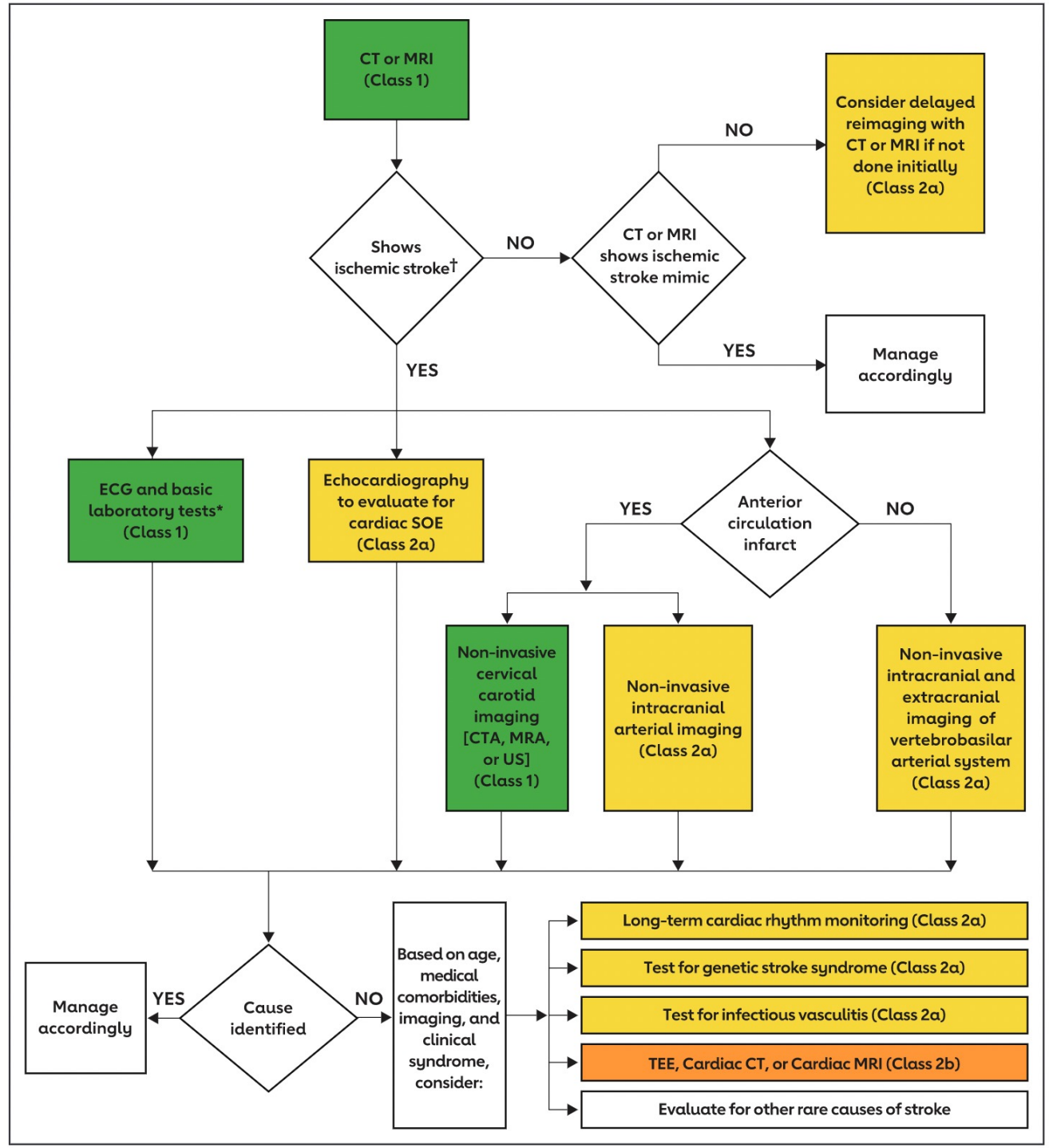
- Brainstem (INO, motor syndrome + CN palsy)
- Movement disorder (hemichorea-hemiballismus, dystonia)
- Vascular cognitive impairment & dementia



Front Neurol. 2017 Sep 22;8:502.
Neurology. 2003 Aug 12;61(3):334-8.

Evaluation



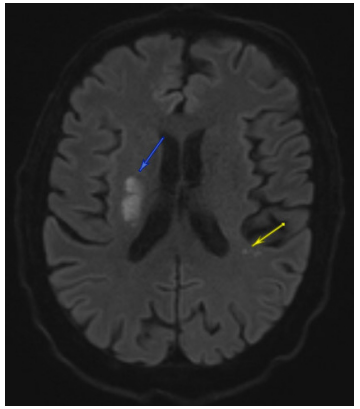


J Am Coll Cardiol. 2020 Apr 21;75(15):1844-1856.
Stroke. 2021 Jul;52(7):e364-e467.

Imaging

CT

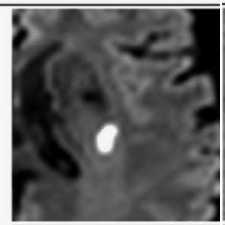
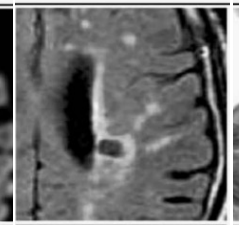
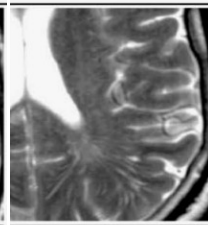
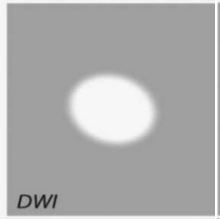
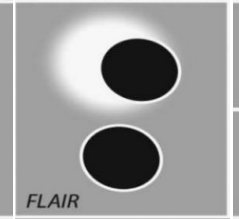
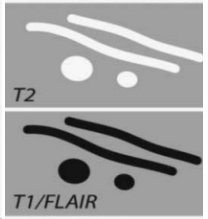
- Difficult to visualize lacunar infarcts <2mm
  *brainstem
- Sensitivity → 30-44%



MRI - DWI

- High sensitivity & specificity
- Acute: ≤20 mm
- Chronic: <15 mm

* Multiple acute/subacute infarcts → embolic source

	Recent small subcortical infarct	Lacune	Perivascular space
Example image			
Schematic	 DWI	 FLAIR	 T2 / T1/FLAIR
Usual diameter[1]	≤ 20 mm	3-15 mm	≤ 2 mm
Comment	best identified on DWI	usually have hyperintense rim	usually linear without hyperintense rim
DWI	↑	↔/(↓)	↔
FLAIR	↑	↓	↓
T2	↑	↑	↑
T1	↓	↓	↓
T2* / GRE	↔	↔ (↓ if haemorrhage)	↔

Lancet Neurol. 2013 Aug;12(8):822-38.

