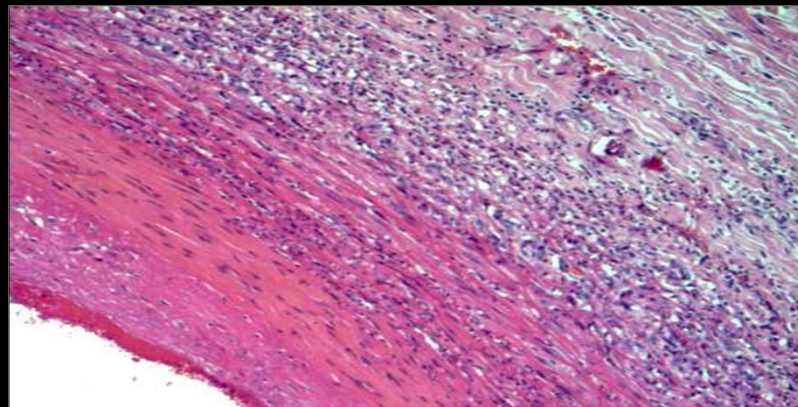
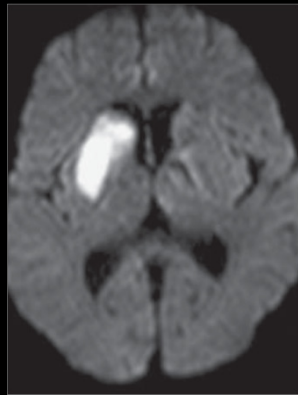


# Infectious causes of stroke



**Myles Connor**

NHS Borders and University of Edinburgh,  
United Kingdom; School of Public Health,  
University of the Witwatersrand, South Africa



## Stroke definition

‘a syndrome characterised by rapidly developing clinical symptoms and / or signs of focal, and at times global (deep coma / subarachnoid haemorrhage), loss of function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.’

So: sudden onset, focal, lasts longer than 24 hours, cardiac or vascular cause

By convention excludes: retinal infarction, subdural / epidural haemorrhage, traumatic intracerebral haemorrhage or infarction, *infection* or tumour

# Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010



*Valery L Feigin, Mohammad H Forouzanfar, Rita Krishnamurthi, George A Mensah, Myles Connor, Derrick A Bennett, Andrew E Moran, Ralph L Sacco, Laurie Anderson, Thomas Truelsen, Martin O'Donnell, Narayanaswamy Venketasubramanian, Suzanne Barker-Collo, Carlene M M Lawes, Wenzhi Wang, Yukito Shinohara, Emma Witt, Majid Ezzati, Mohsen Naghavi, Christopher Murray, on behalf of the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group\**

## Summary

**Background** Although stroke is the second leading cause of death worldwide, no comprehensive and comparable assessment of incidence, prevalence, mortality, disability, and epidemiological trends has been estimated for most regions. We used data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) to estimate the global and regional burden of stroke during 1990–2010.

Published Online  
October 24, 2013  
[http://dx.doi.org/10.1016/S0140-6736\(13\)61953-4](http://dx.doi.org/10.1016/S0140-6736(13)61953-4)

This online publication has

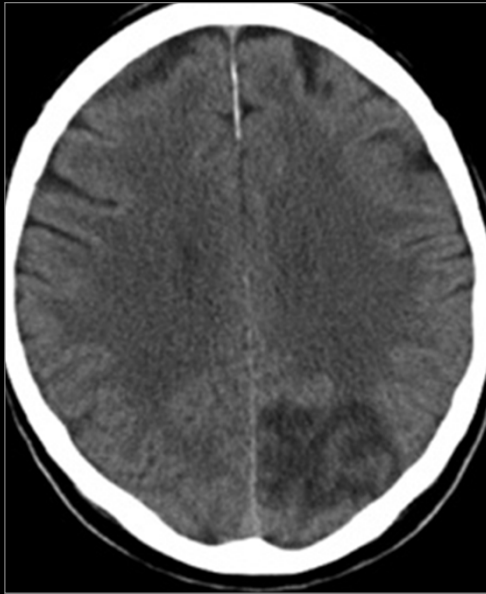
Around a third of all stroke occurred in 20 – 64 year olds, 89% of those in low and middle income countries....

Why?

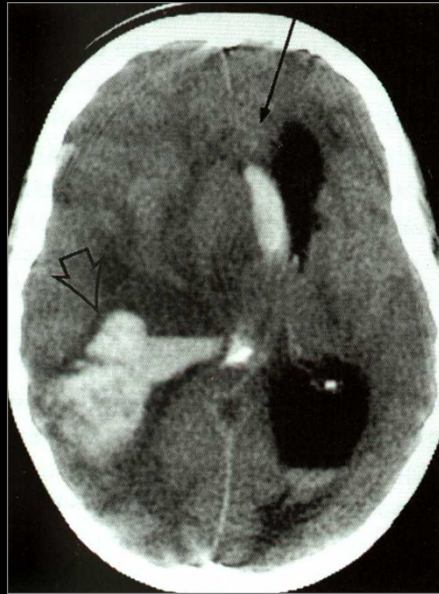
Epidemiological transition .... So increased prevalence of stroke risk factors....

Or other factors such as infection e.g. in Sub-Saharan Africa?

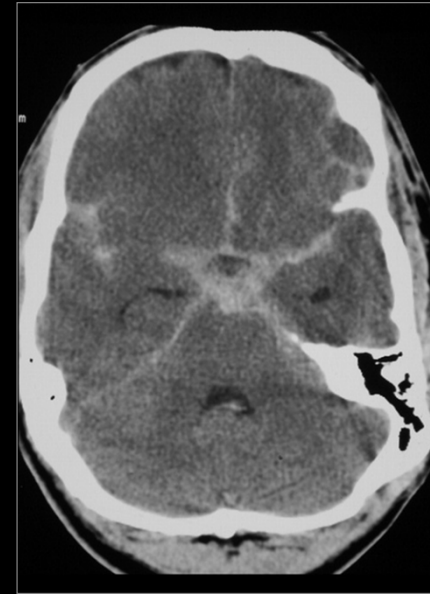
# Pathological stroke type



Ischaemic stroke



Cerebral haemorrhage

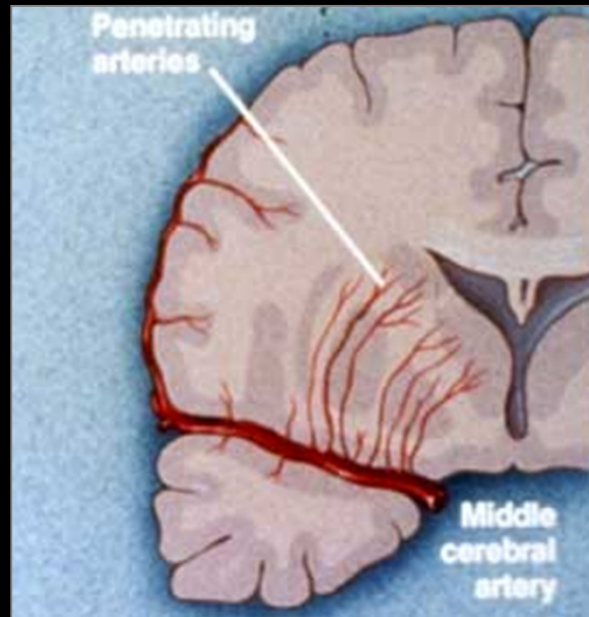


Subarachnoid  
haemorrhage

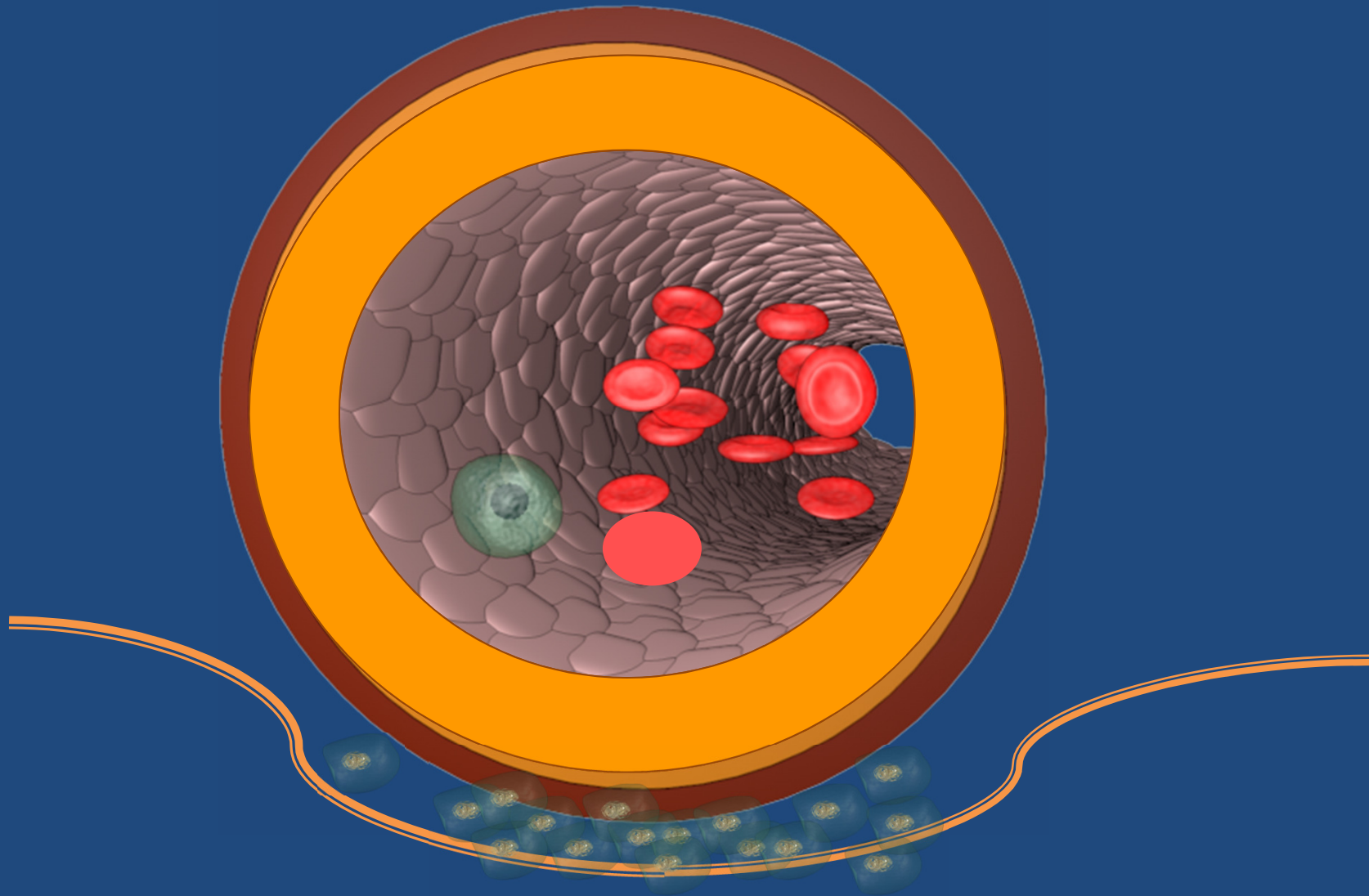
## Risk factors

- **Unmodifiable:** age, male sex etc.
- **Modifiable:** hypertension, smoking, waist to hip ratio, poor diet, physical inactivity, diabetes, alcohol intake, psychosocial factors, cardiac causes (IHD, atrial fibrillation, rheumatic heart disease, prosthetic valve)

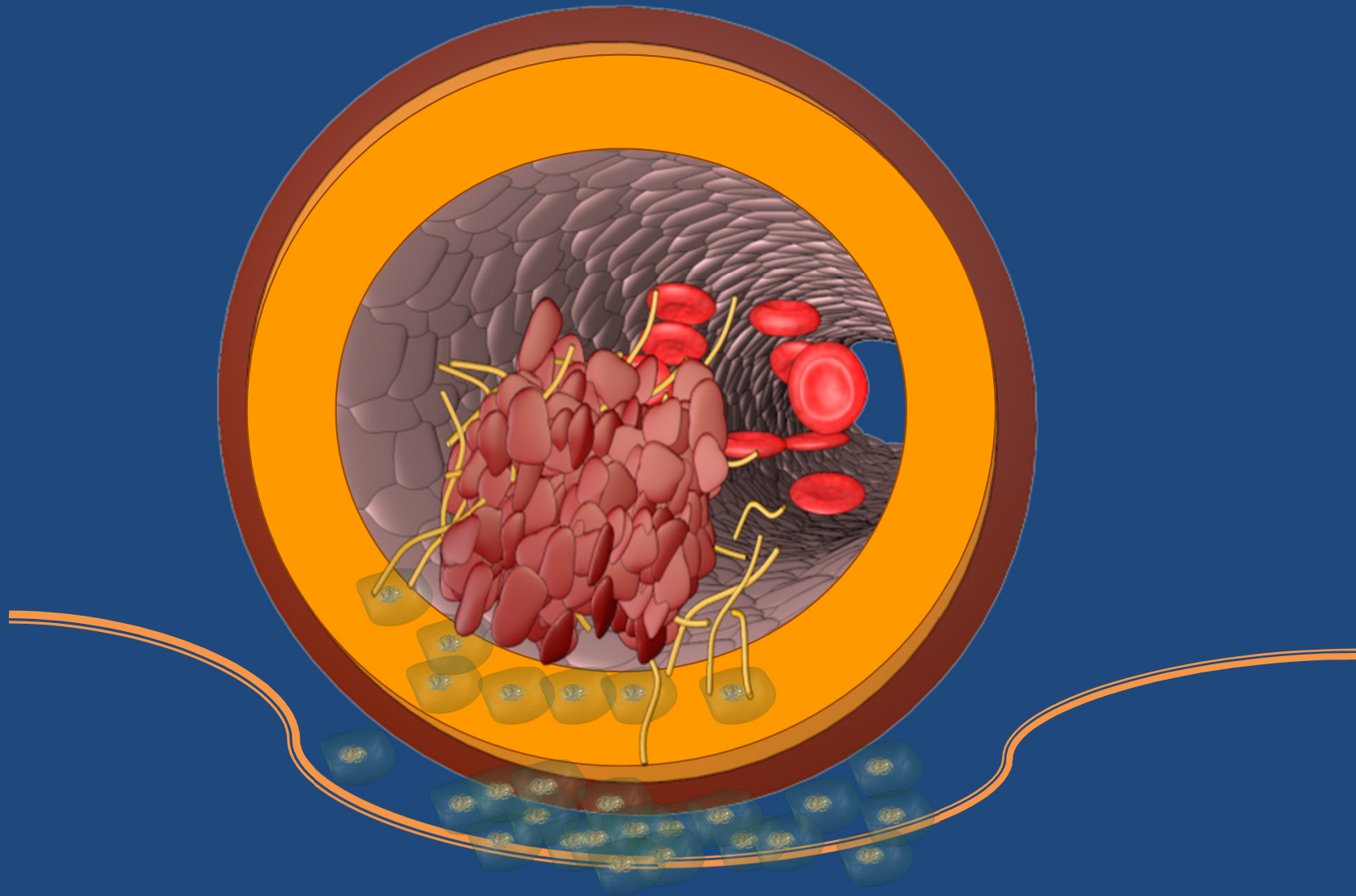




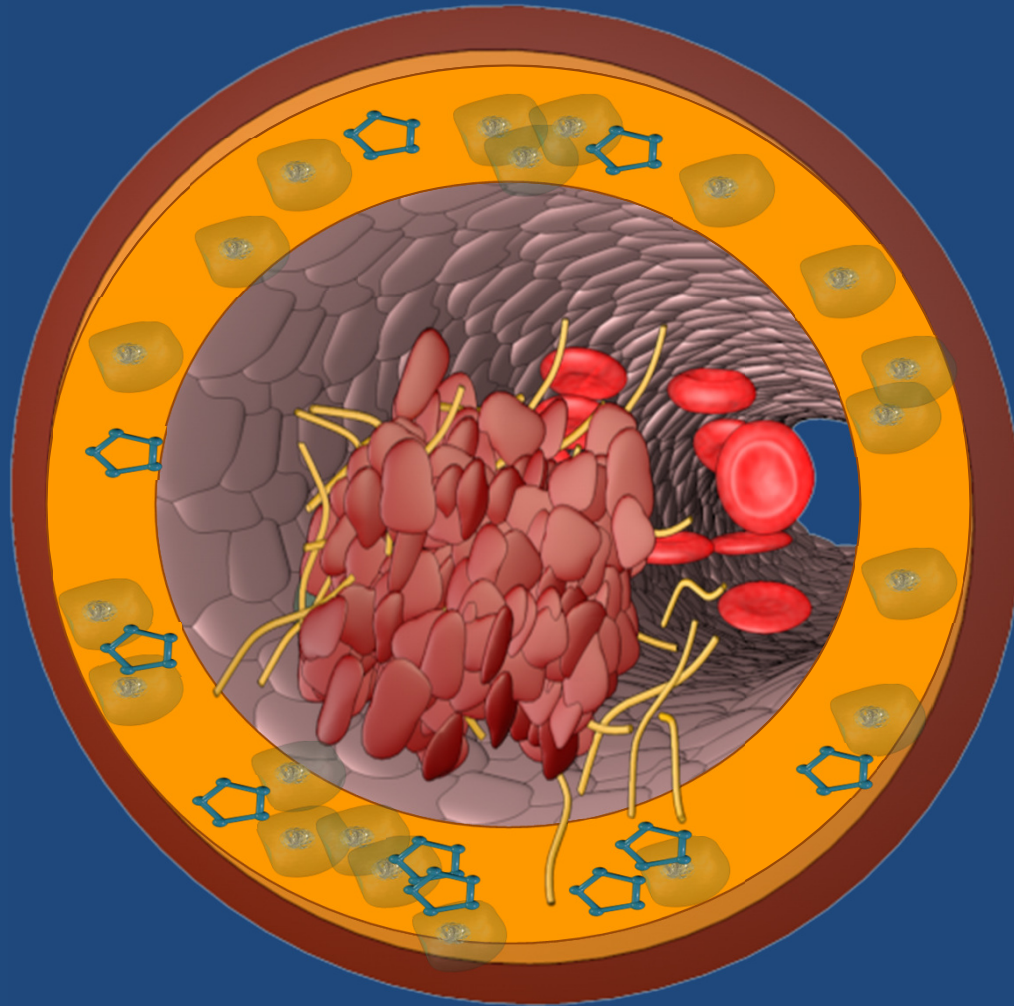
# Mechanisms of stroke in infection - meningitis



