

Vascular Cognitive Impairment

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Disclosure of Potential Conflict of Interest

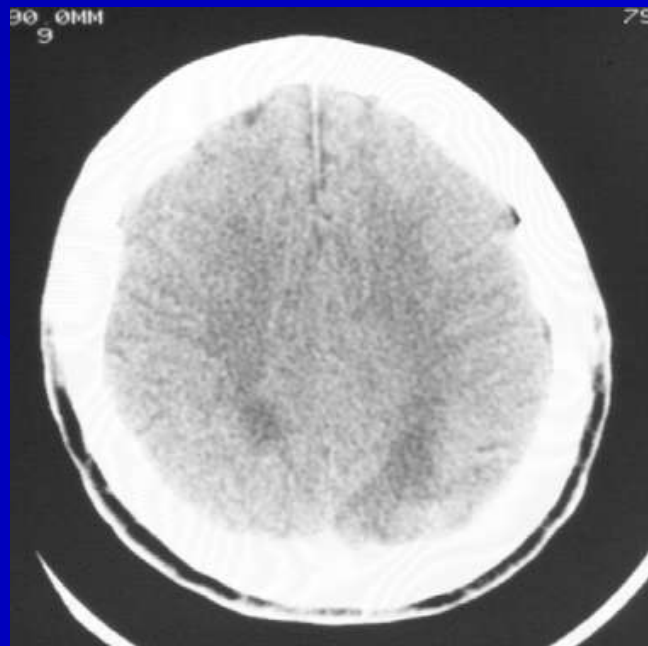
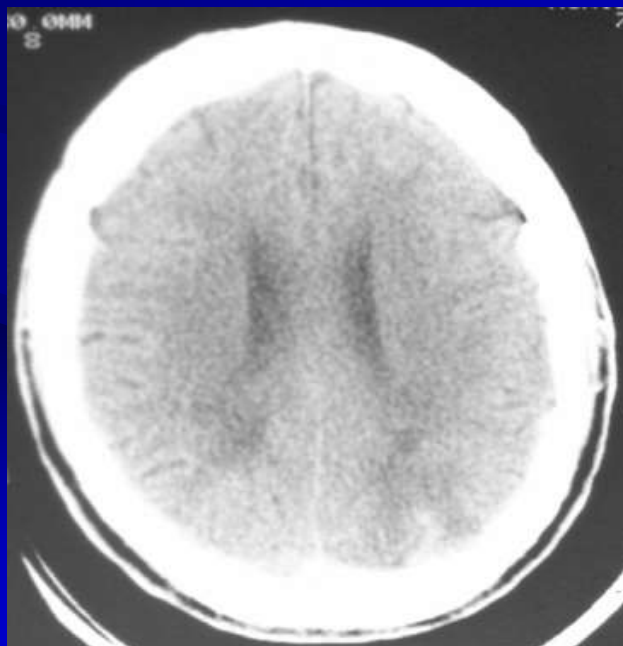
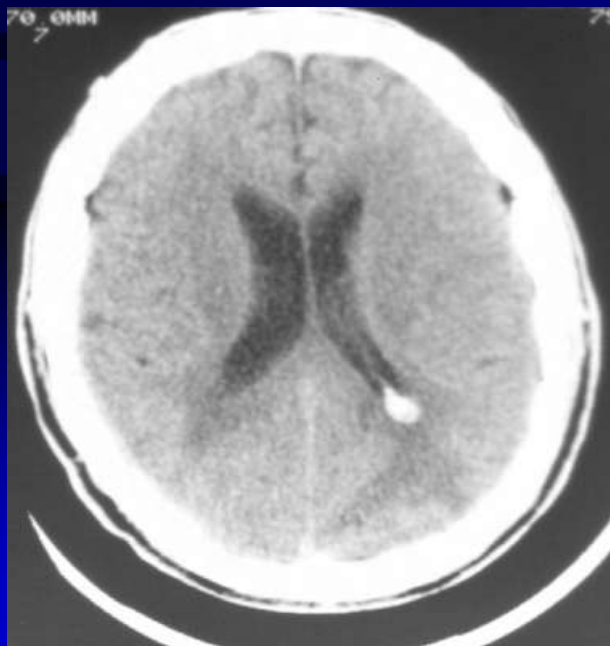
Principal Investigator for Clinical Trials:

Pfizer, Novartis, Myriad, GlaxoSmithKline, Roche

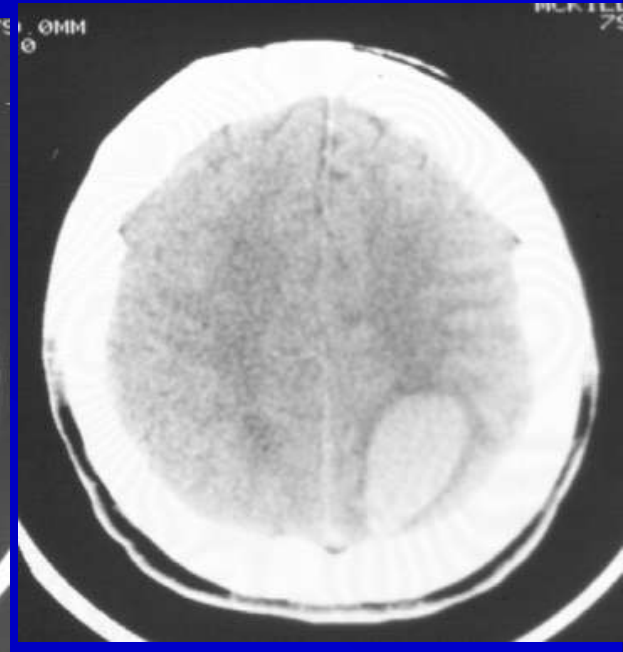
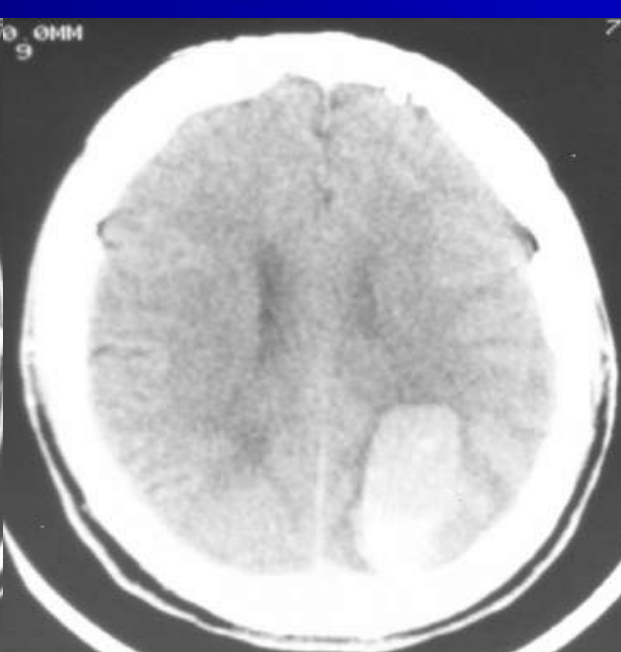
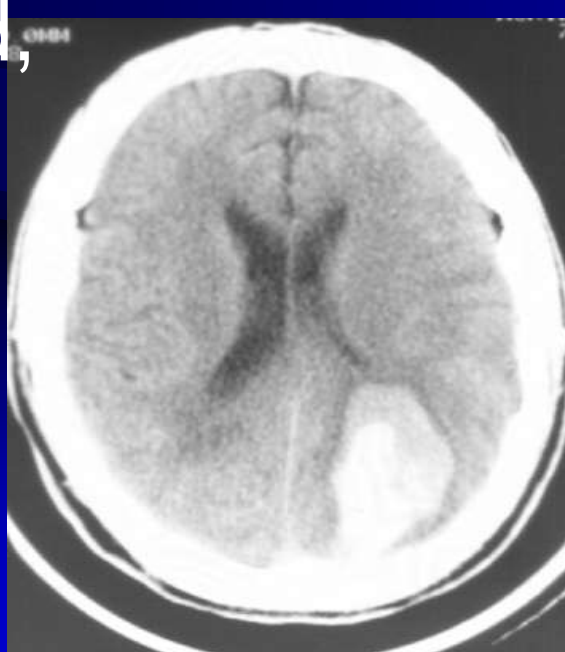
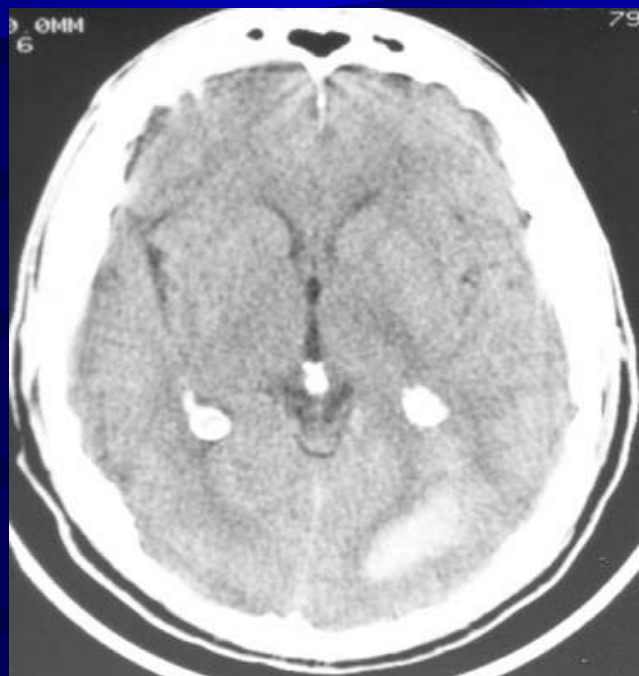
CME Lecturer: Pfizer, Janssen-Ortho, Novartis.
Lundbeck, Eisai