Variable Imaging Evolution

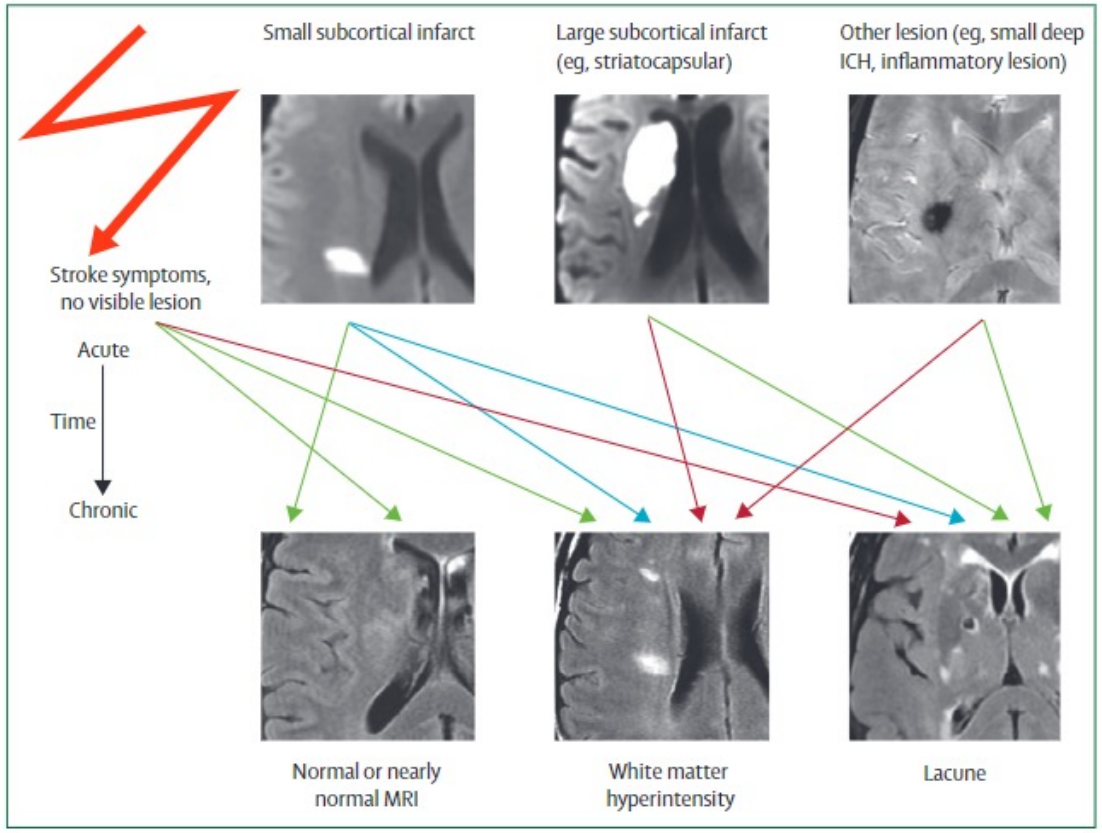


Figure 1: **Variable fates of lesions related to small vessel disease and the convergence of acute lesions with different causes but similar late appearances on MRI**

1. Cavitated, surrounding gliosis
2. Subcortical/periventricular WMH
3. No evidence of prior infarct

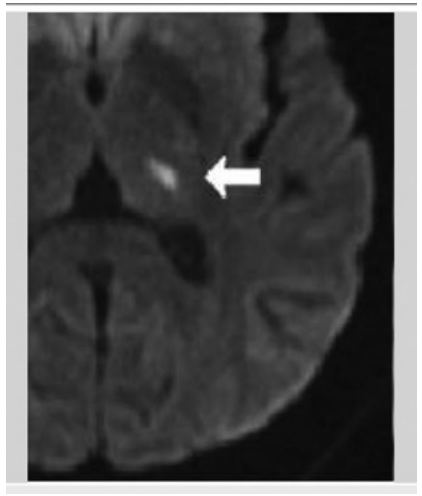
- Subcortical cavitated lesion → T2*-WI to eval for hemorrhage

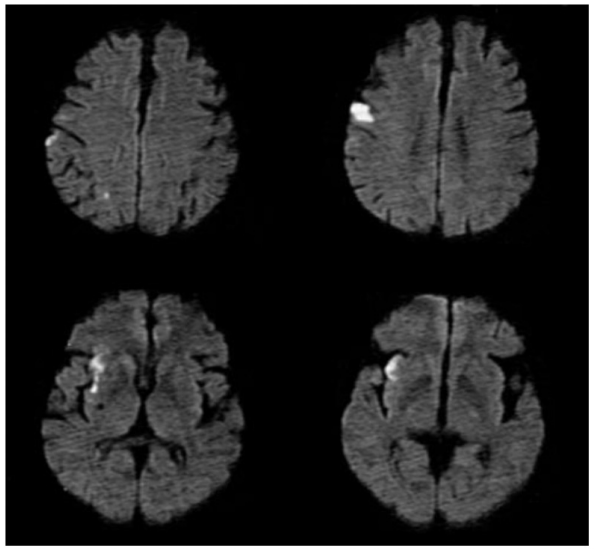
Lancet Neurol. 2013 Aug;12(8):822-38.

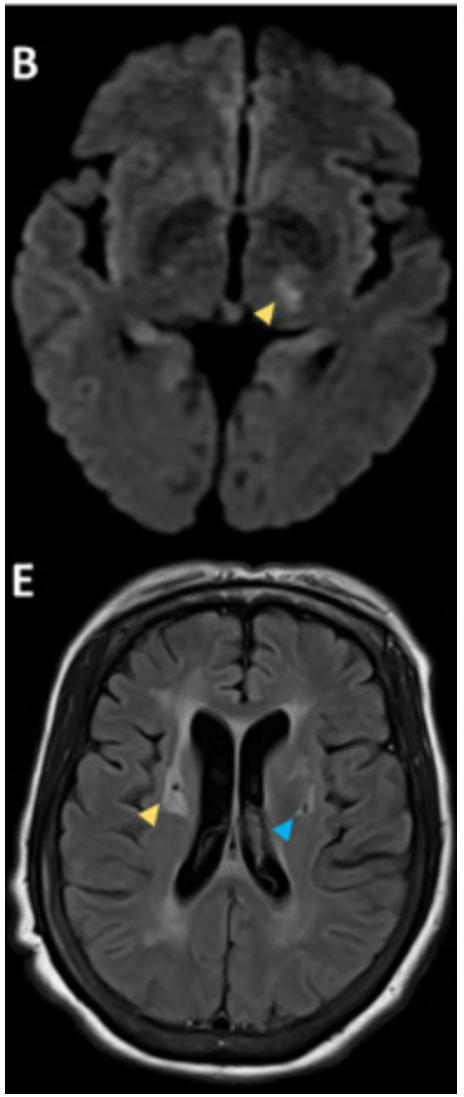
Diagnosis

- Lacunar syndrome
- CT, vascular imaging, CTP not sensitive
- MRI
  - Presentation ≠ Stroke Subtype

Dx → single penetrating artery infarction ≤ 20 mm + risk factors + absence of high-risk alternative etiology







Stroke. 2005 Apr;36(4):757-61.