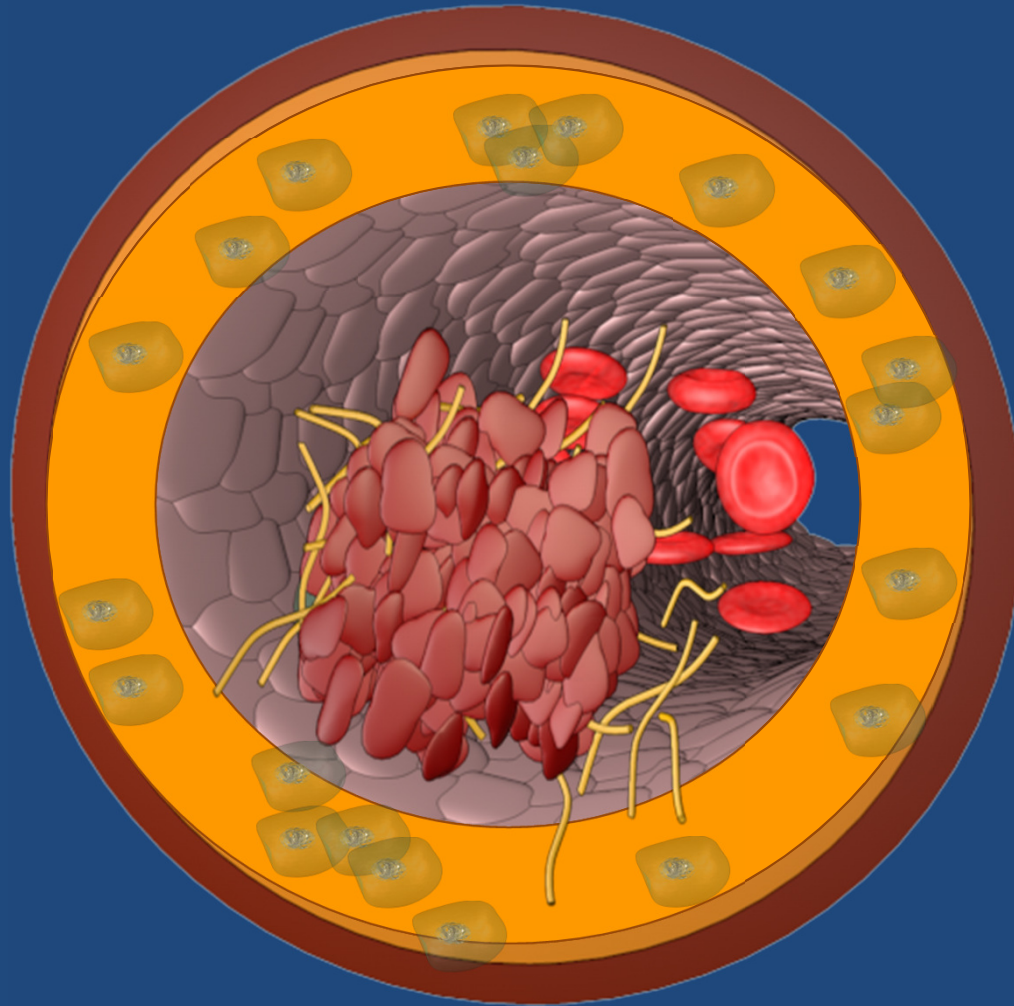
# Mechanisms of stroke in infection - meningitis