Advisory Boards/Consultant: Janssen-Ortho, Pfizer,
Novartis, Myriad, GSK, Eli-Lilly, Schering-Plough,
Bristol Myers Squibb, Wyeth

No stock or equity interests



CT of
61 yo
lawyer
brought
to ER a
few weeks
earlier
confused,
bumping
into
things

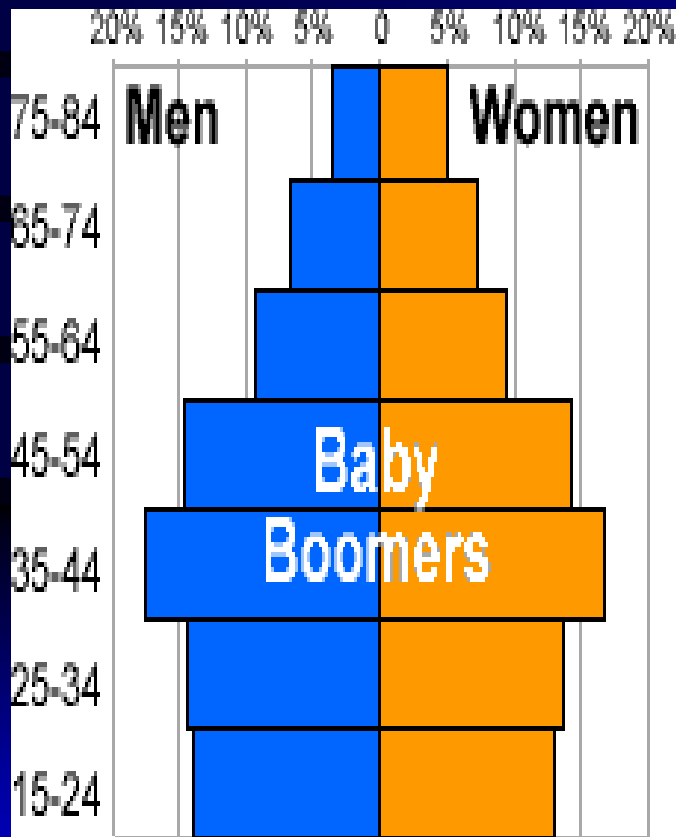


Learning Objectives

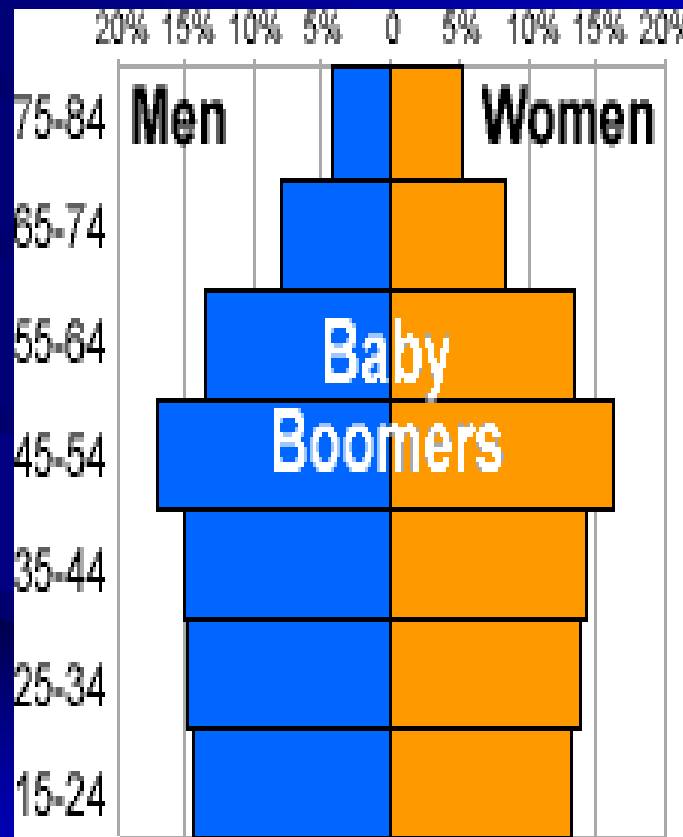
1. Understand definitions, prevalence, subtypes and assessment of Vascular Cognitive Impairment
2. Appreciate role of co-morbid Cerebrovascular disease (CVD) and Alzheimer's Disease (AD) in expressing dementia, and of shared vascular risk factors