Management

IV-tPA

Table 1. Association of Baseline Covariates With Outcome (OR Based on Multiple Outcomes[5]: Univariate Analyses and Treatment Interactions

Variable	OR	95% CI	*P*[1]	Treatment Interaction *P*[2]
Baseline stroke subtypes[3]			.009	.78
Cardioembolic vs small	0.44	0.28-0.68		
Large vs small	0.45	0.29-0.71		
Other vs small	0.69	0.27-1.71		

Capsular Warning Syndrome / Infarct Progression

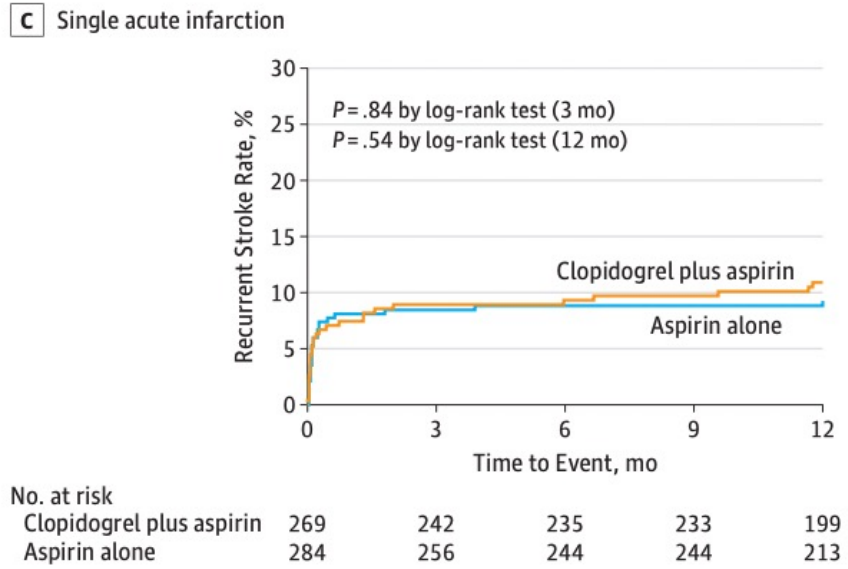
- Extension of thrombosis
- Progressive branch occlusion
- Hemodynamic failure
- Peri-infarct edema

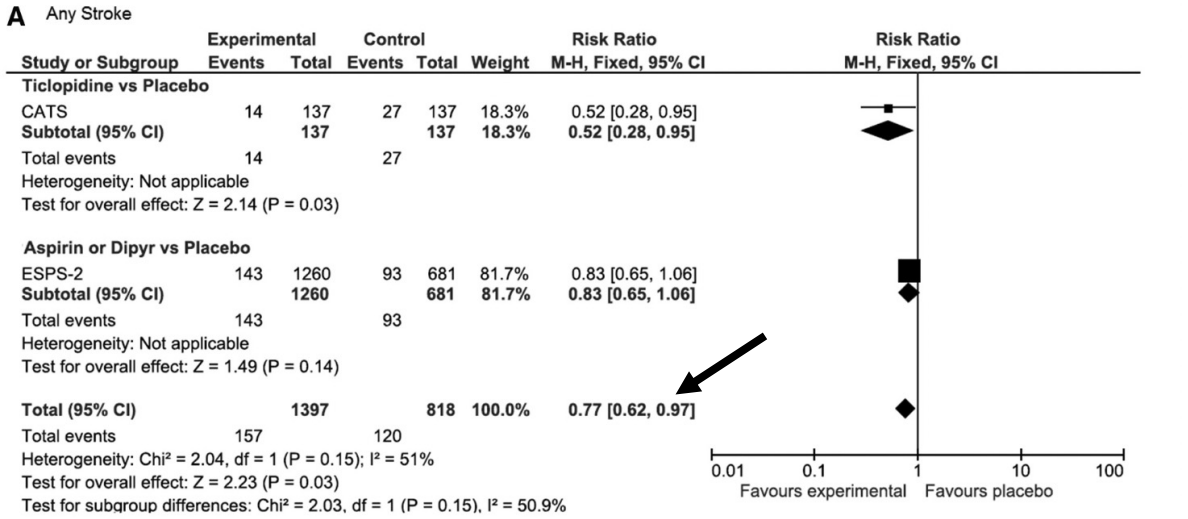
Stroke. 1997 Nov;28(11):2119-25
Int J Stroke. 2012 Jun;7(4):321-9..

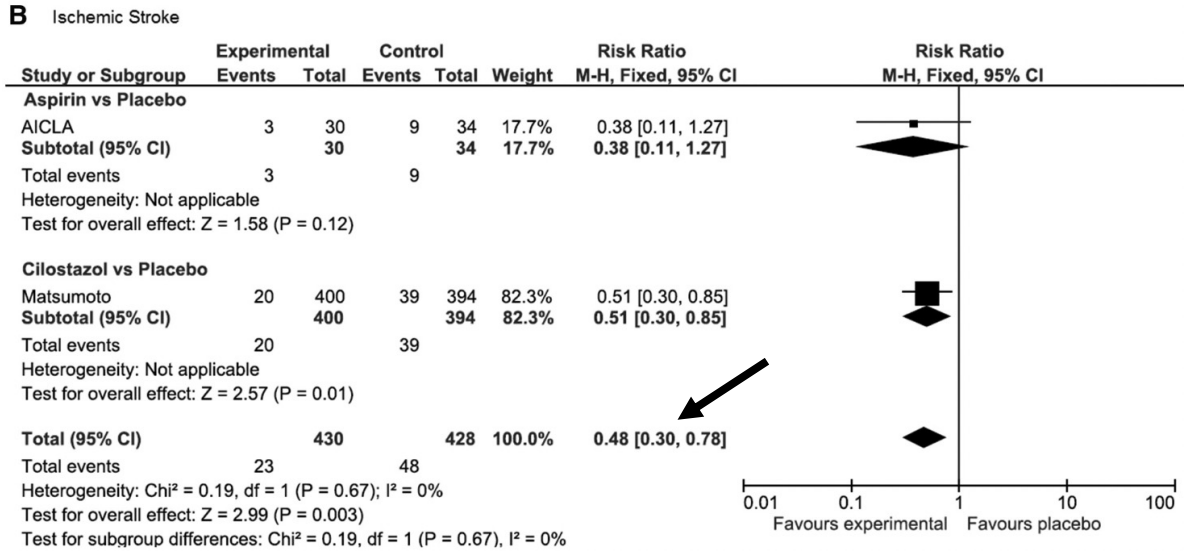
Secondary Prevention

- Antiplatelet Tx

→ Minor lacunar infarct / high-risk TIA: short-term DAPT followed by long-term single AP tx