# Mechanisms of stroke in infection - vasculitis

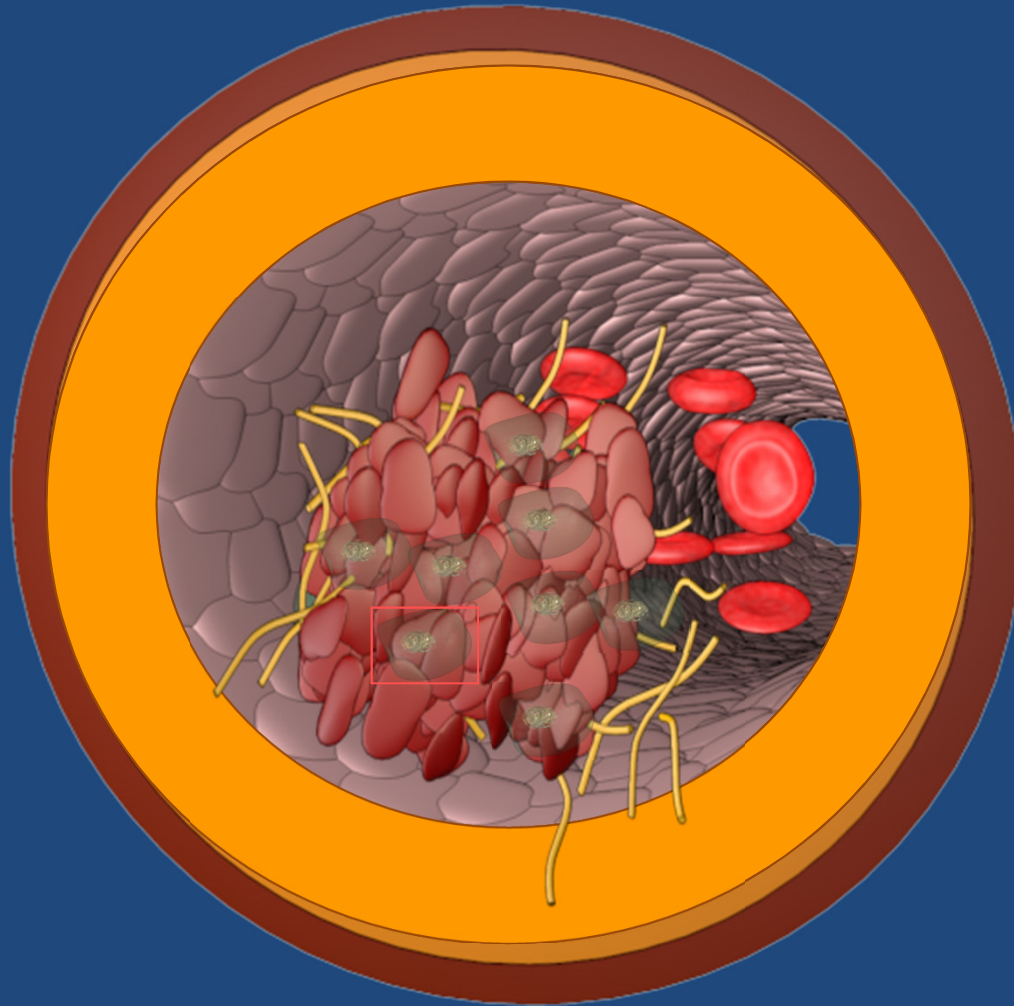


# Mechanisms of stroke in infection - vasculitis



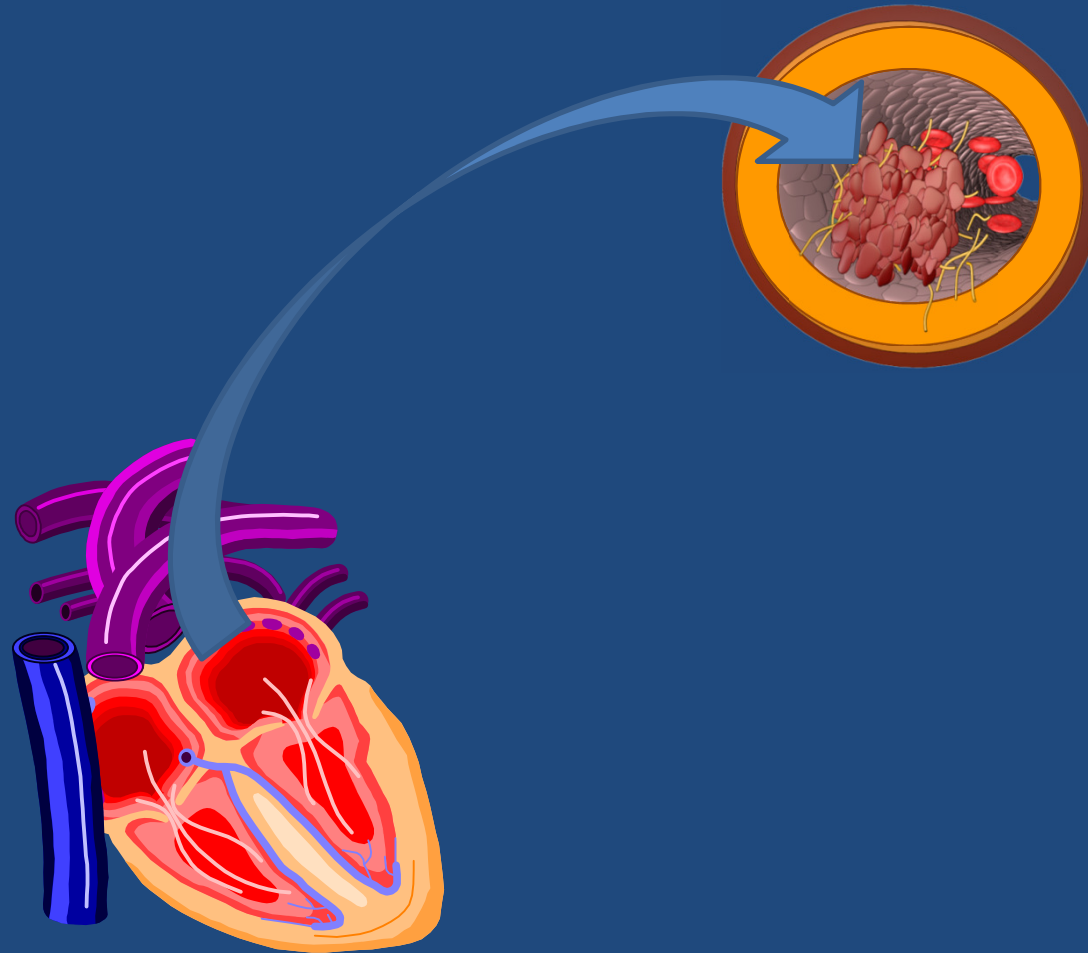


# Mechanisms of stroke in infection – infective endocarditis

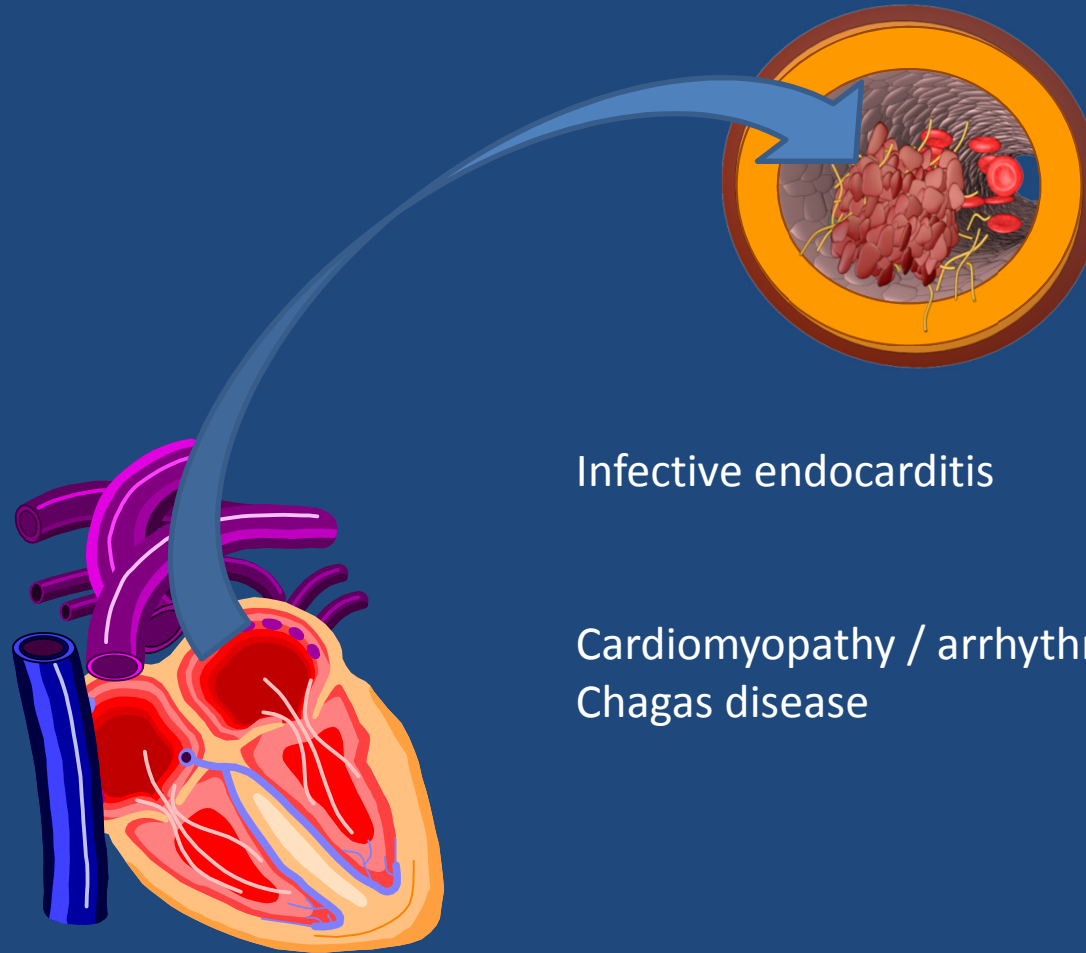




# Mechanisms of stroke in infection – cardiac emboli



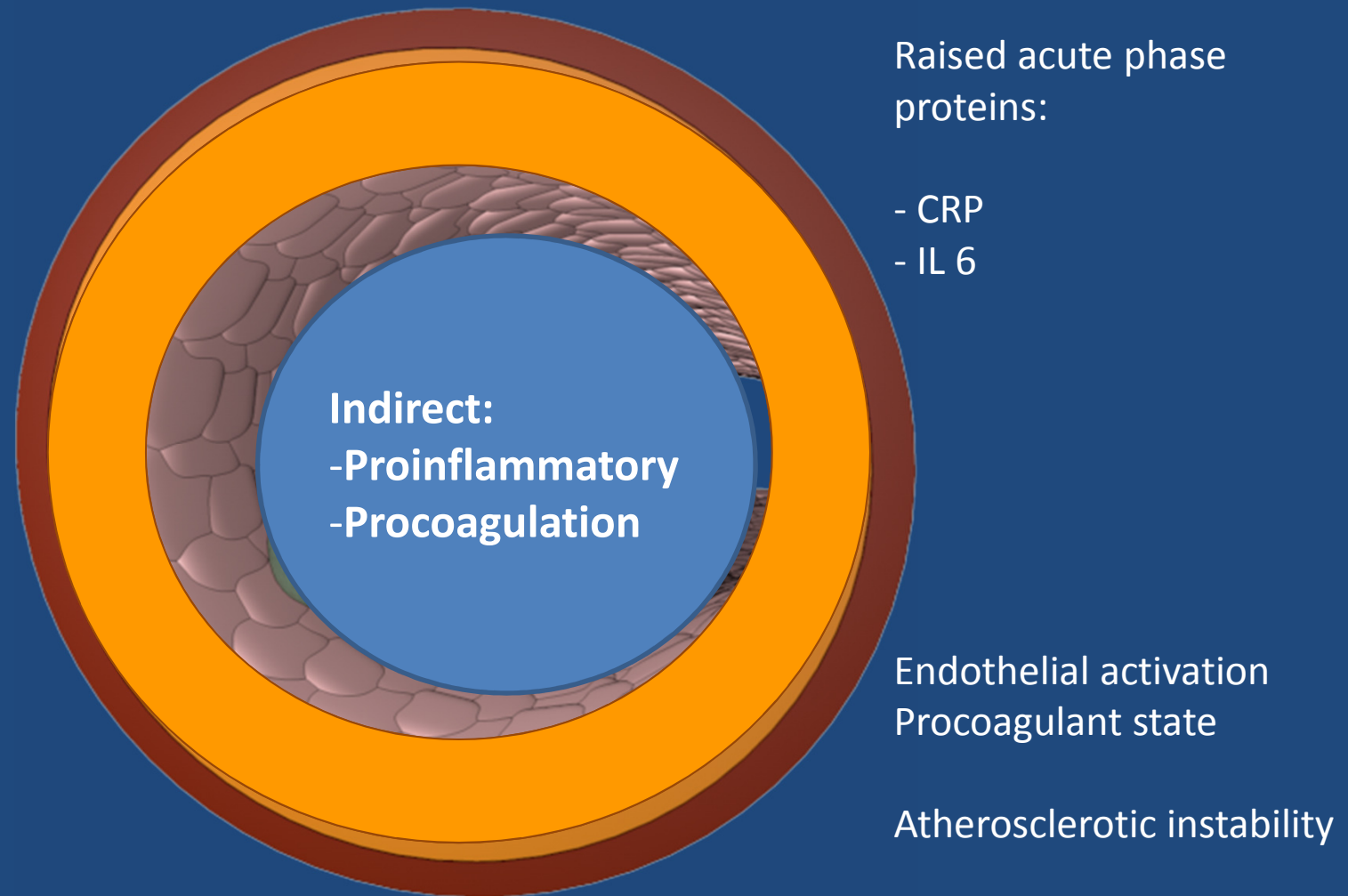
# Mechanisms of stroke in infection – cardiac emboli



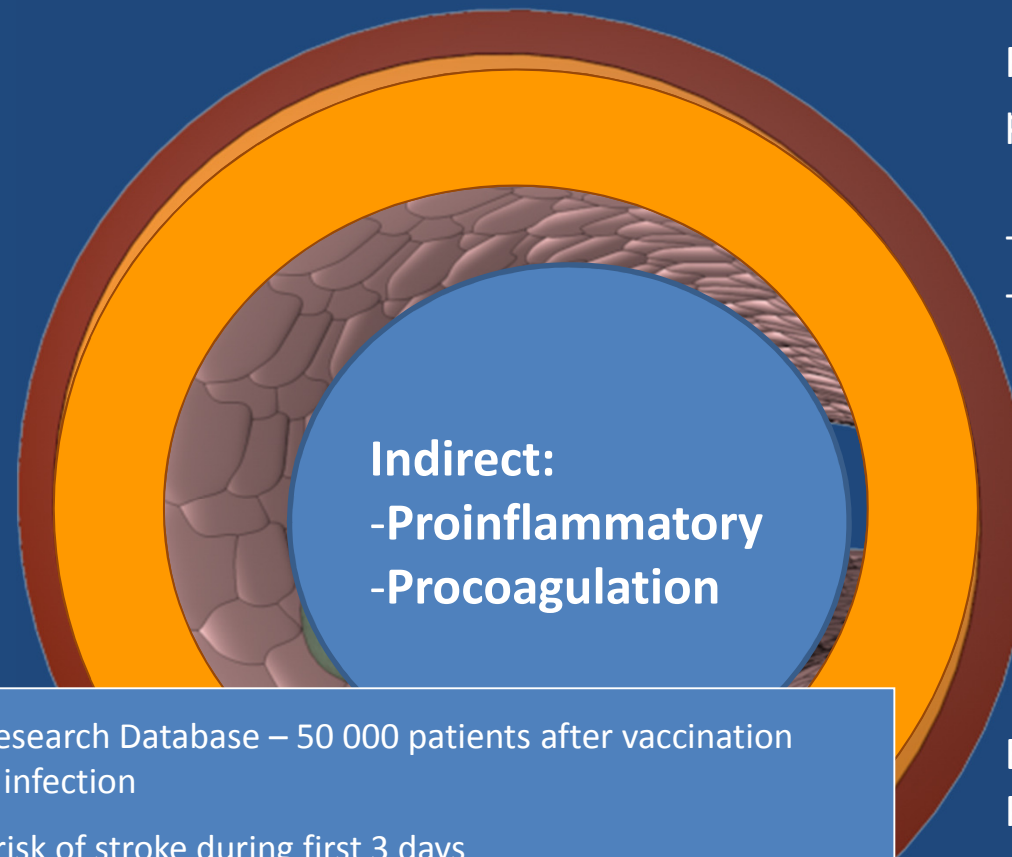
Infective endocarditis

Cardiomyopathy / arrhythmia e.g.  
Chagas disease

# Mechanisms of stroke in infection - Generic



# Mechanisms of stroke in infection - Generic



UK GP Research Database – 50 000 patients after vaccination or acute infection

Highest risk of stroke during first 3 days

Incidence ratio 3.2 (2.8 to 3.6) after respiratory infection, and 2.7 (2.3 to 3.2) after urinary tract infection

Smeeth et al *NEJM* 2004, 351: 2611-18

Raised acute phase proteins:

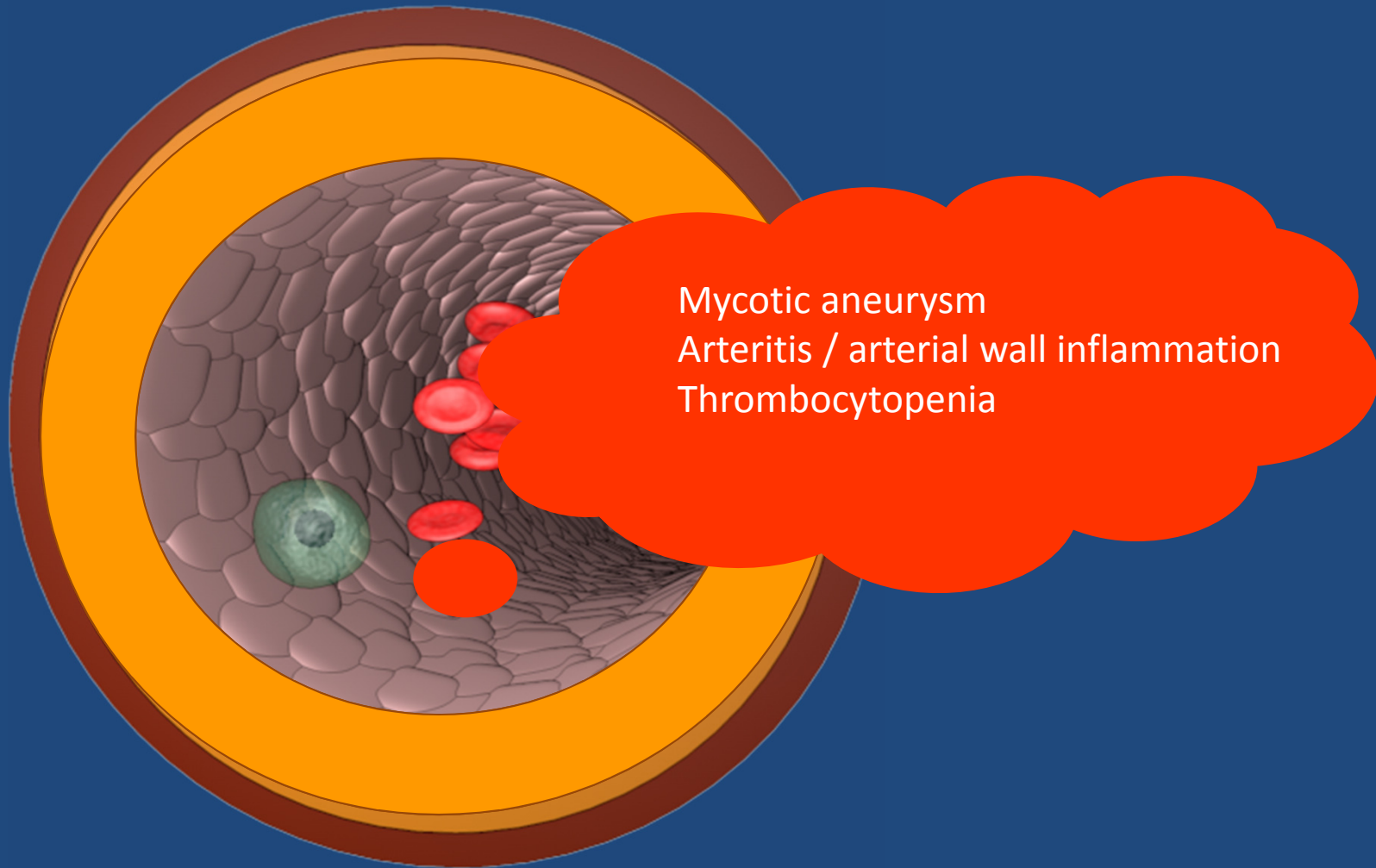
- CRP
- IL 6

Endothelial activation  
Procoagulant state

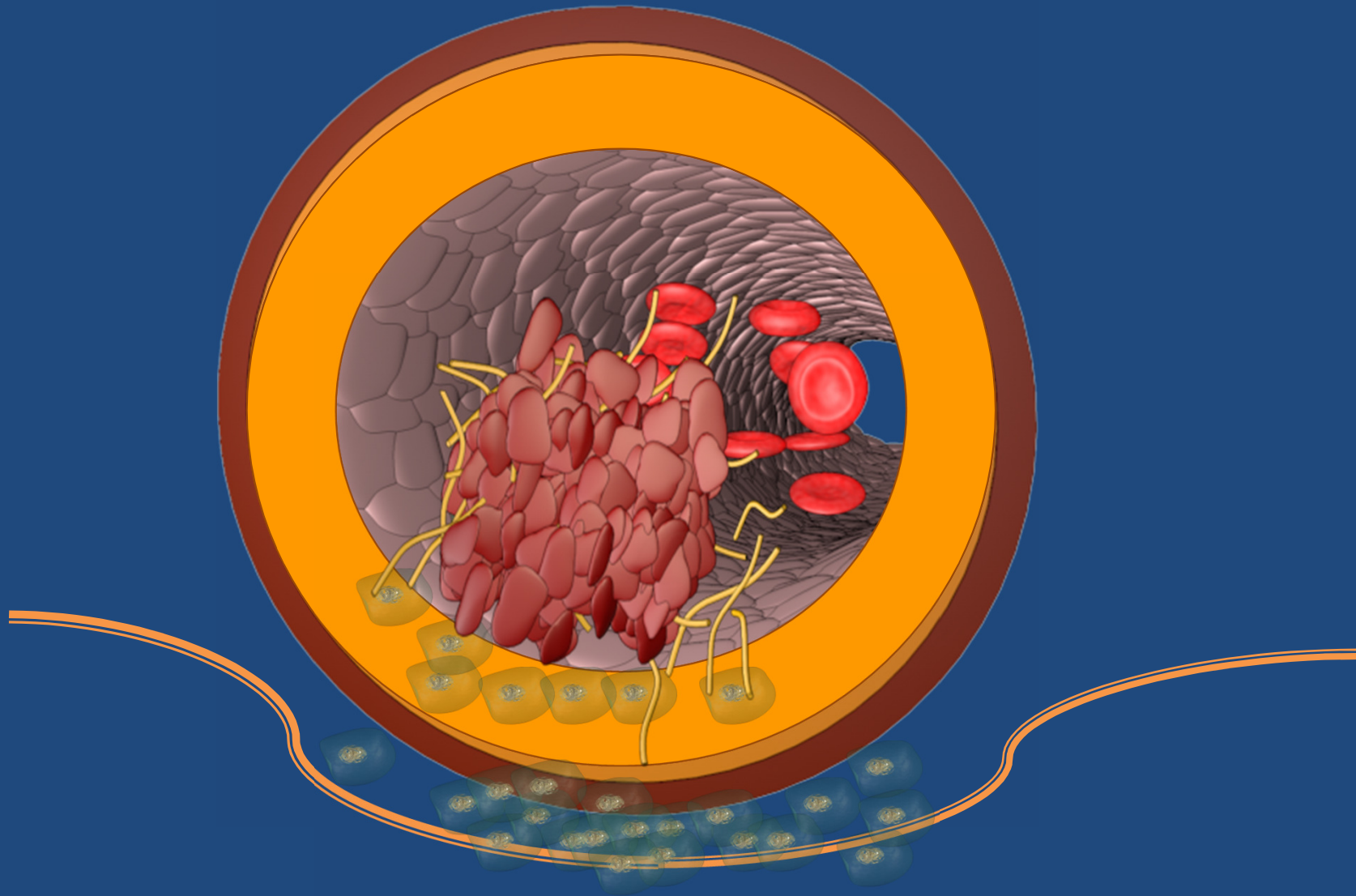
Atherosclerotic instability

Emsley and Hopkins *Lancet Neurology* 2008, 7: 341-53

# Mechanisms of stroke in infection - haemorrhage



# Meningitis





## Infection – Bacterial meningitis

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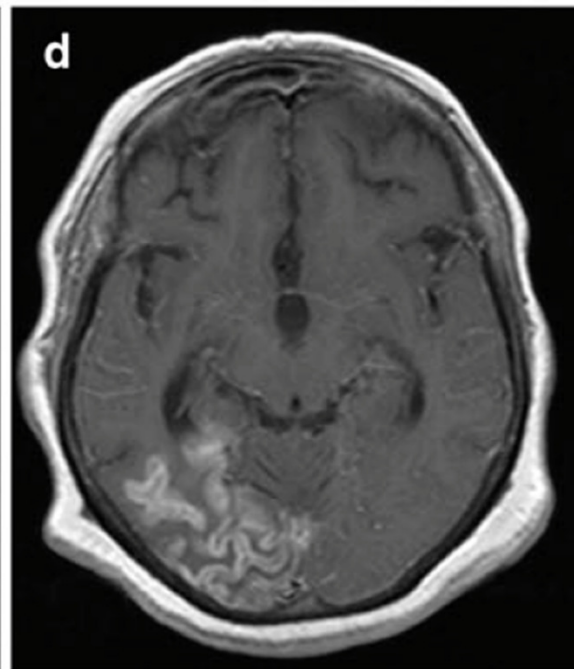
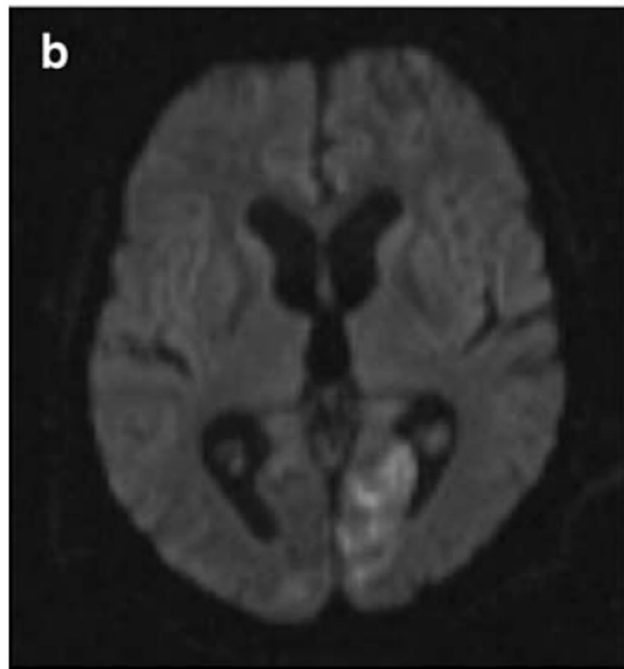
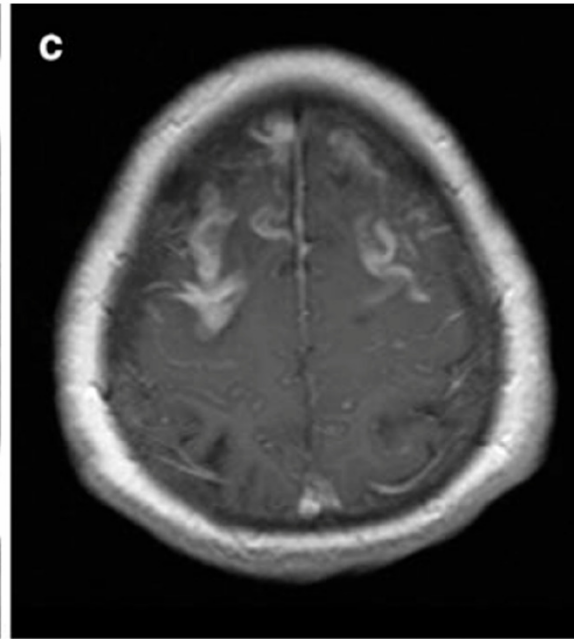
- Prospective study of 86 adults with bacterial meningitis (30 *S pneumoniae*) (Pfister et al *Arch Neurol* 1993, 50: 575 – 81)
  - 13 (15%) had ischaemic stroke
  - 4 (5%) venous infarction
  - 2 (2%) intracerebral haemorrhage (1 after shunt change for hydrocephalus)
- Cerebral angiography performed in 27 (31%) because of focal neurological deficit, abnormality on CT, or persistent coma after three days of antibiotic therapy
  - 13 of 27 had vascular abnormalities
    - Vessel wall irregularities
    - Arterial occlusion
    - Focal arterial bleeding
    - Thrombosis of the superior sagittal sinus and cortical veins