3. Review management and use of cognitive enhancers in Vascular Dementia

The Boomer Bulge

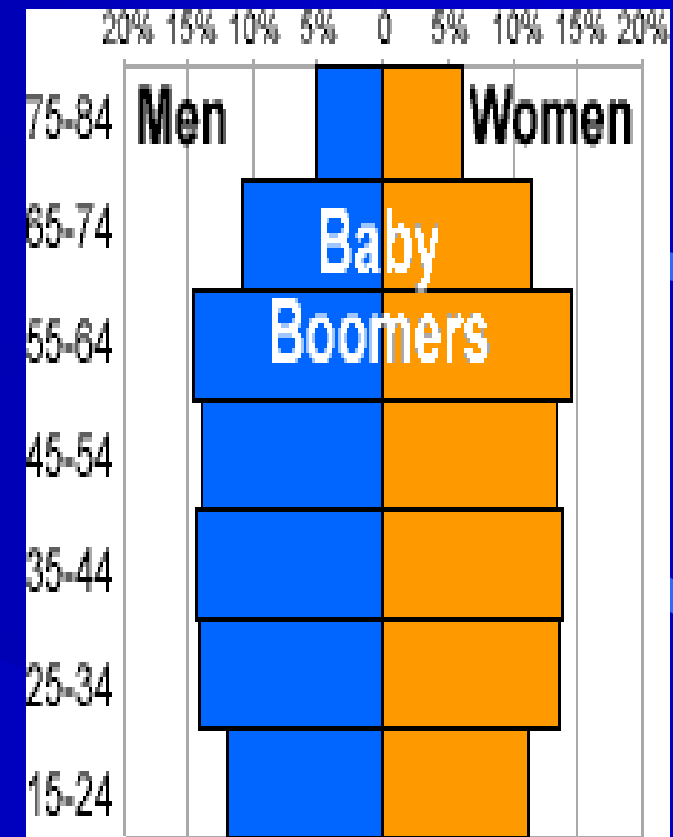
2001



2011



2021



Common Covert Operatives that sabotage successful brain aging

- Alzheimer's Disease
- Small Vessel Disease
- They must be recognized and their impact better understood to develop strategies to ameliorate and treat earlier and more effectively
- Also role for brain "reserve" (?size, synaptic complexity)