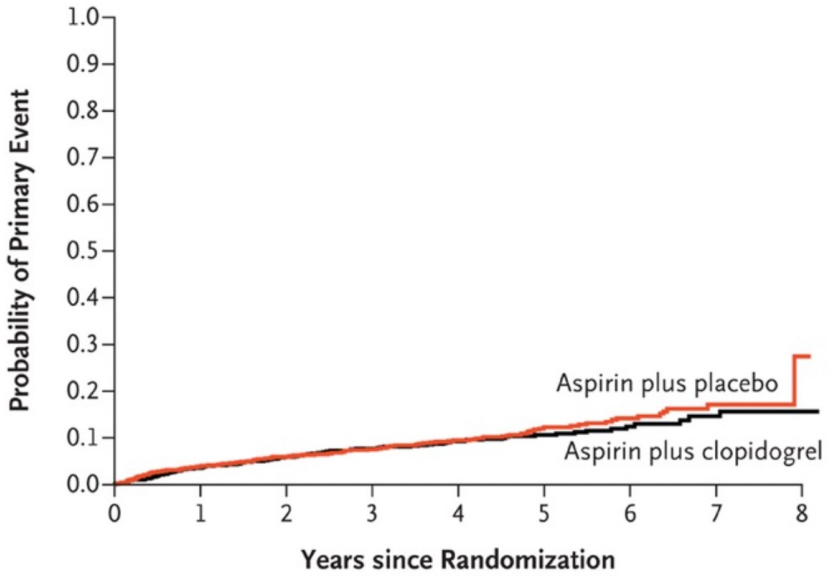
Stroke. 2015 Apr;46(4):1014-23.
JAMA Neurol. 2018 Jun 1;75(6):711-719.

SPS3 (Secondary Prevention of Small Subcortical Strokes)

- P: recent symptomatic lacunar infarction (MRI)
- I/C: 2x2 factorial design
  - **DAPT (ASA + clopidogrel) or ASA**
  - SBP<130 mmHg or SBP 130-149 mmHg
- O: any recurrent stroke

→ Recurrent stroke: HR 0.92 (95% CI 0.72 – 1.16)

- ↑ hemorrhage & mortality (HR 1.52)



No. at Risk									
Aspirin plus placebo	1517	1272	1027	788	574	355	189	83	3
Aspirin plus clopidogrel	1503	1288	1030	802	589	371	205	90	5

Table 3. Safety Outcomes.*

Outcome	Aspirin plus Placebo (N=1503)		Aspirin plus Clopidogrel (N=1517)		Hazard Ratio (95% CI)	P Value
	no.	*rate (%/yr)*	*no.*	*rate (%/yr)*		
All major hemorrhages	56	1.1	105	2.1	1.97 (1.41–2.71)	<0.001
Intracranial hemorrhages†	15*	0.28	22	0.42	1.52 (0.79–2.93)	0.21
Intracerebral	8	0.15	15	0.28	1.92 (0.82–4.54)	0.14
Subdural or epidural	6	0.11	7	0.13	1.23 (0.41–3.64)	0.72
Other	4	0.07	2	0.04	0.53 (0.10–2.89)	0.46
Extracranial bleeding	42	0.79	87	1.7	2.15 (1.49–3.11)	<0.001
Gastrointestinal‡	28	0.52	58	1.1	2.14 (1.36–3.36)	<0.001
Fatal hemorrhages	4	0.07	9	0.17	2.29 (0.70–7.42)	0.17
Intracranial	4	0.07	7	0.13	1.78 (0.52–6.07)	0.36
Extracranial	0	0	2	0.04	—	—

N Engl J Med. 2012 Aug 30;367(9):817-25.

SPS3 (Secondary Prevention of Small Subcortical Strokes)

- P: recent symptomatic lacunar infarction (MRI)
- I/C: 2x2 factorial design
  - DAPT (ASA + clopidogrel) or ASA
  - **SBP<130 mmHg or SBP 130-149 mmHg**
- O: any recurrent stroke

→ Recurrent stroke: HR 0.81 (95% CI 0.64 – 1.03)

- ↓ intracerebral hemorrhage

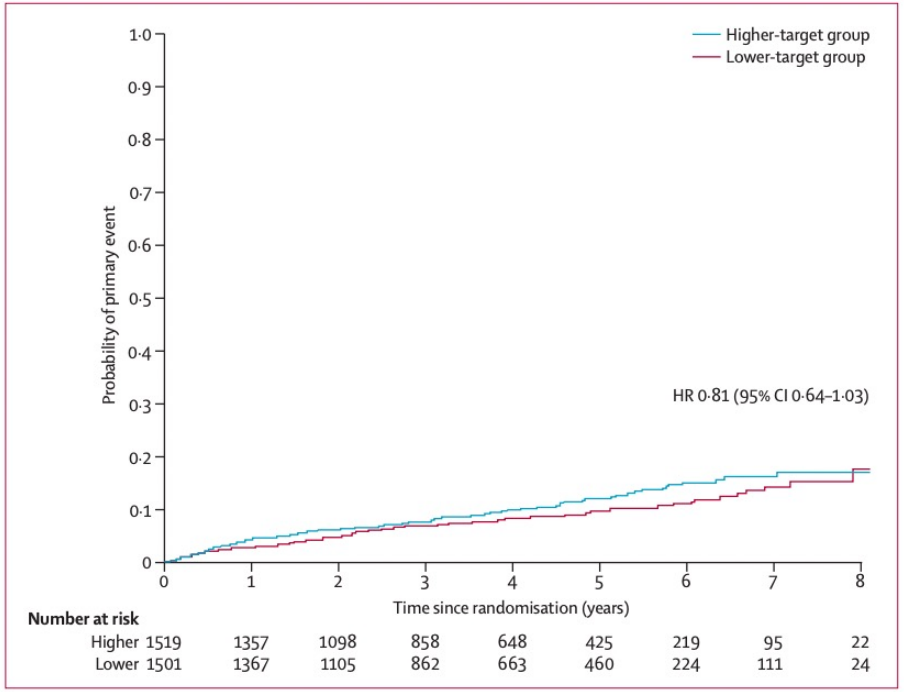


Figure 2: **Probability of patients experiencing a primary event by time after randomisation**