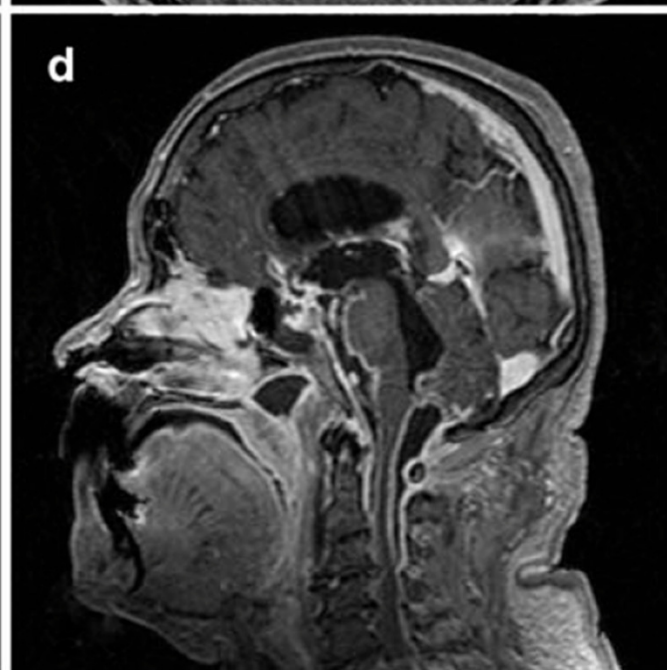
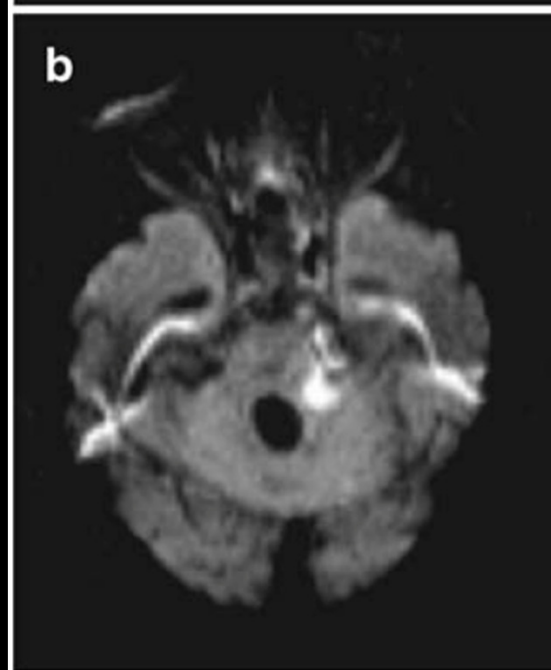
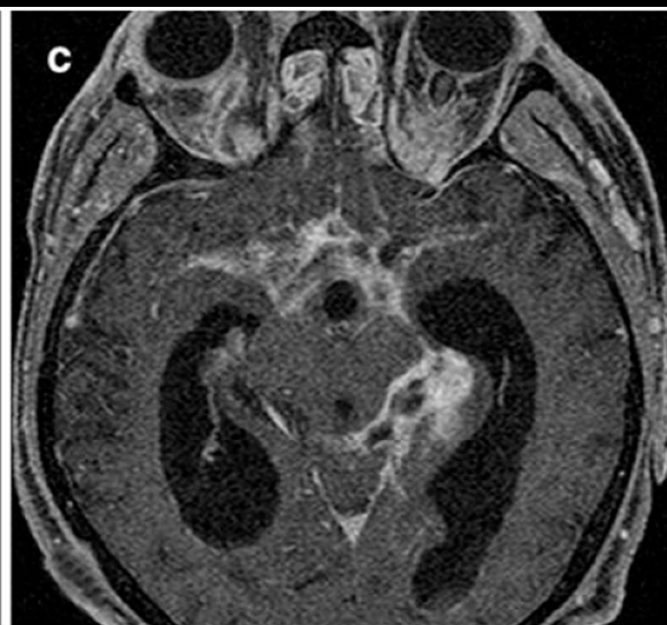
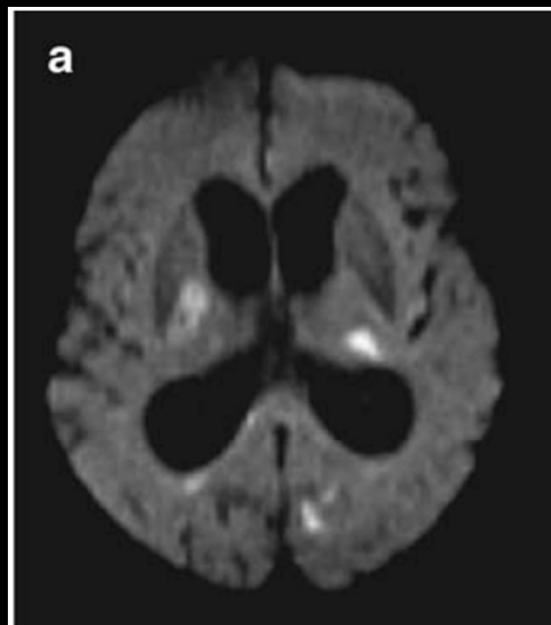
## Infection – Bacterial meningitis

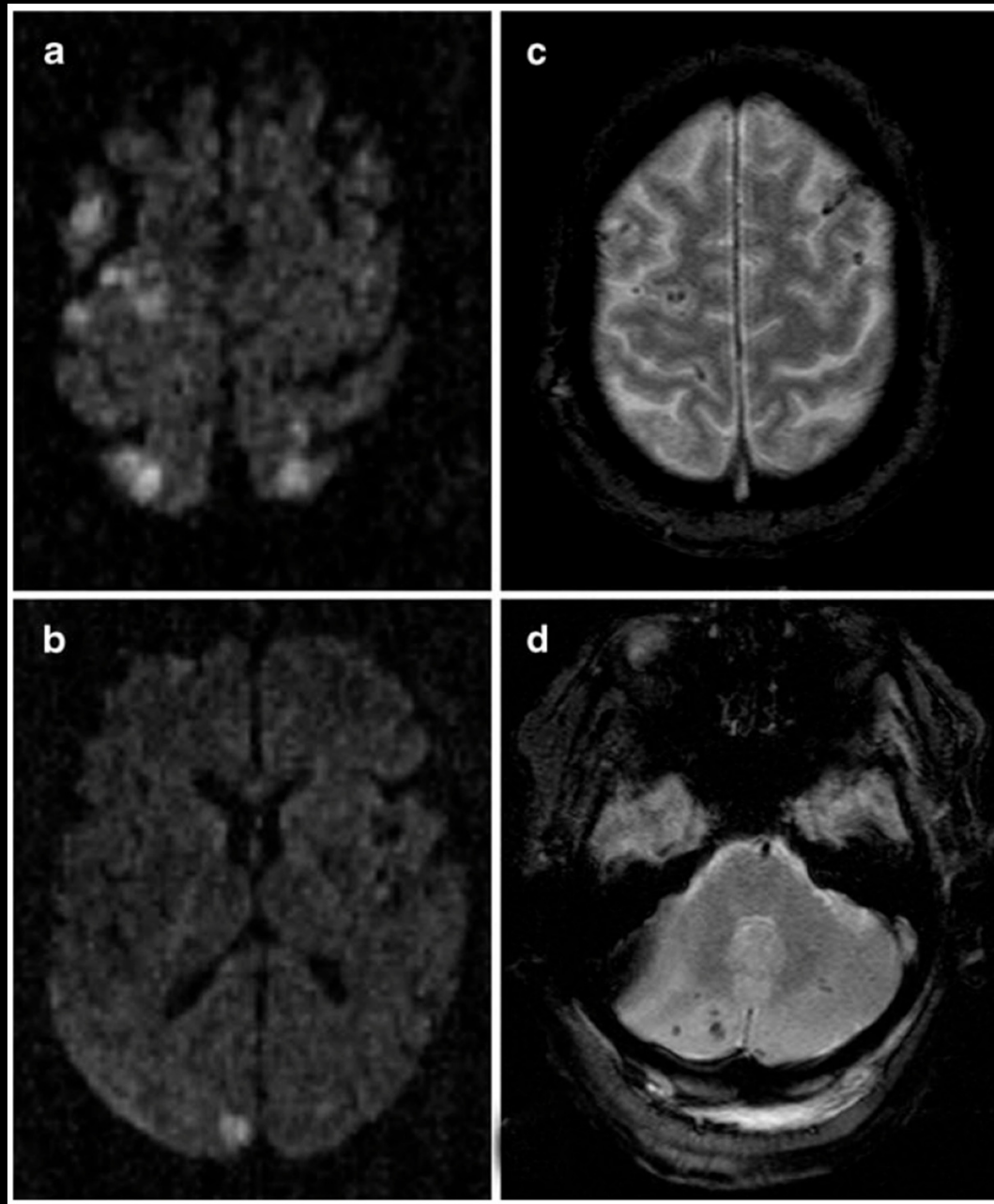
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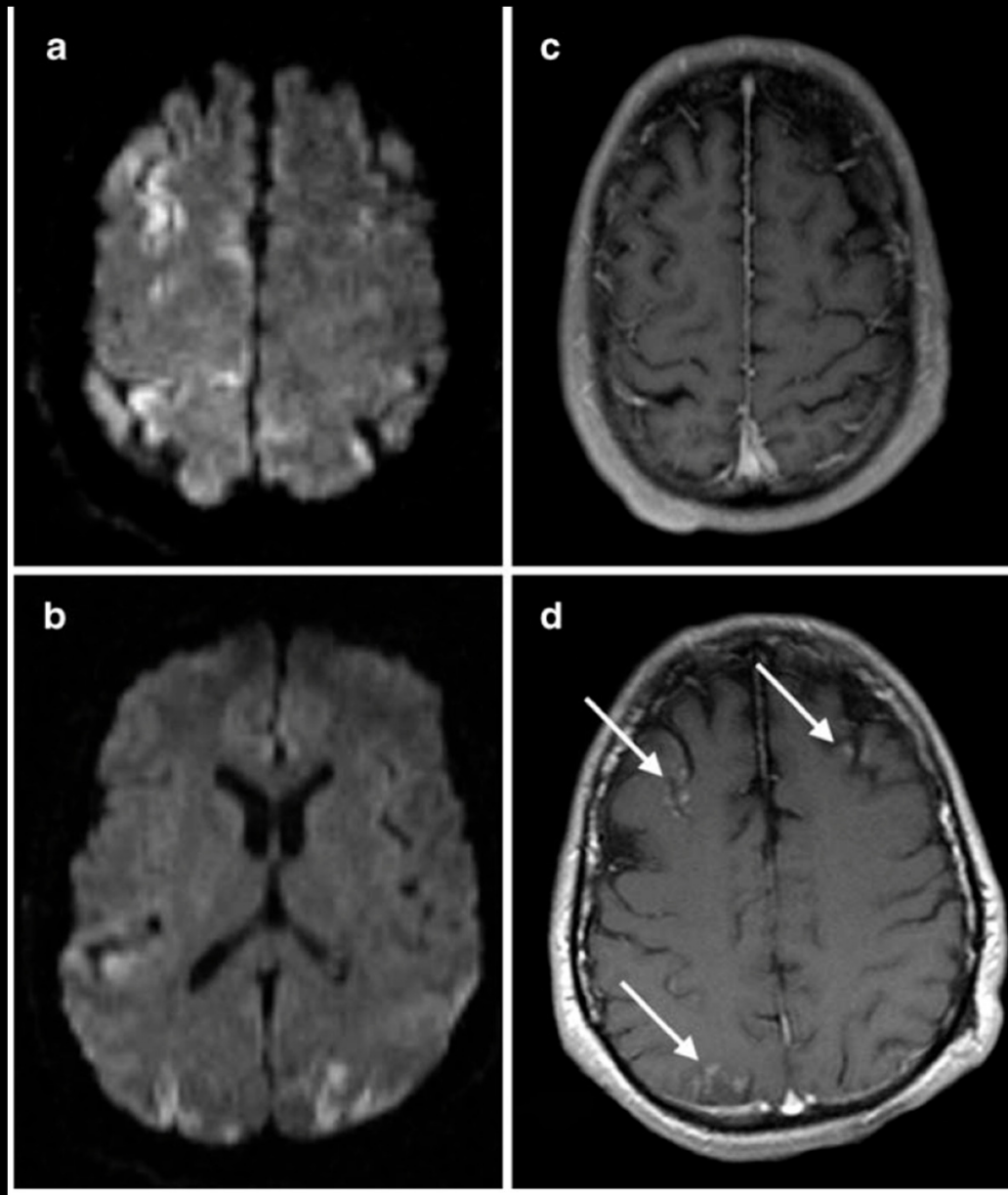
### Blood vessels involved:

- Retrospective review of radiological findings in 68 adults admitted to ICU in Berlin (Katchanov et al *Neuroradiology* 2009, 51: 723-9)
- 7 patients had ischaemic brain lesions (*S pneumoniae* (3), *N meningitidis* (1), *beta-haemolytic strep* (1), *no growth* (2))
- four patterns:
  - territorial (large / medium vessel ischaemia)
  - perforator ischaemia (small vessel)
  - cardioembolic (normal cerebral angiography)
  - isolated cortical lesions (normal cerebral angiography)











## Infection – Tuberculous meningitis

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Tubercular protein in subarachnoid space produces intense hypersensitivity reaction with inflammation mostly around the base of the brain. Results in:

- Arachnoiditis with strangulation, spasm and constriction of vessels
- Periarteritis and panarteritis with secondary thrombosis