Definition of Dementia DSM IV (R)

- **Memory impairment** and at least one of:
Language difficulty; Apraxia; Visuospatial difficulty; Executive dysfunction
- Impaired occupational or social functioning
- Decline from previous level of functioning
- DSM5-demotes memory, proposes to replace term dementia with **Major and Minor Neurocognitive Disorder**, depending on degree of autonomy in ADL's
www.dsm5.org

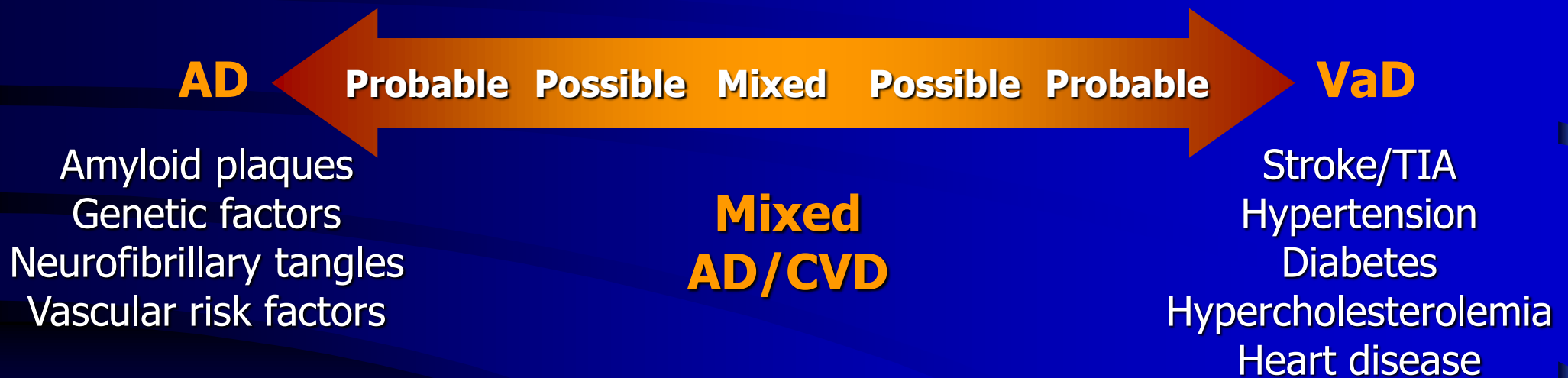
Diagnosis of Probable Alzheimer's Disease: NINCDS – ADRDA Criteria

- Dementia clinically and by appropriate testing
- Deficits in two or more areas of cognition
- Progressive loss of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40-90
- Absence of other causes

Diagnosis of Probable Vascular Dementia: NINDS-AIREN Criteria

- Diagnosis of dementia
 - Cognitive decline (memory and two other domains)
 - Impaired functional abilities as a result of cognitive decline
- Evidence of cerebrovascular disease (CVD)
 - Focal neurological signs consistent with stroke
 - Brain CT or MRI required
- Relationship between dementia and CVD
 - Temporal association between the two – abrupt onset of dementia after CVD event
 - Sudden stepwise cognitive deterioration

Spectrum of Alzheimer's Disease and Vascular Cognitive Impairment



AD, CVD, or both together account for approximately 80% of dementias

A New, More Inclusive Concept: Vascular Cognitive Impairment (VCI)

Spectrum of conditions including:

1. **Vascular Cognitive Impairment-No Dementia (VCIND)**
2. **Vascular Dementia**
 - Subtypes:
 - Multi-infarct dementia (MID)
 - Single strategic infarct
 - Subcortical ischemic vascular dementia (SIVD)
3. **Mixed Alzheimer's and Cerebrovascular Disease (CVD)**

VCI: A Heterogeneous Disorder

Cardiovascular Risk Factors

Hypertension Diabetes Genetics Hypercholesterolemia Heart Disease

Damage to Cerebral Vasculature

Multiple Distinct Pathologies

Large Vessel Infarcts

- Strategic Single Infarcts
- Multi-infarct Dementia

Small Vessel Infarcts

- Multiple Lacunae
- Binswanger's /CADASIL

Hemorrhage

- ◆ Chronic SDH
- ◆ SAH
- ◆ ICH

Hypoperfusion

- ◆ Global (e.g., cardiac arrest)
- ◆ Hypotension

Final Common Pathway

Damage to critical cortical and subcortical structures

↓ Cholinergic transmission

Damage/interruption of subcortical circuits and projections

VCI/VaD

SEBlack, SHSC, UT



Vascular Cognitive Impairment

*Harmonization
Consensus
Criteria
Hachinski et al
Stroke 2006*

60 and 30 Minute Protocols

Executive-Activation

Phonemic (FAS) Fluency

Semantic (Animal Naming) Fluency

WAIS-III Digit Symbol

Trailmaking Test

Language

Boston Naming Test – 15 item

Spatial

Complex Figure Copy

Memory

Hopkins or California Verbal Learning

(Immediate, Delayed, Recognition)

Complex Figure Delayed Recall

Incidental Learning: Boston Naming Test
and Digit Symbol

Mood, Neuropsychiatric

CES-D

NPIQ

Other

IQCODE

MMSE

5 Minute Protocol

1. 5 word memory
(registration, recall, recognition)
2. 6 item orientation
3. phonemic fluency

Montreal Cognitive Assessment

Hachinski et al Stroke 2006
(MoCA)

Montreal Cognitive Assessment (MoCA)

- 30-point scale
- 10 minutes to administer
- One page
- All AD patients scored < 25
- Using cutoff < 25, MCI was discriminated from normals with
 - Sensitivity 80%
 - Specificity 91%

www.mocatest.org

Nasreddine et al. J AGS. 2005

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Date of birth :
Education :
Sex :