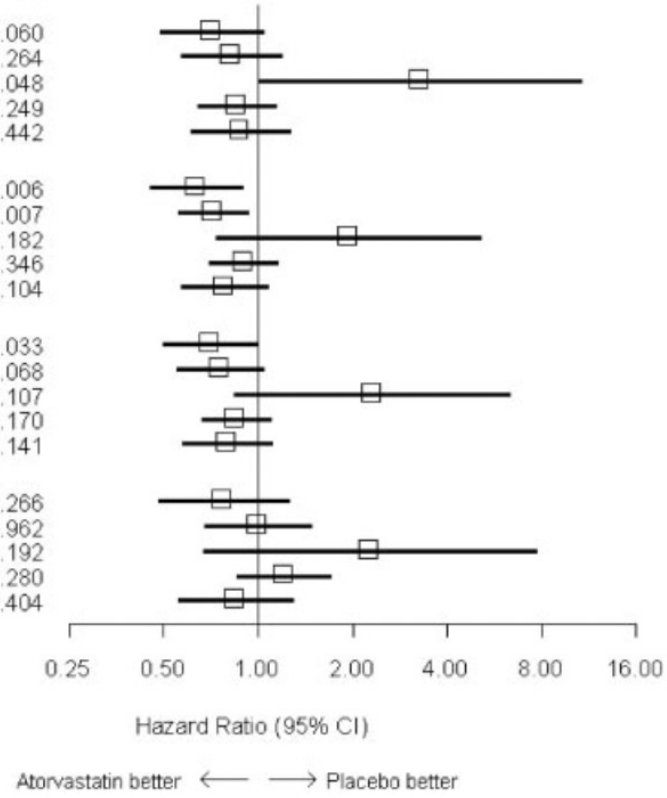
	Higher-target group (n=1519)		Lower-target group (n=1501)		Hazard ratio (95% CI)	p value
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)		
Stroke						
All stroke	152	2·77%	125	2·25%	0·81 (0·64–1·03)	0·08
Ischaemic stroke or unknown	131	2·4%	112	2·0%	0·84 (0·66–1·09)	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 (0·15–0·95)	0·03
Subdural or epidural	5	0·091%	6	0·11%	1·18 (0·36–3·88)	0·78
Other	2	0·036%	4	0·072%	1·97 (0·36–10·74)	0·43
Disabling or fatal stroke‡	49	0·89%	40	0·72%	0·81 (0·53–1·23)	0·32

Lancet. 2013 Aug 10;382(9891):507-15.

Secondary Prevention

- Blood Pressure
  - Long-term target SBP<130 mmHg
- High-intensity statin therapy (target LDL-C<70 mg/dL)
- Lifestyle modifications
  - Tobacco cessation, Limit ETOH
  - Physical activity
  - Mediterranean diet (HTN - Na restriction)

	Atorvastatin Events (%)	Placebo Events (%)	HR (95% CI)n	P Value
Stroke				
Large Vessel	48 (13.1)	71 (18.6)	0.70 (0.49, 1.02)	0.060
TIA	54 (7.6)	66 (8.8)	0.81 (0.57, 1.17)	0.264
Hemorrhagic	10 (22.2)	4 (8.3)	3.24 (1.01, 10.4)	0.048
Small Vessel	93 (13.1)	109 (15.5)	0.85 (0.64, 1.12)	0.249
Unknown	60 (11.2)	61 (12.7)	0.87 (0.61, 1.24)	0.442
Stroke or TIA				
Large Vessel	59 (16.1)	95 (24.9)	0.63 (0.46, 0.87)	0.006
TIA	106 (15.0)	151 (20.1)	0.71 (0.56, 0.91)	0.007
Hemorrhagic	11 (24.4)	7 (14.6)	1.92 (0.74, 4.99)	0.182
Small Vessel	124 (17.5)	138 (19.7)	0.89 (0.70, 1.13)	0.346
Unknown	75 (14.0)	85 (17.6)	0.77 (0.57, 1.05)	0.104
Major Cardiovascular Event				
Large Vessel	58 (15.8)	86 (22.5)	0.70 (0.50, 0.97)	0.033
TIA	71 (10.0)	93 (12.4)	0.75 (0.55, 1.02)	0.068
Hemorrhagic	11 (24.4)	6 (12.5)	2.28 (0.84, 6.21)	0.107
Small Vessel	120 (16.9)	141 (20.1)	0.84 (0.66, 1.08)	0.170
Unknown	74 (13.8)	81 (16.8)	0.79 (0.58, 1.08)	0.141
Death				
Large Vessel	31 (8.4)	44 (11.5)	0.77 (0.48, 1.22)	0.266
TIA	53 (7.5)	53 (7.0)	0.99 (0.68, 1.45)	0.962
Hemorrhagic	7 (15.6)	5 (10.4)	2.24 (0.67, 7.55)	0.192
Small Vessel	77 (10.9)	64 (9.1)	1.20 (0.86, 1.67)	0.280
Unknown	47 (8.8)	45 (9.3)	0.84 (0.56, 1.27)	0.404



Stroke. 2009 Apr;40(4):1405-9.