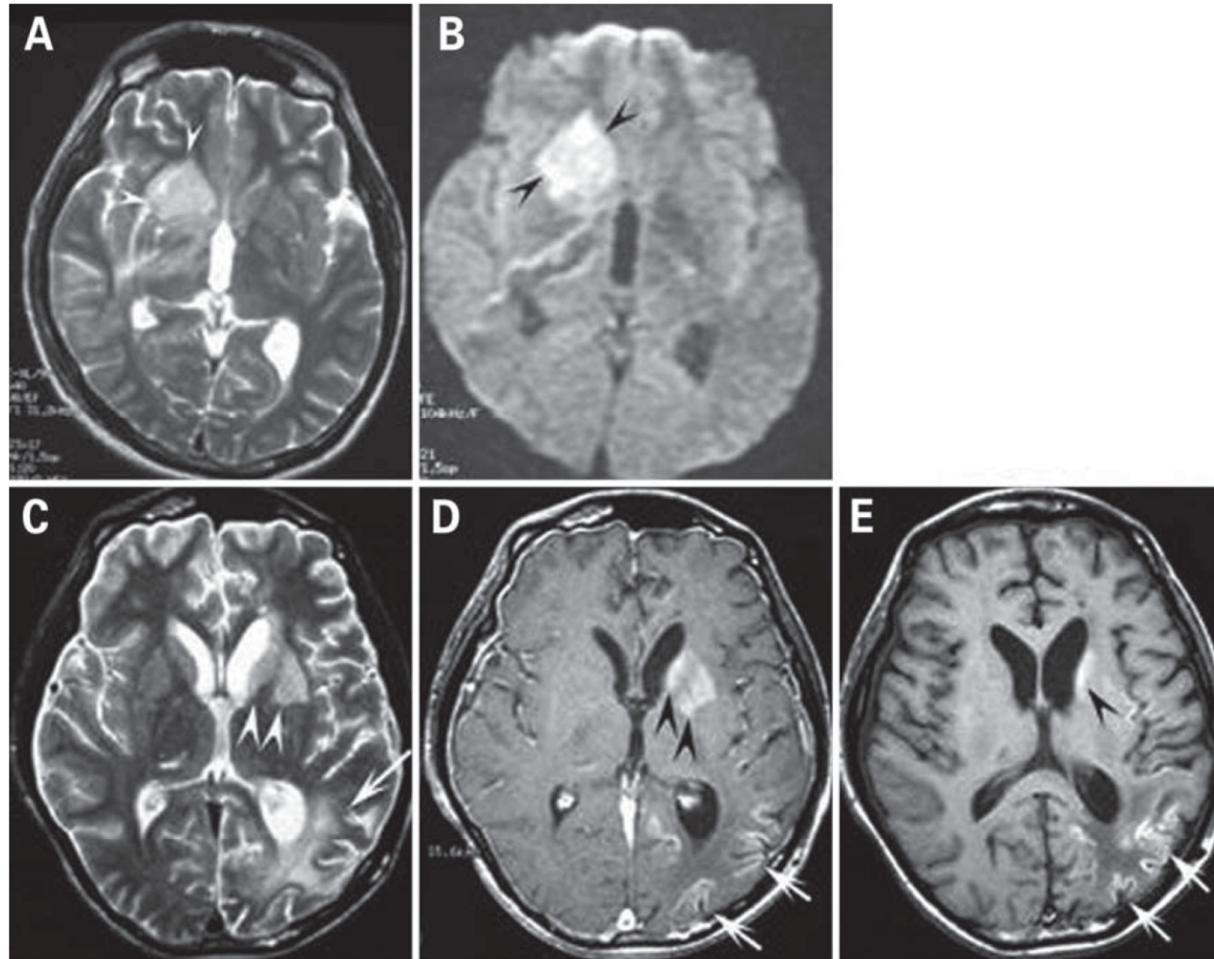
Prospective study of 40 patients with TBM, all had an initial CT brain scan, CT / MRI three months after presentation and CT for deterioration (Chan et al *Cerebrovasc Dis* 2005, 19: 391-5). Corticosteroids for six weeks.

- 12 (30%) had ischaemic stroke (symptomatic in 9)
- 7 'large artery' and 5 'lacunar infarction'
- Patient characteristics did not determine ischaemic stroke subtype and stroke subtype did not determine outcome

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Stroke

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**Fig. 1.** A patient with TBM complicated by right basal ganglia large artery infarct (arrowheads) shown on T<sub>2</sub>-weighted (**A**) and diffusion-weighted (**B**) images on MRI scan. **C** Subacute CI over left caudate nucleus and lentiform nucleus (arrowheads) and left parieto-occipital lobe (arrow) on T<sub>2</sub>-weighted image on MRI scan in another patient with TBM complicated by large artery infarcts. **D** Hyperintense signal over left caudate nucleus on T<sub>1</sub>-weighted image compatible with blood product complicating infarction (arrowheads) and similar hemorrhagic transformation over the left parieto-occipital lobe (arrows). **E** T<sub>1</sub>-weighted image with gadolinium injection shows mild enhancement and hemorrhagic transformation over LAI over left caudate nucleus and lentiform nucleus (arrowhead).

**TABLE 2.** *Infections associated with cerebrovascular disease*

Infection	References
Spirochetal	
Syphilis	Del Mar Saez de Ocariz et al., 1996
Leptospirosis	Forwell et al., 1984
Bacterial	
Bacterial meningitis ( <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> , <i>Escherichia coli</i> , <i>Streptococcus milleri</i> )	Igarashi et al., 1984; Perry et al., 1992; Weststrate et al., 1996
Infective endocarditis	Valtonen et al., 1993
Toxic shock syndrome	Black and Maw, 1984
Lyme disease	Uldry et al., 1987; Reik, 1993; Oksi et al., 1998
Tuberculosis	
Tuberculous meningitis	Lan et al., 2001
Fungal	
Cryptococcal meningitis	Lan et al., 2001
Aspergillus meningitis	Del Brutto, 2000
Coccidioidomycosis	Mischel and Vinters, 1995
Candidiasis	Del Brutto, 2000
Mucormycosis	Del Brutto, 2000
Viral	
Herpes zoster	Eidelberg et al., 1986; Fukumoto et al., 1986; Sigal, 1987; Melanson et al., 1996
Chickenpox	Askalan et al., 2001; Leopold, 1993
HIV/AIDS	Visudtibhan et al., 1999; Dubrovsky et al., 1998; Picard et al., 1997; Pinto, 1996; Connor et al., 2000
Hepatitis C	Tembl et al., 1999
Mumps	Grau et al., 1998b
Rubella	Connolly et al., 1975
Coxsackie A9	Roden et al., 1975
California encephalitis virus	Leber et al., 1995
Mycoplasma	Fu et al., 1998; Mulder and Spierings, 1987; Dowd et al., 1987
Worms	
Cysticercosis	Barinagarrementeria and Cantú, 1998; Del Brutto, 1992
Neurotrichinosis	Fourestie et al., 1993
Hydatid disease	Benomar et al., 1994
Cat-scratch disease	Selby and Walker, 1979
Carotid inflammation	
Pharyngitis, tonsillitis, lymphadenitis	Bickerstaff, 1964

## Case 1

---

A 66 year old, retired fitness instructor presented with a sudden onset left hemiparesis. She was shopping with her daughter, complained of a sudden increase in headache, appeared 'not right' and vague and then collapsed. She did not lose consciousness and responded normally but could not move her left arm and leg.

About six months earlier she developed almost daily headaches following shingles which involved her right forehead but not her eye. No vascular risk factors. Depression diagnosed eight months earlier.

General examination apart from evidence of mild scarring around the site of previous zoster rash was normal. She had a left hemiparasis and reduced sensation on the left side of her face and body.

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Stroke

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## Case 1

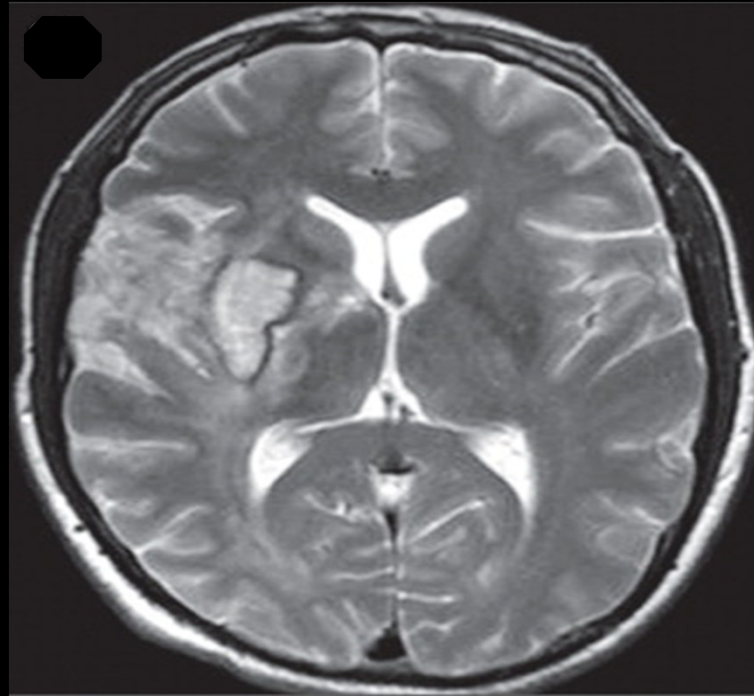
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What would you do now?

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Stroke

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## Case 1

---

Normal: CXR, ECG, cardiac echo normal, electrolytes, FBC, glucose, CRP 28, HIV negative, vasculitic screen negative, antiphospholipid antibodies negative

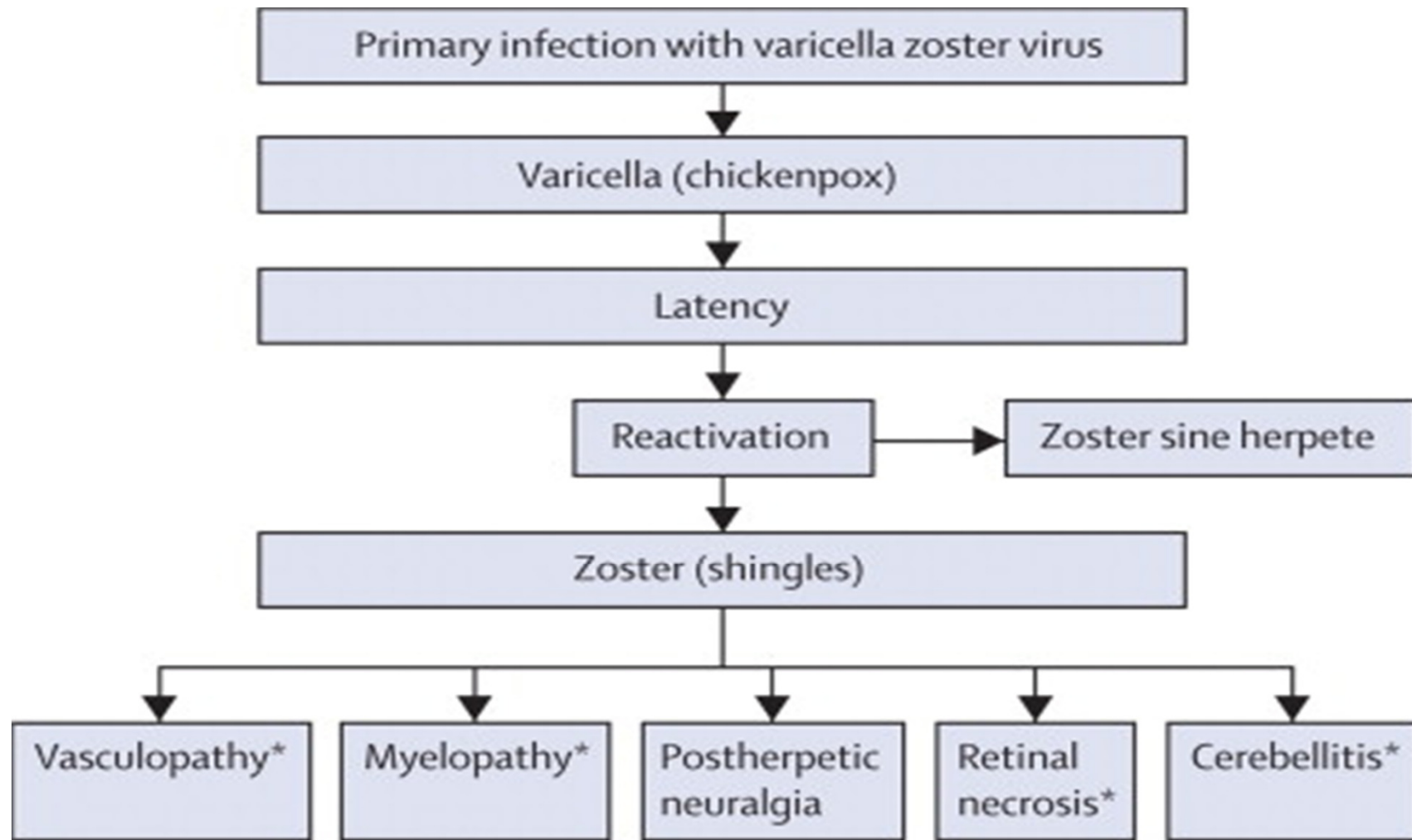
### CSF:

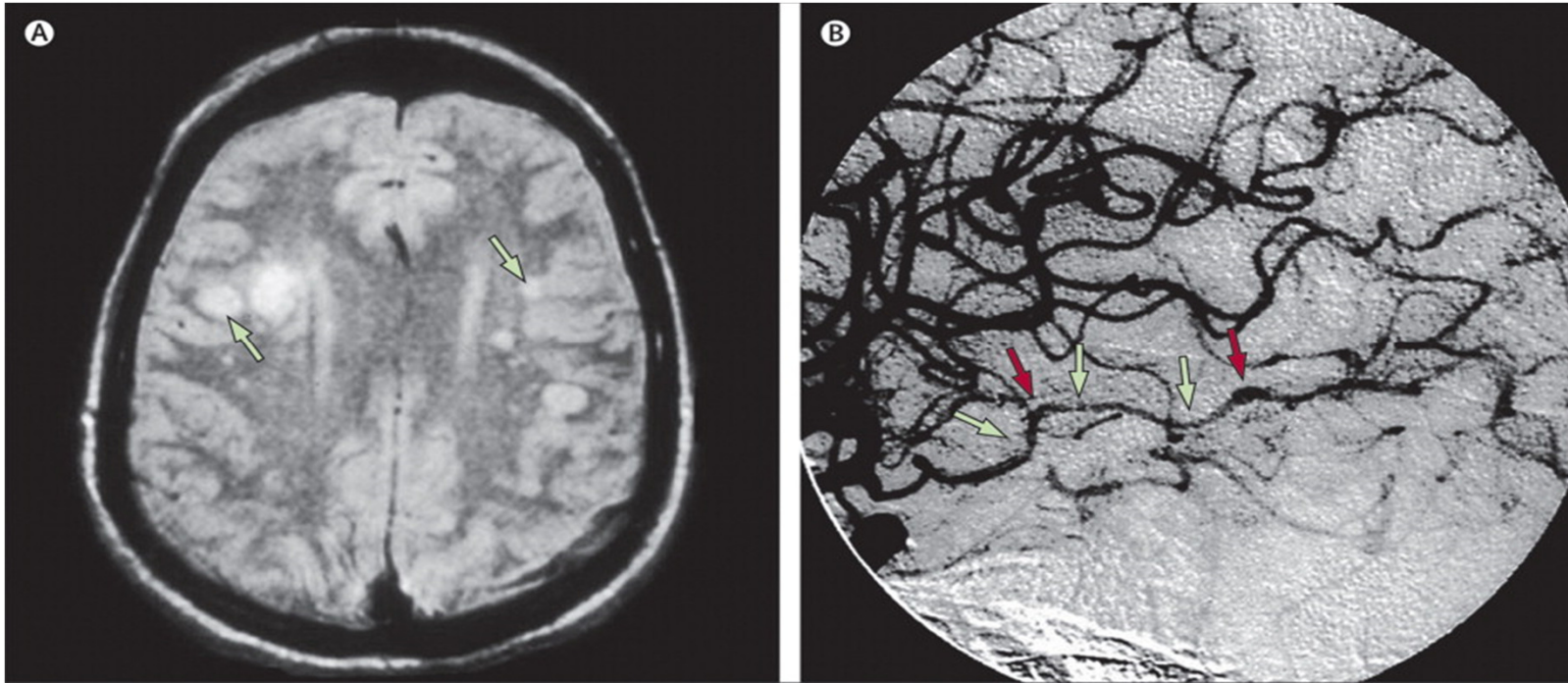
White cell count	80 (75% lymphocytes) cells/mm <sup>3</sup>
Red cell count	50 cells/mm <sup>3</sup>
Glucose	normal
Protein	normal
TB culture	negative
Crypto (India ink / ag)	negative
Syphilis	negative
VZV IgG	positive
VZV PCR	positive

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Stroke

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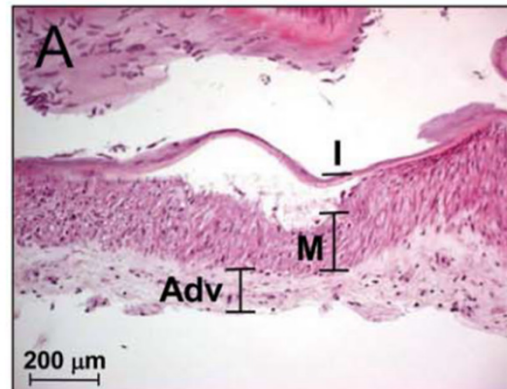


Arteries

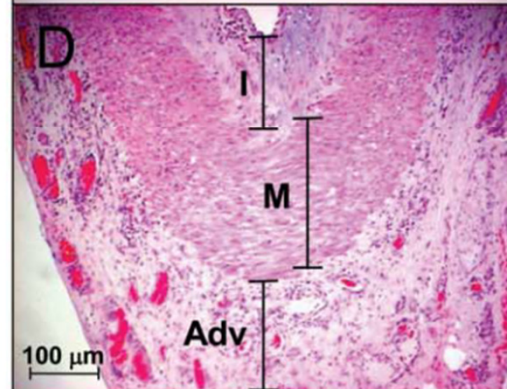
Stain

H&E

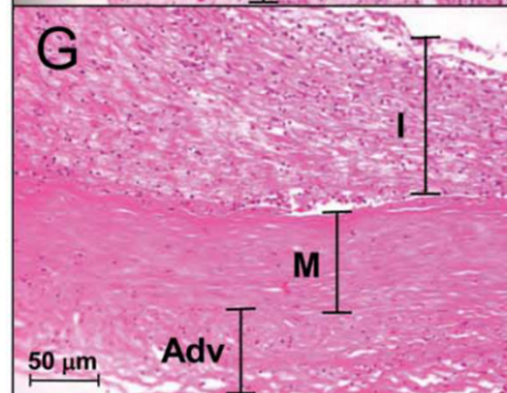
Normal



Early  
VZV  
vasc



Late  
VZV  
vasc



## Case 1

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Recommended treatment:

Aciclovir for 14 days

5 days of oral prednisolone 1mg/kg

(Gilden et al *Lancet Neurology* 2009, 8 :731-40)

## Case 2

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35 year old man admitted to the acute admission ward at Johannesburg Hospital, South Africa. He worked as a gardener at the local Botanic Gardens and lived with his partner and 5 year old daughter.