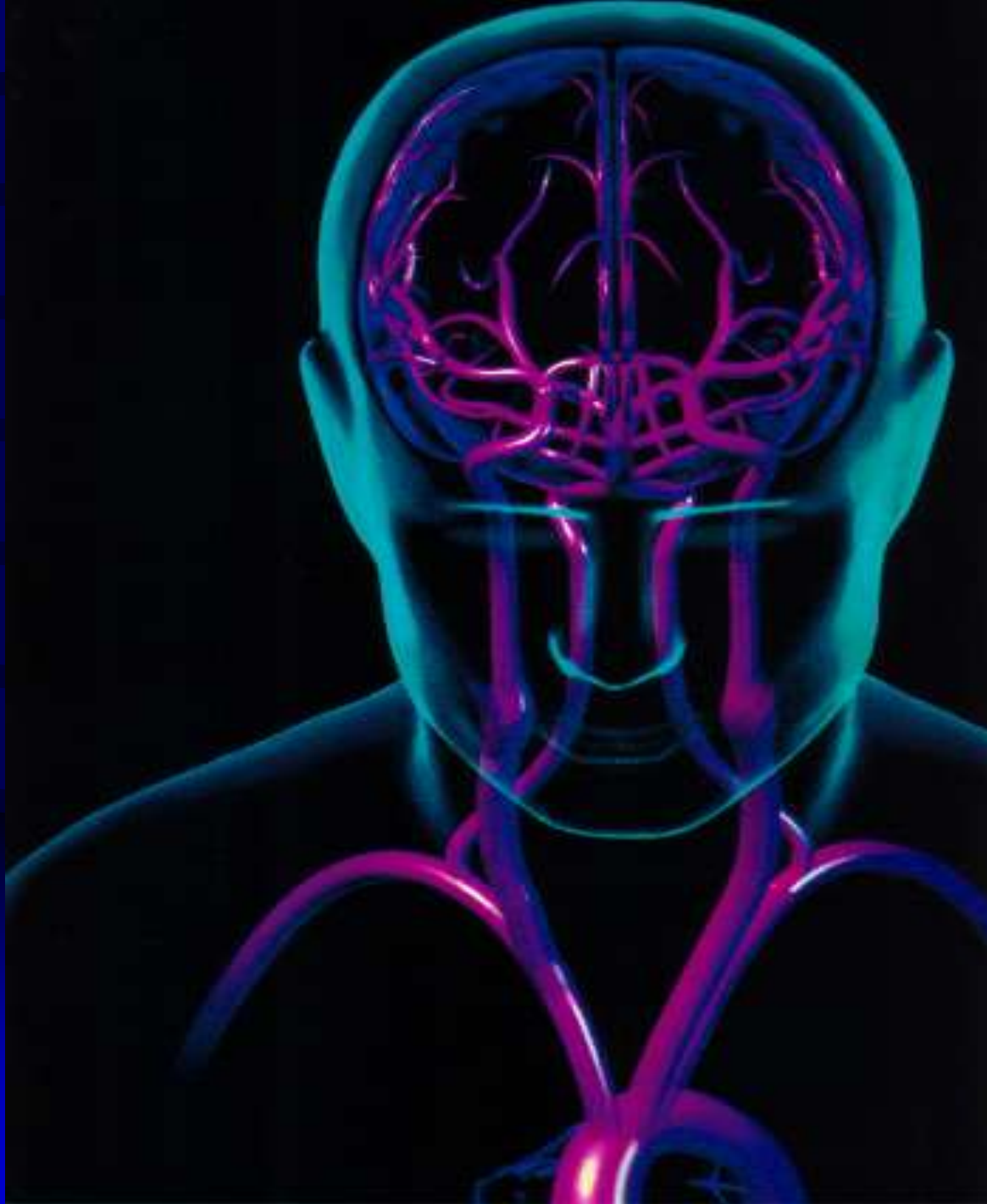
NAME :
DATE :

VISUOSPATIAL / EXECUTIVE		CLOCK (Ten past eleven)	POINTS			
	[]	[]	1 point for each [] correct ___/3			
NAMING			___/3			
MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.						
	FACE	VELVET	CHURCH	DAISY	RED	
1st trial						
2nd trial						
Recall > 5 min.	[]	[]	[]	[]	[]	___/5
Cues : Category						
Multiple choice						
ATTENTION Subject has to repeat them in the forward order [] 2 1 8 5 4 Read list of digits (1 digit/ sec.) Subject has to repeat them in the backward order [] 7 4 2 Read list of letters. The subject must tap with his hand at each letter A. No points if > 1 error [] FBACMNAAJKLBAFAKDEAAAJAMOF AAB Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65				___/2 ___/1 ___/5		
LANGUAGE Repeat : I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. [] Fluency / Name maximum number of words in one minute that begin with the letter F [] ____ (N > 10)				___/2 ___/1		
ABSTRACTION Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler Memory recall > 5 min. If unable to recall, give category cue (e.g. body part, musical instrument...) or multiple choices				___/2		
ORIENTATION [] Date [] Month [] Year [] Day [] Place [] City				___/6		
© Z.Nasreddine MD Version May 8th, 2003			TOTAL ___/30			

Best Practice Recommendations: VCI & Dementia

Patients considered at high risk for cognitive and perceptual impairment are those with vascular risk factors such as hypertension, age > 65 year, hyperlipidemia, diabetes, clinical stroke, neuroimaging findings of covert stroke or white matter disease, damage to other target organs, and/or those patients with cognitive or functional changes that are clinically evident or reported during history taking.