Concurrent Potential Causes

Carotid Stenosis

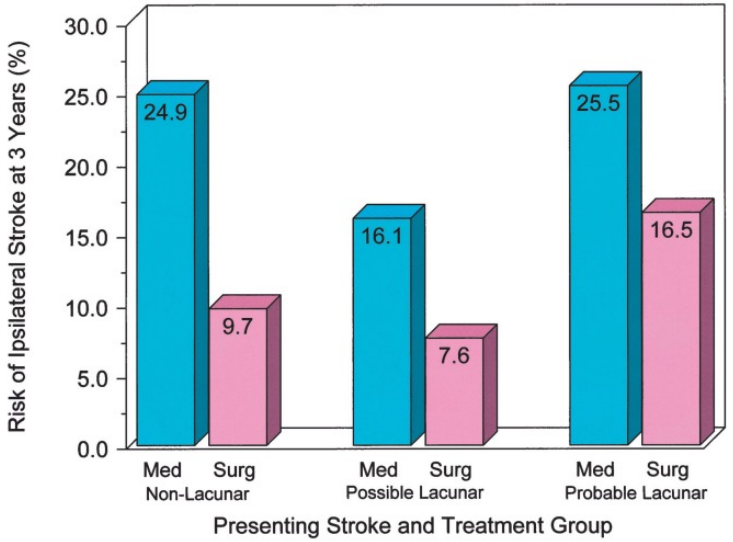
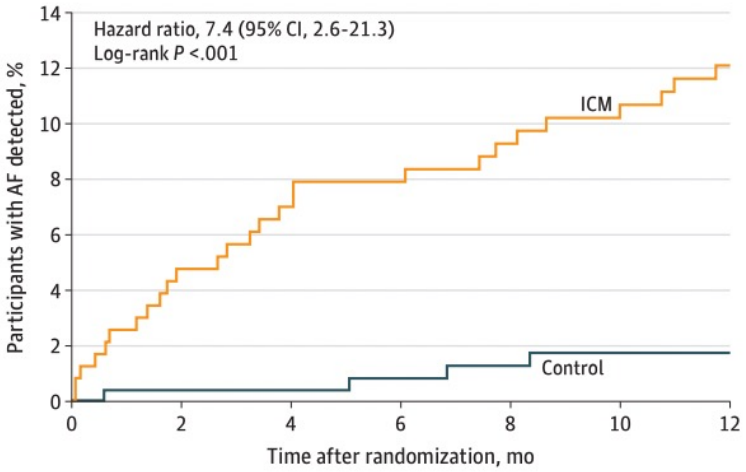


Figure 4. Risk of ipsilateral stroke at 3 years by presenting stroke category and treatment group for patients with 50 to 99% internal carotid artery stenosis. The numbers of patients represented in each bar, from left to right, are 172, 160, 57, 69, 41, and 38. Med = medically treated; Surg = surgically treated.

Neurology. 2000 Feb 8;54(3):660-6.

Atrial Fibrillation

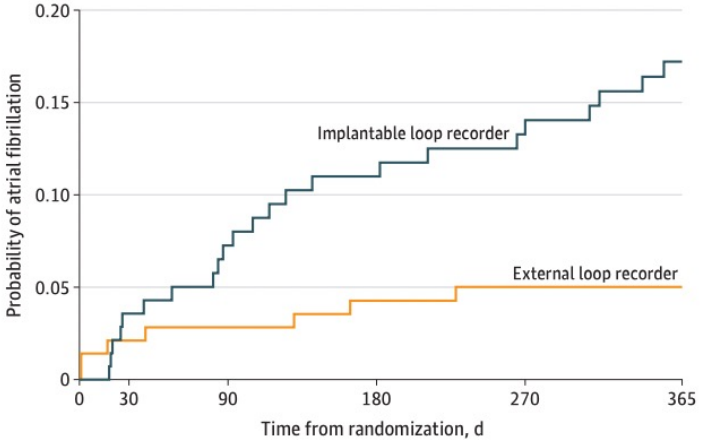
Figure 2. Time to First Detection of Atrial Fibrillation at 12 Months in a Study of Long-term Continuous Cardiac Monitoring vs Usual Care on Detection of Atrial Fibrillation (AF) in Patients With Stroke Attributed to Large- or Small-Vessel Disease



No. of participants at risk

Control	250	237	237	225	214	209	203
ICM	242	216	207	204	197	190	186

Figure 2. Secondary Outcome of the Probability of New Atrial Fibrillation or Flutter Lasting 2 Minutes or Longer Within 12 Months



No. at risk

External loop recorder	142	136	130	125	86
Implantable loop recorder	142	124	119	113	90

Prognosis

- Early Neurological Deterioration
  - IL-6, TNF-∝, ICAM-1
  - Preceding TIA, fluctuating course
- Functional Recovery
  - Lower infarct volumes
  - Delayed recovery

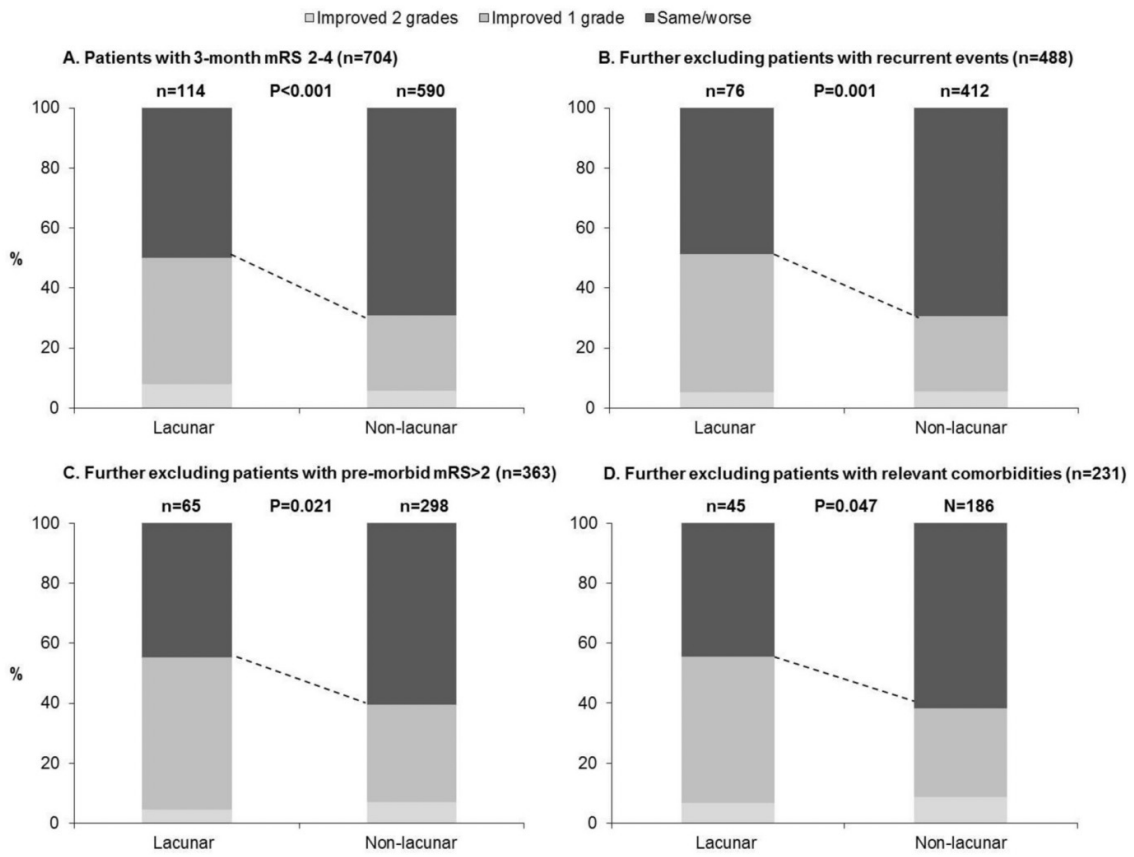
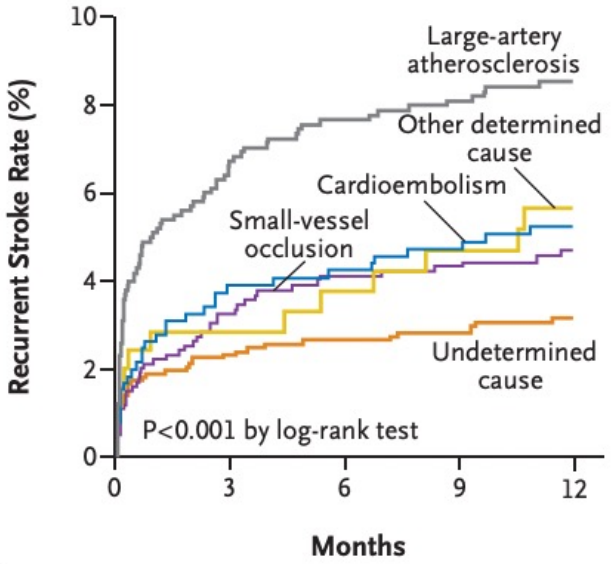