He was previously well apart from left sided Bell's Palsy 12 months earlier. He woke that morning unable to move his right side. No vascular risk factors.

Neurological examination: left hemiparesis and loss sensation

The A+E team note that his HIV serology is positive.

What would you do now?

---

Stroke

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## Case 2

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Scan



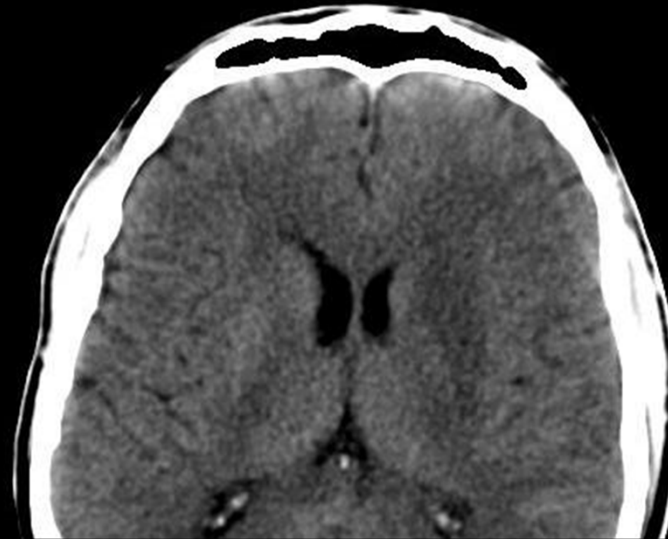
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Stroke

## Case 2

---

Scan



What would you have done if he  
was eligible for thrombolysis on admission?

---

## Stroke

---

## Case 2

---

Normal: CXR, ECG, cardiac echo normal, electrolytes, FBC, glucose, vasculitic screen negative, antiphospholipid antibodies negative, syphilis negative, CD 4: 380

### CSF:

White cell count	15 (100% lymphocytes) cells/mm <sup>3</sup>
Red cell count	0 cells/mm <sup>3</sup>
Glucose	normal
Protein	normal
TB culture	negative
Crypto (India ink / ag)	negative
Syphilis	negative
VZV IgG	negative

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Stroke

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## Case 2

---

Normal: CXR, ECG, cardiac echo normal, electrolytes, FBC, glucose, vasculitic screen negative, antiphospholipid antibodies negative, syphilis negative, CD 4: 489

CSF:

White cell count

Red cell count

Glucose

Protein

TB culture

Crypto (India)

Syphilis

VZV IgG

Does HIV cause stroke?

---

Stroke

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.

	Prevalence		All Stroke (WHO definition)				
	All stroke(n=223)	Controls (n=503)	Unadjusted OR (95% CI) p value		Adjusted OR (95% CI) p value		PAF
<b>HIV Status</b>							
HIV negative	152 (68)	408 (81)	1				
Untreated	37(17)	47 (9)	2.11	(1.32,3.38) 0.002	3.84	(2.16,6.85) <0.001	8 (4,12)
Had cART for <6 months	16 (7)	7 (1)	6.13	(2.48,15.2) <0.0001	12.1	(4.18,34.8) <0.001	5 (3,7)
Had cART for ≥6 months	14 (6)	38 (8)	0.98	(0.52,1.88) 0.973	1.12	(0.54,2.33) 0.758	0.3 (-2,3)
<b>CD4 T-lymphocyte cell count</b>							
HIV negative	152 (68)	408 (81)	1				
≥ 500 cell cells/mm <sup>3</sup>	4 (2)	27 (5)	0.40	(0.14,1.16) 0.090			
350-500 cells/mm <sup>3</sup>	11 (5)	23 (5)	1.28	(0.61,2.69) 0.510			
<350 cells/mm <sup>3</sup>	48 (22)	39 (8)	3.30	(2.08,5.24) <0.0001			
<b>Hypertension<sup>¶</sup></b>	165 (74)	273 (54)	2.44	(1.72,3.46) <0.0001	3.53	(2.27,5.49) <0.001	39 (26,49)



### **Panel 1: Possible HIV-related causes of stroke**

#### **Ischaemic**

*HIV-associated vasculopathy (abnormality of the cerebral blood vessels as a direct or indirect result of HIV infection, but excluding opportunistic infection vasculitis)*

- Associated with aneurysm formation (either intracranial or extracranial)
- Vasculitis (as a direct result of HIV infection, excluding opportunistic infection)
- Accelerated atherosclerosis
- Other disease of cerebral blood vessels associated with HIV infection (including small vessel disease changes and altered vasoreactivity)

#### *Opportunistic infection or neoplasia*

- Opportunistic infection causing stroke (eg, tuberculous meningitis, varicella zoster virus vasculitis, meningovascular syphilis)
- Neoplasia, such as lymphoma involving cerebral blood vessels

#### *Cardioembolism*

- Bacterial endocarditis
- Marantic endocarditis
- HIV-associated cardiac dysfunction
- Ischaemic heart disease

#### *Other established cause*

- Coagulopathy (eg, antiphospholipid syndrome)
- HIV-associated hyperviscosity

#### **Haemorrhagic**

- HIV-associated vasculopathy (aneurysm or vasculitis-associated)
- HIV-associated thrombocytopenia
- Mycotic aneurysm (secondary to bacterial endocarditis)

Benjamin et al *Lancet Neurology* 2012; 11: 878-90

## Coagulopathy

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### *Protein C and S deficiency*

- Usually associated with intracranial venous thrombosis rather than arterial stroke
- Deficiencies have been noted in HIV
- One case series from South Africa in 33 patients with HIV and stroke compared to an unmatched group of HIV negative stroke patients found no difference in Protein C and S deficiency (Mochan et al *JNNP* 2005, 76: 1455-56)

*Antiphospholipid antibodies* found in HIV infection but no evidence to suggest this is a clinically relevant cause of stroke

*Factor V Leiden* not associated with HIV related stroke

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## HIV & Stroke

## Cardioembolism

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*Ischaemic heart disease* (post-myocardial infarction / atrial fibrillation)

*Endocarditis* (Marantic or Bacterial)

*HIV-associated cardiac dysfunction*

- Dilated cardiomyopathy frequently reported in sub-Saharan Africa  
(? HIV or opportunistic infection related / high prevalence of non-ischaemic cardiomyopathy and rheumatic heart disease in SSA)

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## HIV & Stroke

## Opportunistic infections

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*Mycobacterium tuberculosis*, syphilis, varicella zoster virus (VZV) – well recognised causes of stroke but HIV infection increases the risk

VZV: rash may be absent in a third of immunosuppressed stroke patients

Cytomegalovirus and *Candida albicans* associated with stroke in case series

cART may unmask occult opportunistic infection

Infection outside the nervous system results in a prothrombotic state and increases the risk of ischaemic stroke

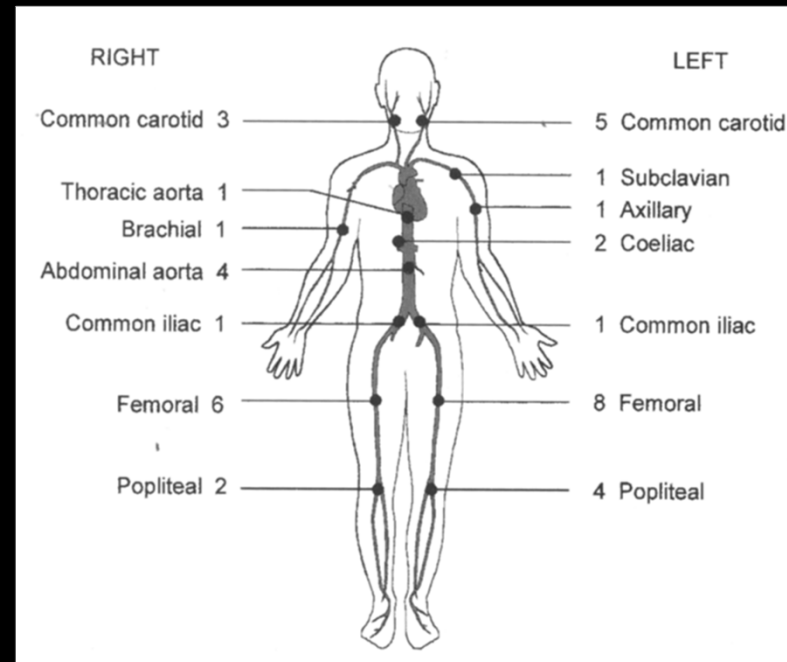
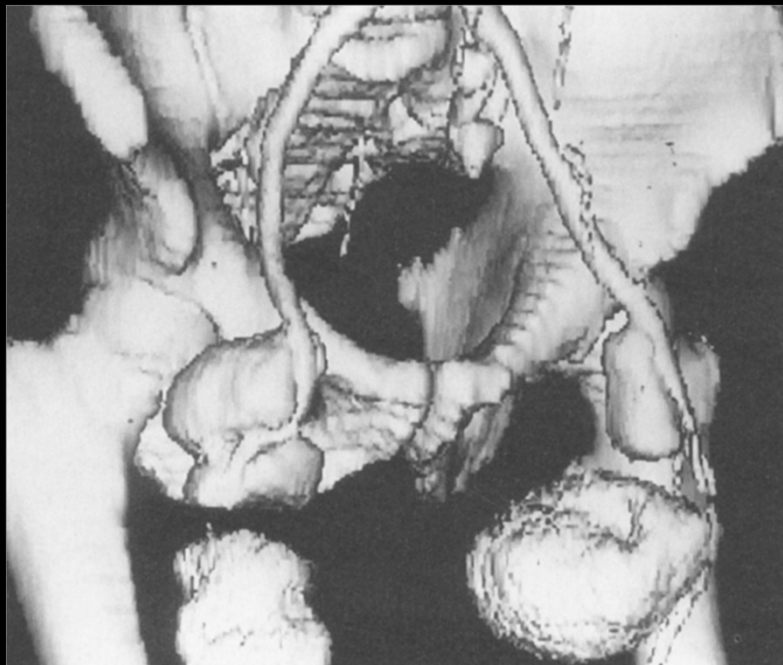
## HIV-associated vasculopathy

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*‘Any abnormality of the cerebral blood vessels as a direct or indirect result of HIV infection, but excluding opportunistic infection vasculitis’*

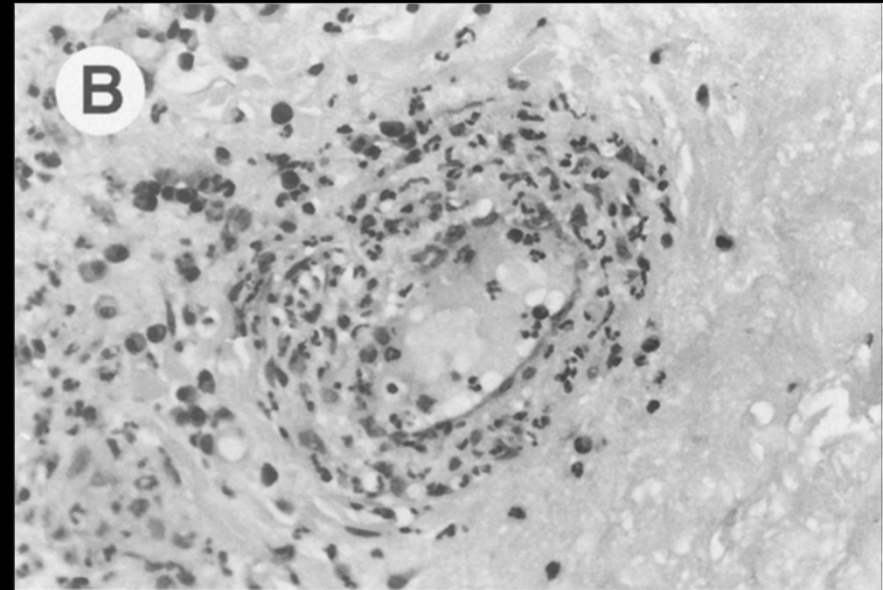
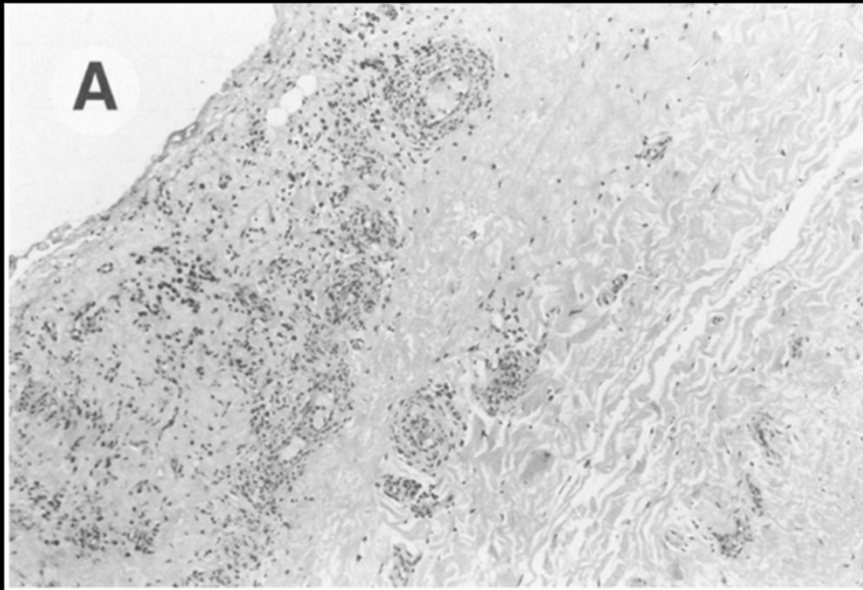
- Associated with aneurysm formation (intracranial or extracranial)
- Vasculitis (once opportunistic infection excluded)
- Accelerated atherosclerosis
- Other:
  - Small vessel disease change
  - Altered vasoreactivity

# Extracranial - HIV associated vasculopathy



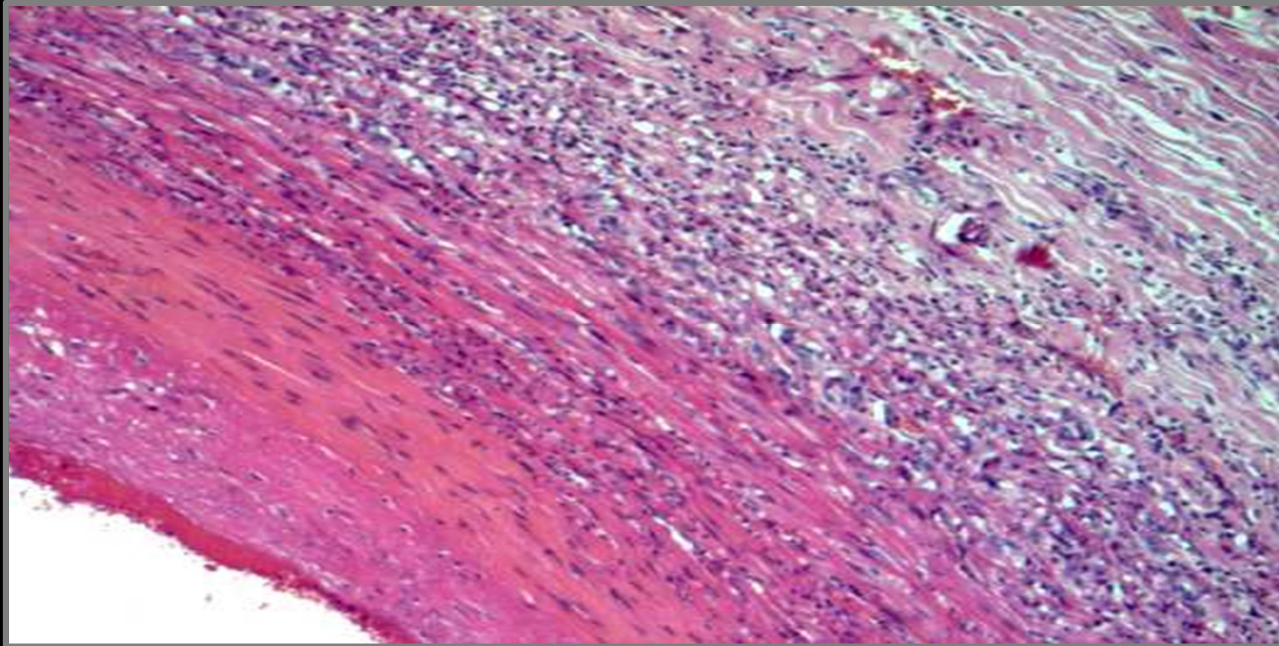
Chetty et al *Human Pathology* 2000, 31:374-379





Chetty et al *Human Pathology* 2000, 31:374-379

Adventitial leucocytoclastic vasculitis of the vasa vasorum



A Bryer, GSH HIV stroke study

Media and intima infiltration with neutrophils; intimal fibrosis with myocyte atrophy and fragmentation of internal elastic lamina. Stains for all organisms were negative. HIV P24 Ag neg.



Modi et al *JNNP* 2008, 79:44-6

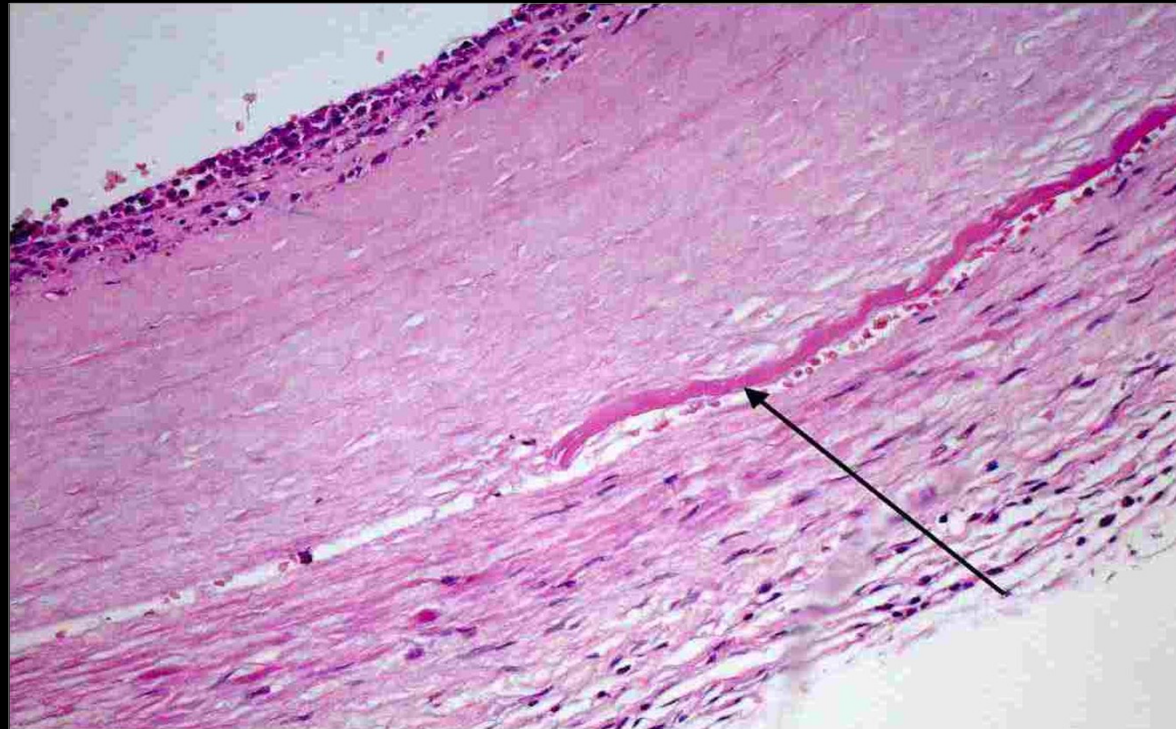


A Bryer, GSH HIV stroke study



A Bryer, GSH HIV stroke study





A Bryer, GSH HIV stroke study

Luminal neutrophilic infiltrate, intimal hyperplasia,  
fragmentation of internal elastic lamina



## HIV-associated vasculopathy – Aneurysm formation

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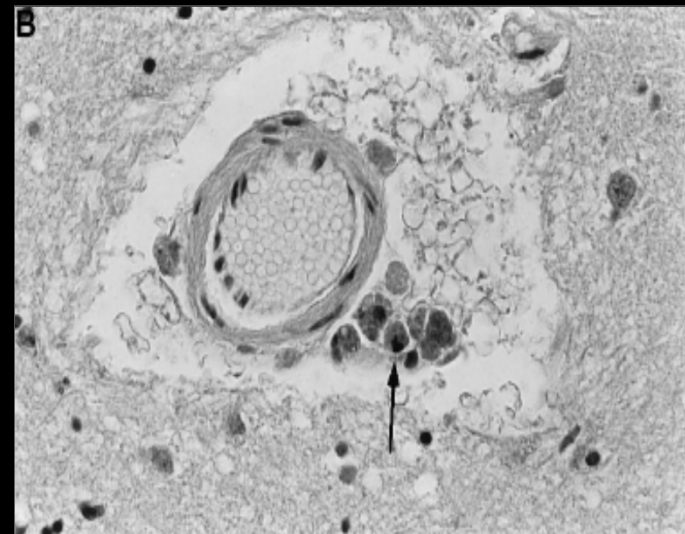
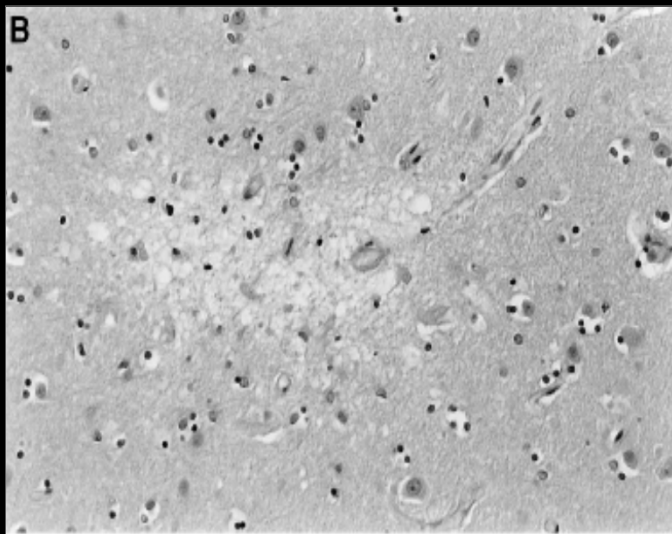
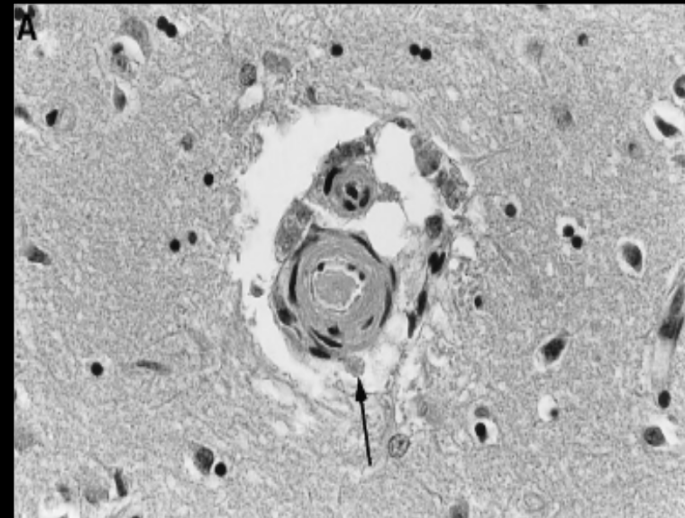
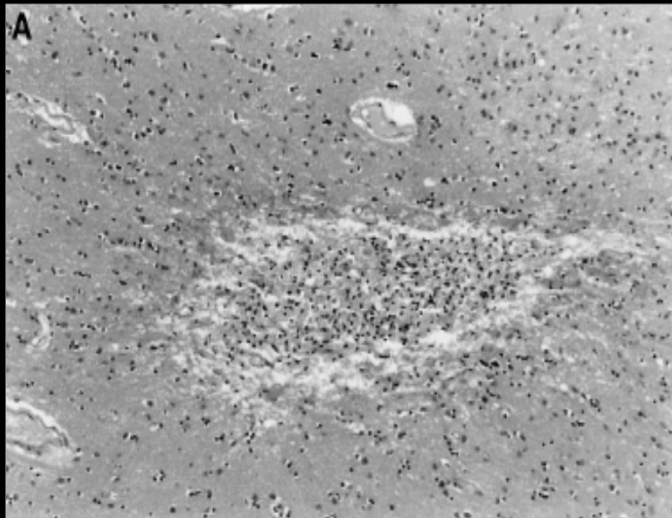
*BUT* could this vasculopathy be due to Varicella Zoster Virus (VZV) rather than HIV? (Nagel et al *Infect Disord Drug Targets* 2010, 10:105-111; Nagel et al *Neurology* 2013, 80: 62-8)

- Some patients CSF tested and negative for VZV PCR, but none tested for anti-VZV IgG
- HIV not detected in the vessel wall of any patients
- Isolated cases of resolution of aneurysmal vasculopathy with ART ... does that imply HIV related
- Changes seen are very similar to those seen in VZV vasculopathy

## Human Immunodeficiency Virus (HIV) infection – Vasculitis

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- Heterogeneous array of extra-cerebral vasculitides been described (Chetty *J Clin Path* 2001, 54: 275-8)
- HIV antigen and particles in perivascular cells in two patients, and HIV-like particules in another patient (Gherardi et al *Arthritis Rheum* 1993, 36: 1164-74)
- Possible mechanisms: direct vessel wall infection, immune deposition, indirect damage caused by cytokines and T cell derived growth factors
- Diagnosis requires exclusion of all other possible causes of vasculitis



# Human Immunodeficiency Virus (HIV) infection – Endothelial dysfunction

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- Endothelium role is to provide:
  - *Selective barrier* to blood contents
  - *Non-thrombotic surface*
  - Protection against *inflammation*

and **Endothelial dysfunction** results in:

- Impaired ability to regulate inflammation and prevent thrombosis

This in turn may lead to atherosclerosis or thrombosis of the cerebral blood vessels and cause stroke

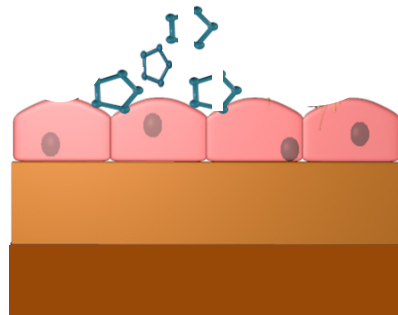
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Stroke

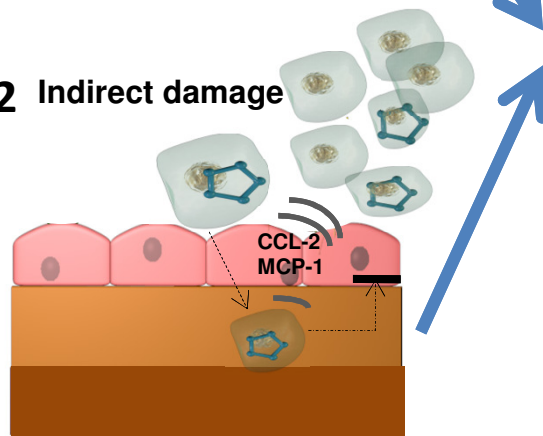
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# Hypotheses on the mechanism of HIV-associated vasculopathy

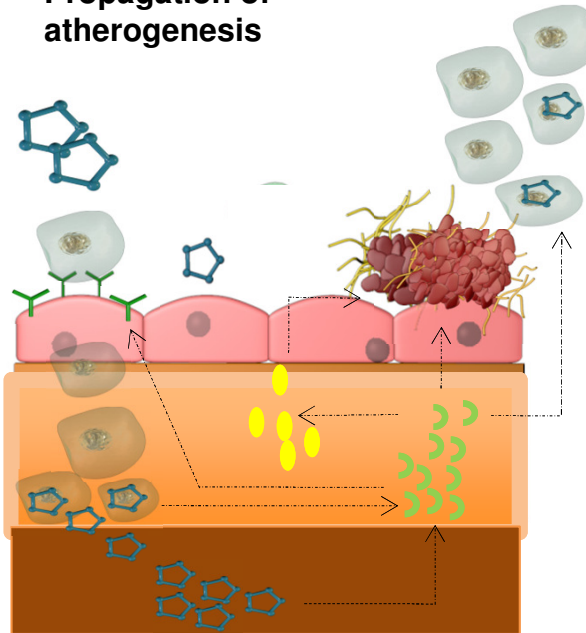
## 1 Direct damage



## 2 Indirect damage

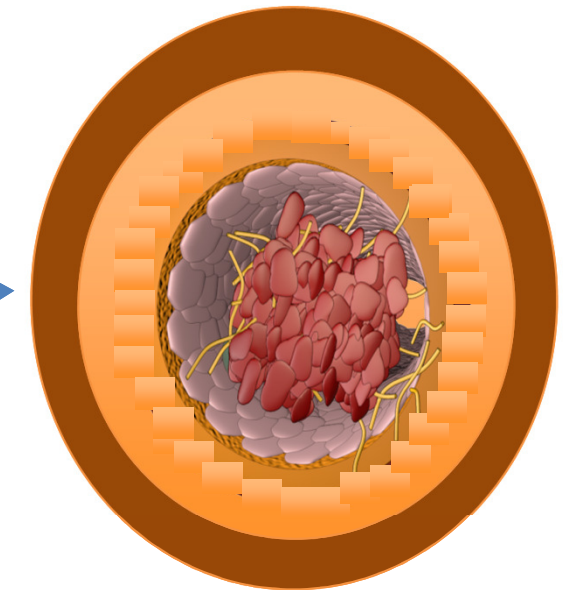


## 3 Progression of damage/ Propagation of atherogenesis



## 4 Exacerbated by vasculitis

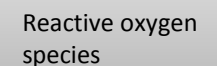
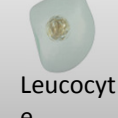
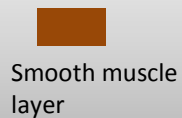
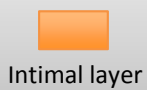
## 5 Vascular event