Figure 2 Changes in mRS between 3-months and 1-year post-stroke for 3-month survivors of lacunar versus non-lacunar stroke, (A) including all patients with 3-month mRS of 2 to 4, and then progressively excluding patients with: (B) recurrent vascular events over follow-up, (C) pre-morbid mRS>2, and (D) relevant comorbidities including peripheral vascular disease, heart failure, valve disease, and/or cancer. P-values are from Wilcoxon rank-sum tests for trend.

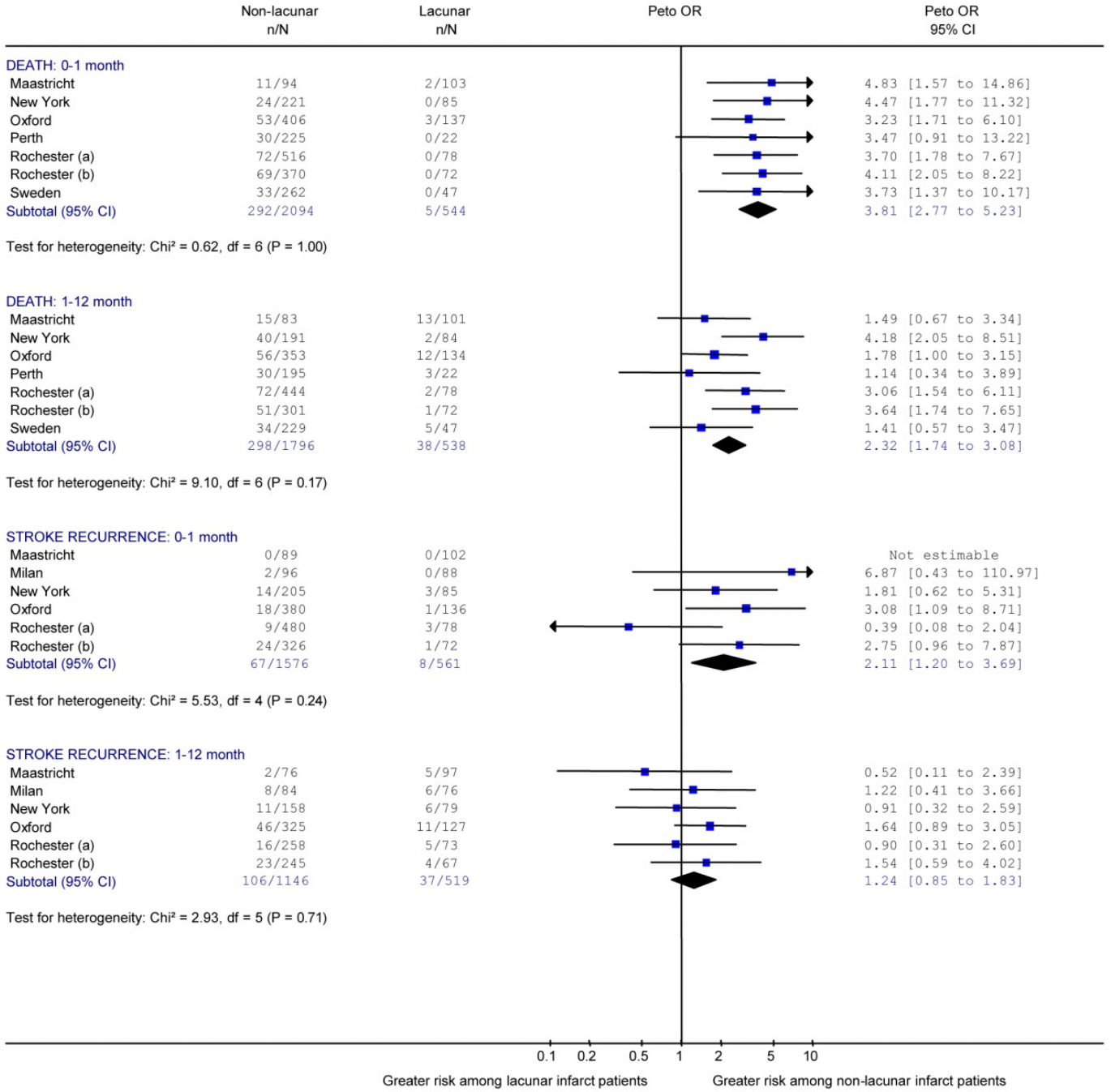
J Neurol Neurosurg Psychiatry. 2018 Dec;89(12):1301-1307.

Recurrent Stroke & Survival

D Rate of Recurrent Stroke According to Cause of TIA or Minor Stroke (TOAST Classification)



No. at Risk					
Large-artery atherosclerosis	987	892	863	853	799
Small-vessel occlusion	983	905	862	857	790
Cardioembolism	641	584	570	561	494
Other determined cause	244	214	205	198	184
Undetermined cause	1354	1263	1206	1199	1085



Brain. 2005 Nov;128(Pt 11):2507-17.
N Engl J Med. 2016 Apr 21;374(16):1533-42.
N Engl J Med. 2018 Jun 7;378(23):2182-2190.