## 6 Exacerbated by HAART

Benjamin et al. Lancet Neurol 2010

### KEY



## Human Immunodeficiency Virus (HIV) infection – Antiretroviral therapy and the endothelium

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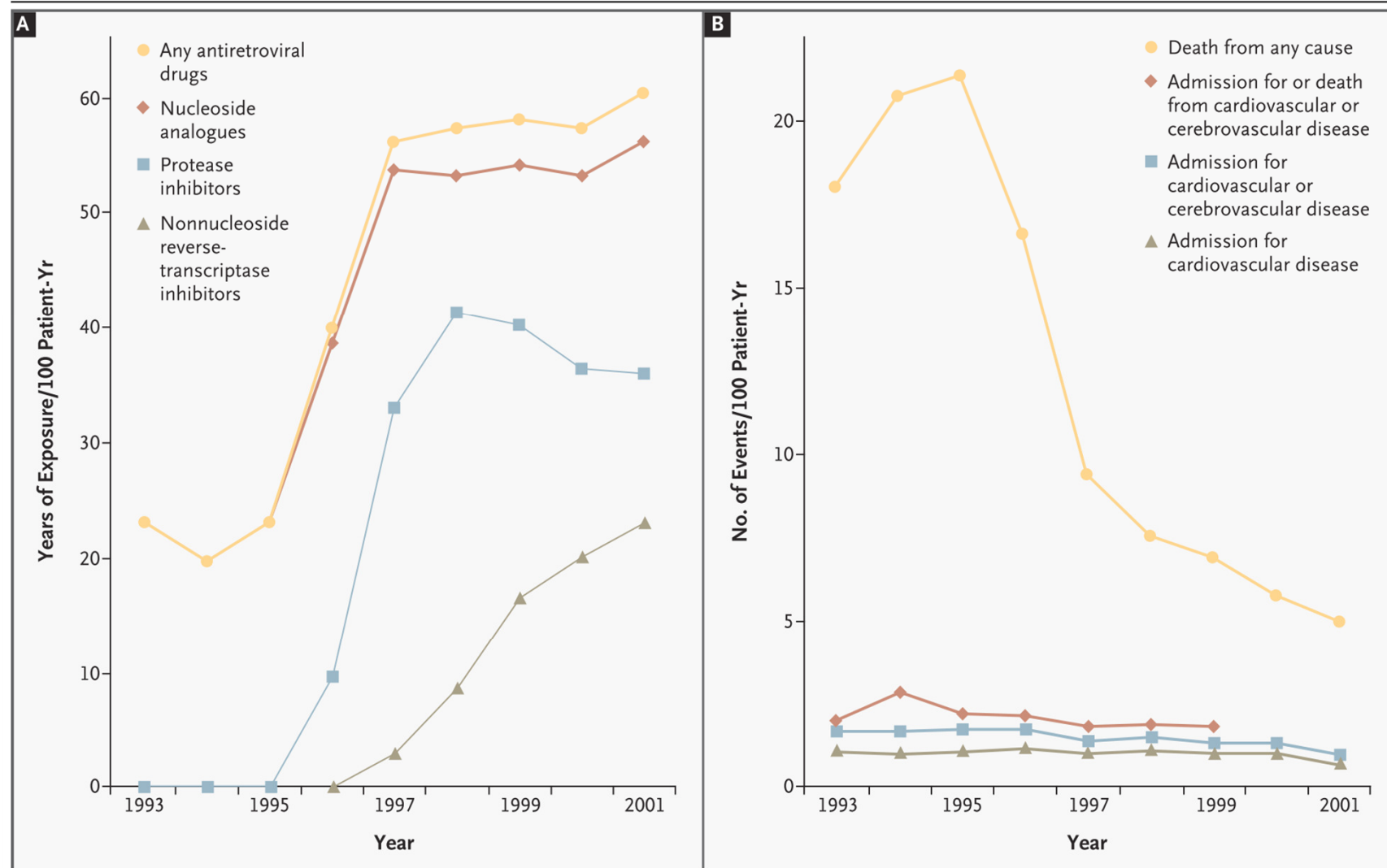
cART and related metabolic changes together with chronic low grade inflammation result in pro-atherosclerotic state

- Dyslipidaemia
  - Insulin resistance
  - Diabetes
  - Low-grade chronic inflammation
  - ? Co-infection with hepatitis C or Cytomegalovirus
  - Mitochondrial dysfunction
- Surrogate markers such as carotid intima media thickness (cIMT) remain abnormal on ART

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Stroke

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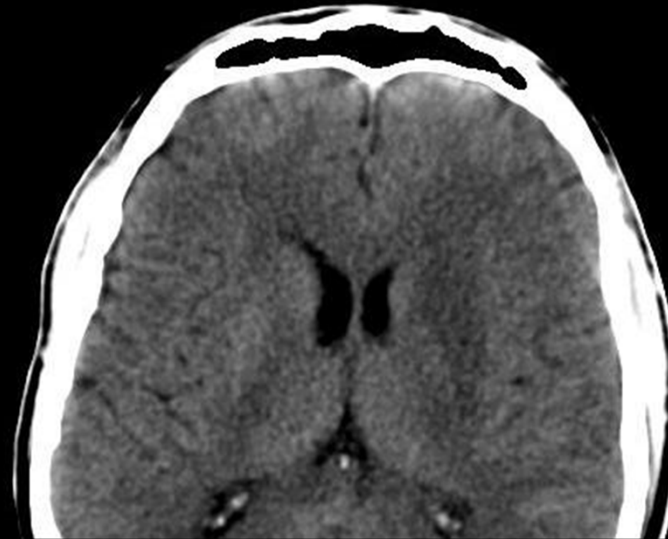
**Figure 1.** Changing Rates of Use of Antiretroviral Drugs (Panel A) and Vascular Events and Death (Panel B).



## Case 2

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Scan

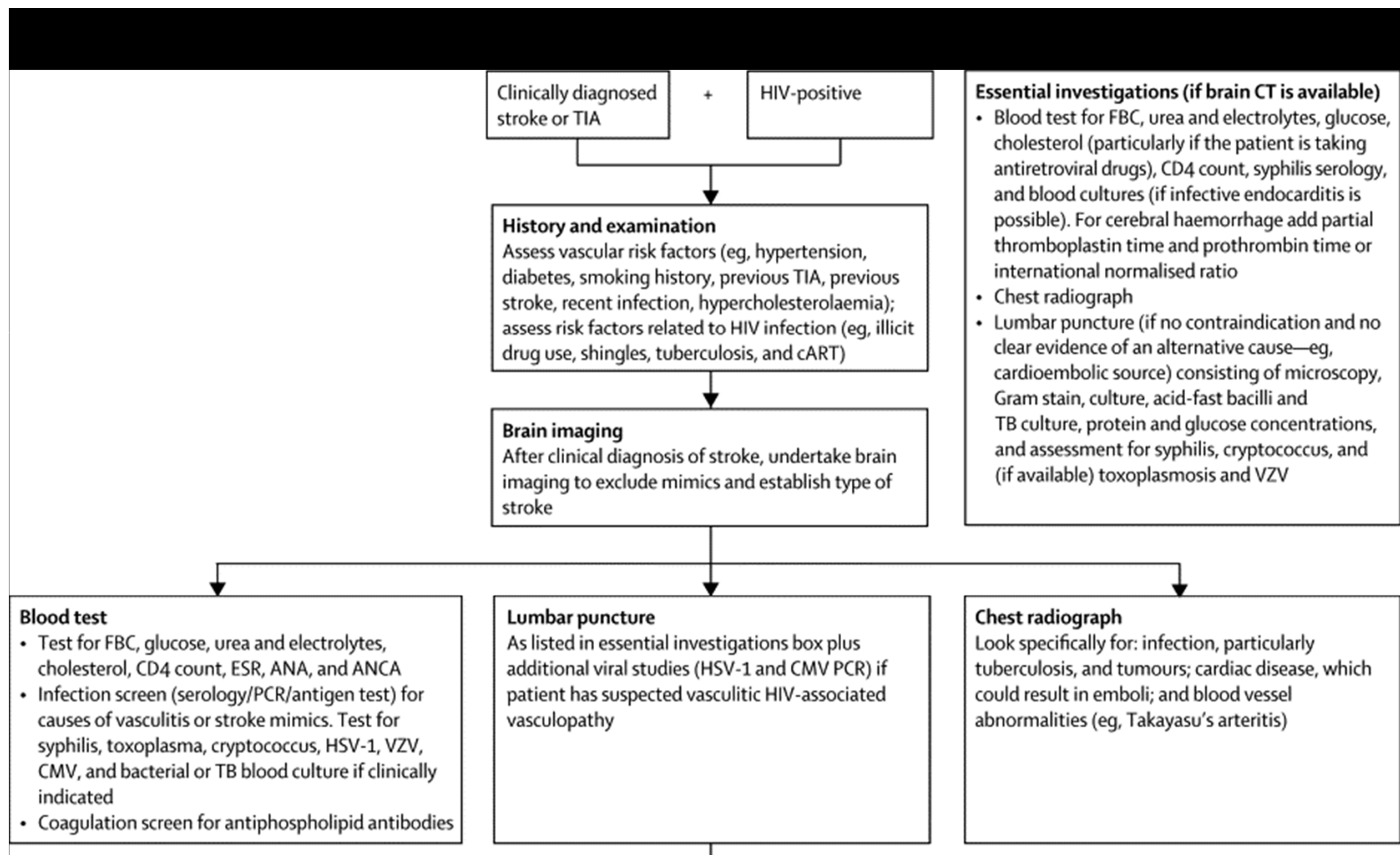


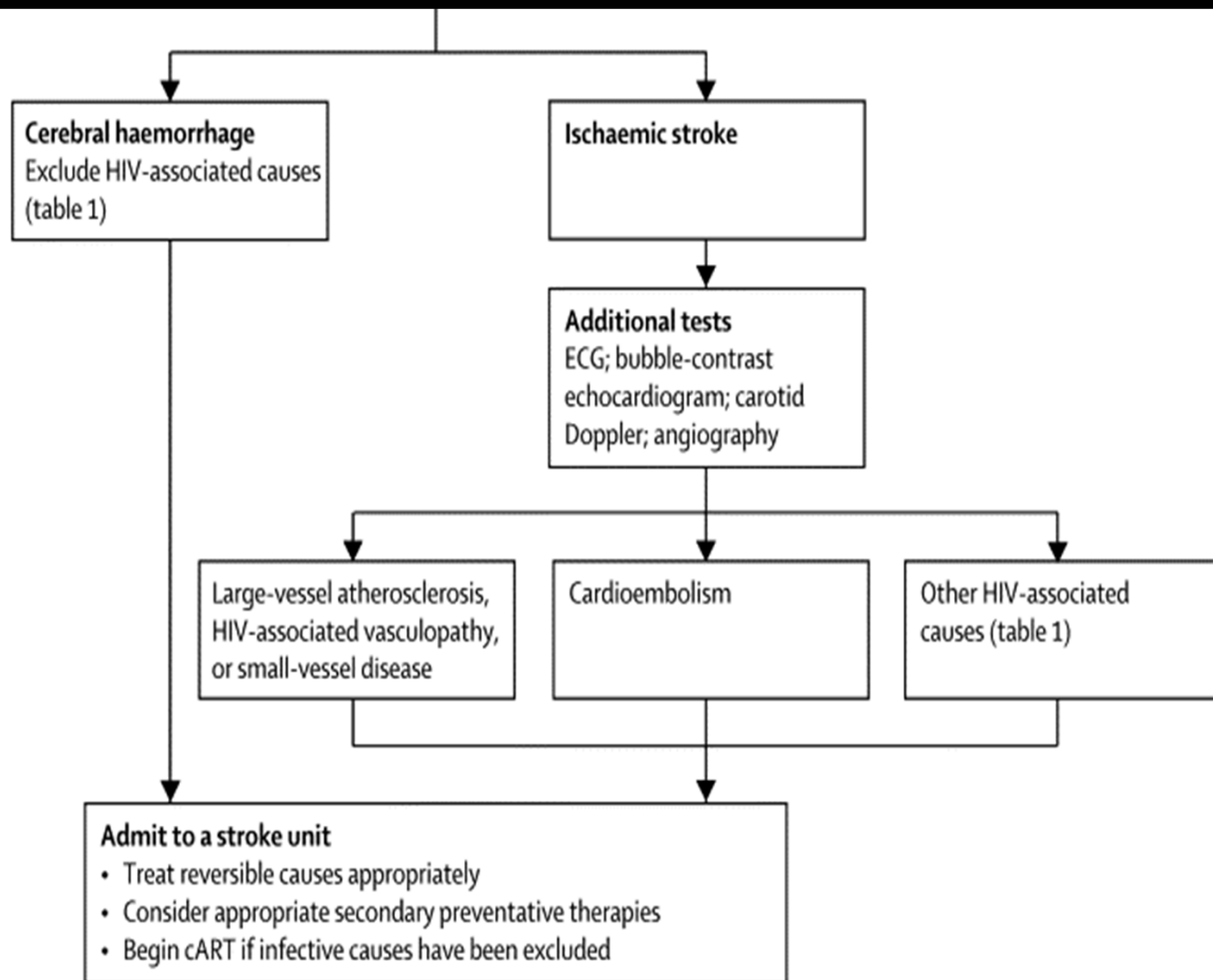
What would you have done if he  
was eligible for thrombolysis on admission?

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## Stroke

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## Human Immunodeficiency Virus (HIV) infection – Secondary prevention

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No good evidence to guide secondary prevention of stroke associated with HIV infection

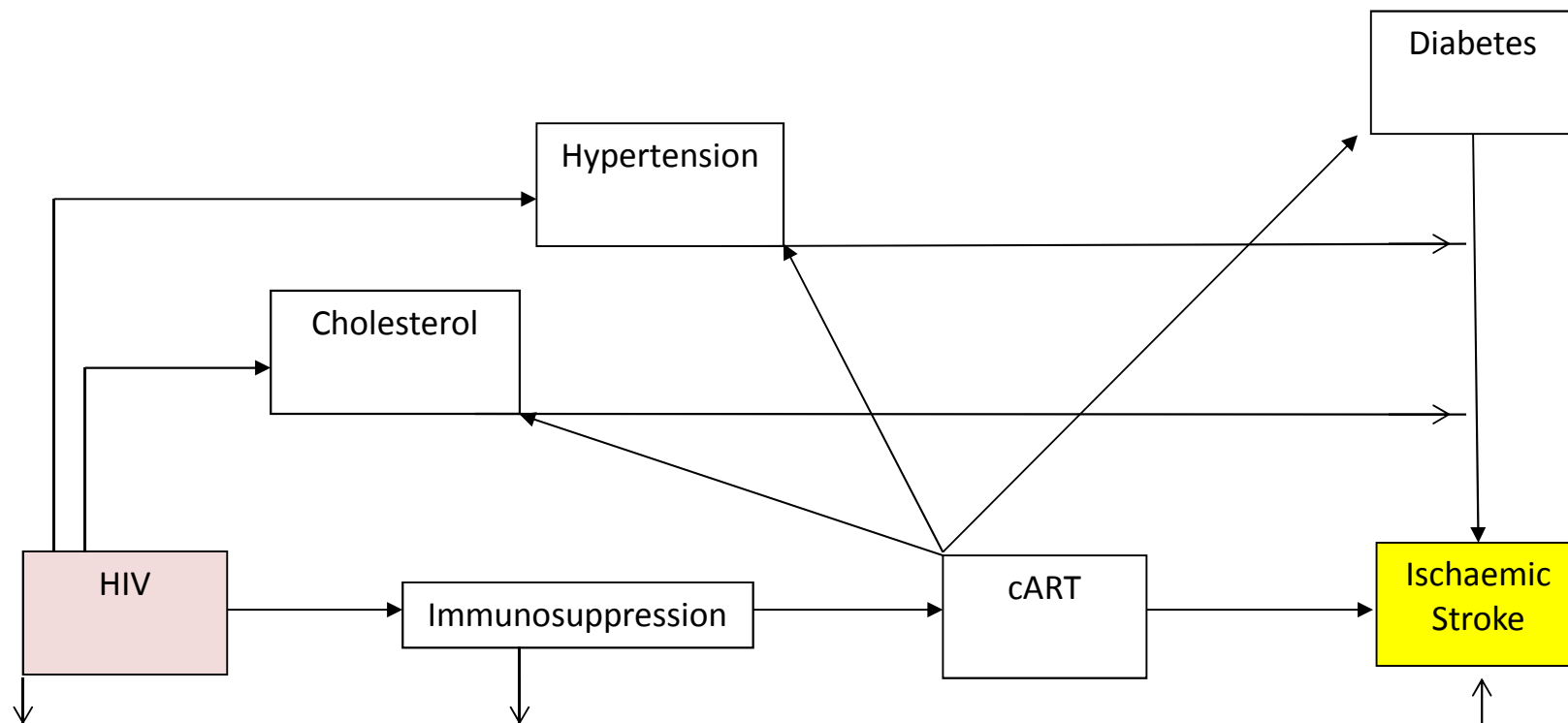
? Antiplatelet agents

? Statins

? Antihypertensives

Certainly lifestyle advice including giving up smoking and risk of drug misuse

# HIV infection and the potential relationship with established vascular risk factors – a conceptual framework



## Human Immunodeficiency Virus (HIV) infection – Conclusions

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- Increasing evidence to suggest HIV is a risk factor for stroke, and changes the nature of stroke
  - Younger
  - More ischaemic stroke, less cerebral haemorrhage
- There are multiple mechanisms by which HIV may cause stroke but the most important in the ART era is likely to be mediated by endothelial dysfunction
- Optimal treatment of acute stroke and secondary prevention of stroke in HIV infected individuals is not clear
- How conventional risk factors and HIV / ART induced endothelial dysfunction interact requires further investigation

# Collaborators

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## United Kingdom

- Laura Benjamin
- Tom Solomon
- Hedley Emsley
- Saye Khoo
- Charles Warlow

## South Africa

- Alan Bryer

## Malawi

- Laura Benjamin

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Stroke

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