Table 2. *Factors associated with recurrent ischemic stroke: multivariable analysis*

Feature	Derivation cohort hazard ratio (95% CI)	Validation cohort hazard ratio (95% CI)	All participants hazard ratio (95% CI)
Male sex	1.7 (1.1, 2.6)	1.3 (.9, 1.9)	1.5 (1.1, 1.9)
Black race	2.0 (1.4, 3.0)	1.5 (1.0, 2.3)	1.7 (1.3, 2.3)
Diabetes	2.1 (1.5, 3.0)	1.9 (1.3, 2.7)	2.0 (1.5, 2.5)
Prior symptomatic lacunar stroke or TIA	2.5 (1.7, 3.7)	1.9 (1.3, 2.8)	2.2 (1.6, 2.9)

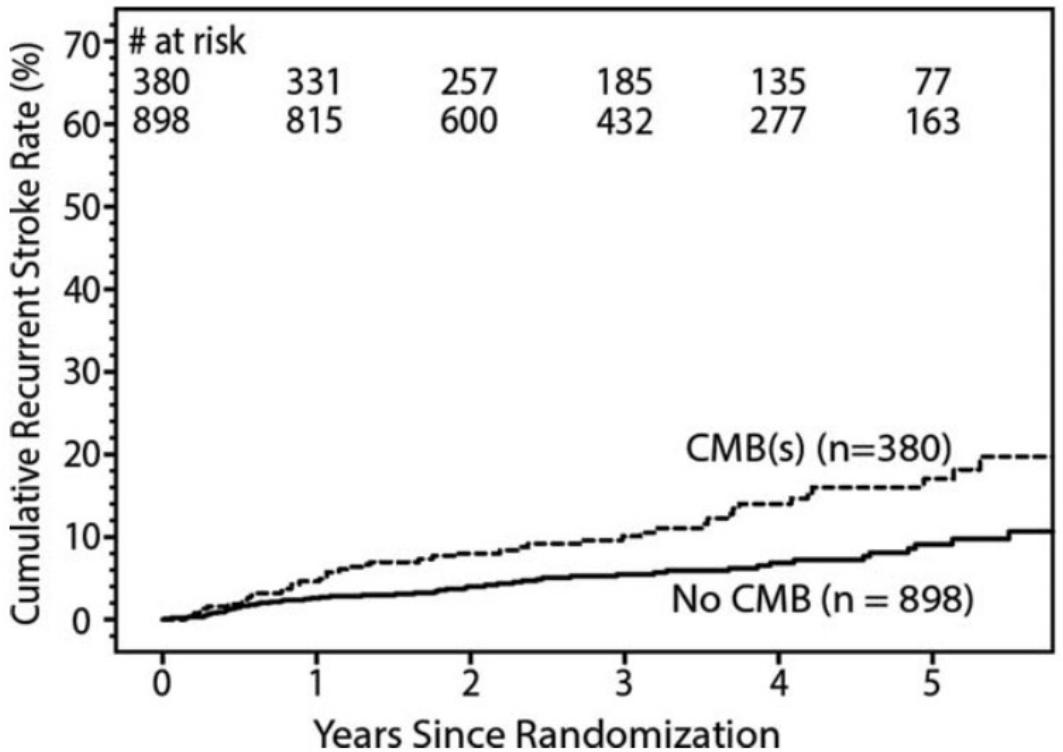


FIGURE 1: Kaplan–Meier curve for recurrent stroke by cerebral microbleed (CMB) status.

J Stroke Cerebrovasc Dis. 2014 Apr;23(4):618-24.
Ann Neurol. 2017 Aug;82(2):196-207.

Uncertainties and Opportunities

- Management
  - Microangiopathy
  - Branch atheromatous disease
  - Novel therapeutics
- Epidemiology
- VCID
- Subclinical infarcts
  - ≥ 5X more common
    - Majority lacunar

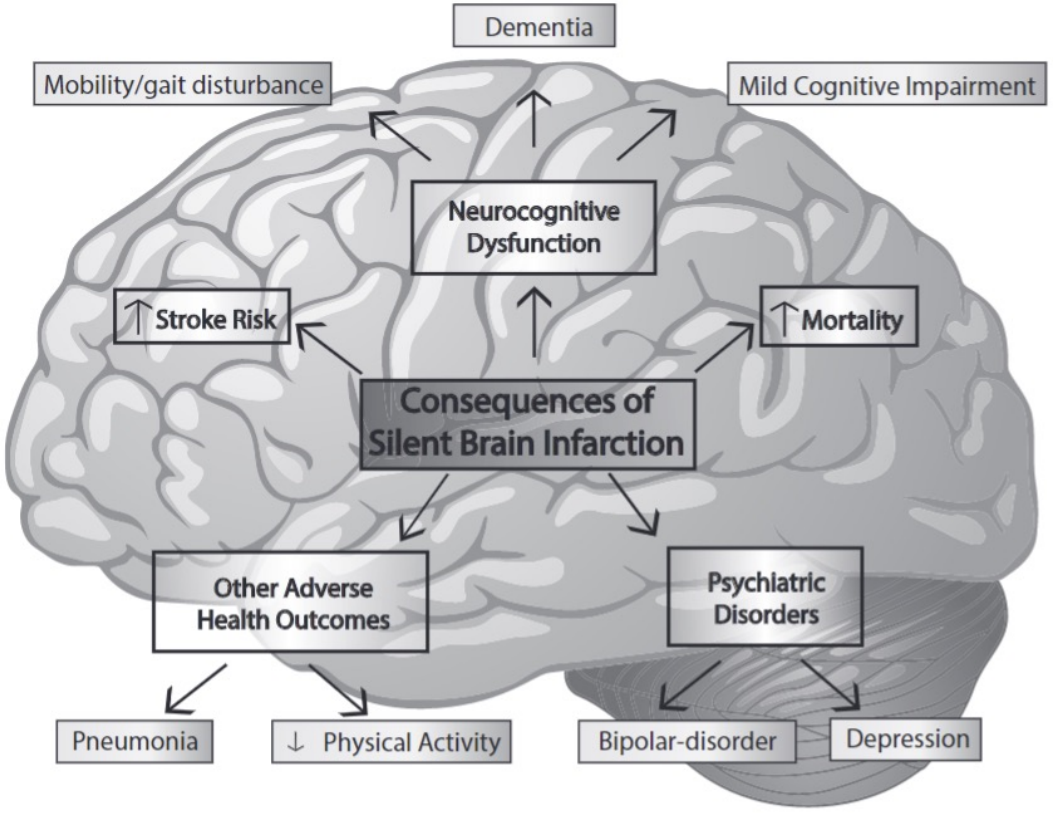


Figure 5. Consequences of silent brain infarction.

Stroke. 2014 Nov;45(11):3461-71.

Questions?