CMAJ Dec 2, 2008



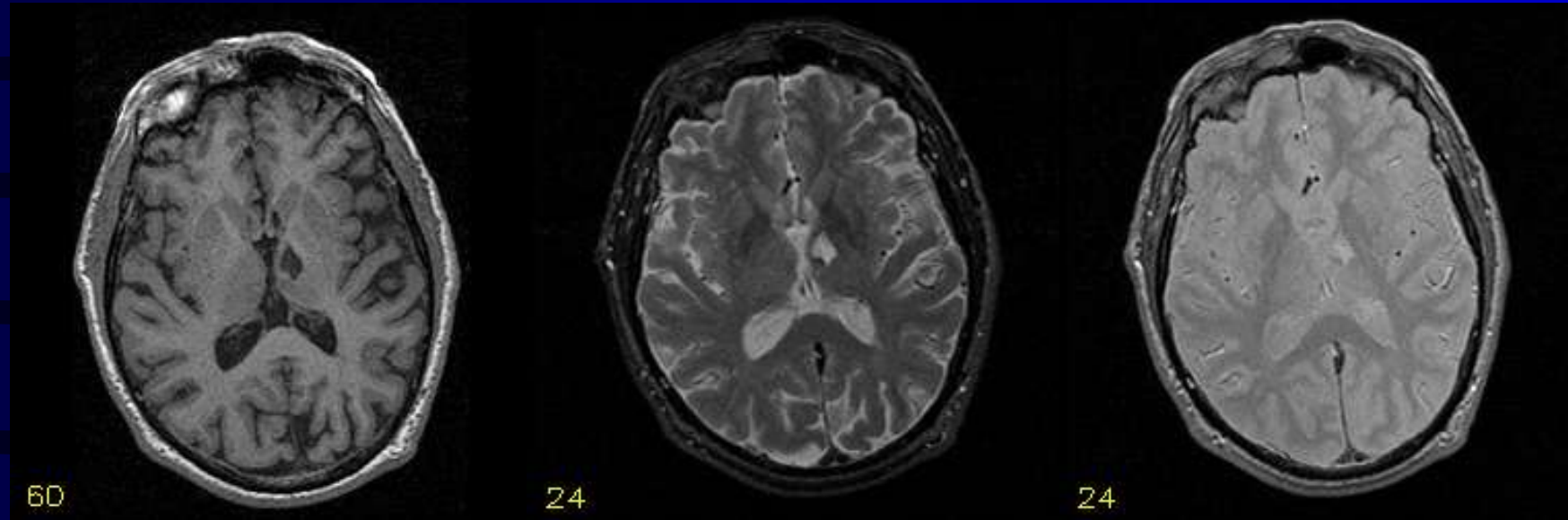
Overt Disease with Case examples

The Overt Disease: Post-Stroke Dementia

- By 3 months post-stroke , **65%** cognitively impaired
 - **26%-36%** meet criteria for dementia (vs **3%** in age-matched controls) ^{1,2}
- Depressive symptoms post-stroke occur in **25-50%** ^{4,5}
- Cognitive impairment increases long term dependence and is associated with higher mortality (**61% vs 25%**)^{1,2}

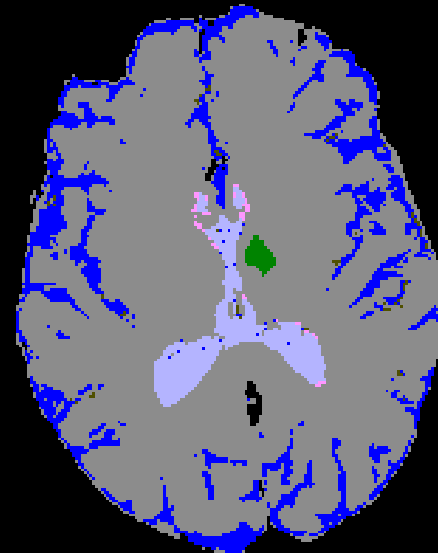
1. Tatemichi et al. *Neurology*. 1992 2. Desmond et al. *Stroke*. 2002 3. Pohjasvaara et al. *Stroke*. 1997 4. Pohjasvaara et al. *Stroke*. 1998 5. Herrmann et al. *Stroke*. 1998

Strategic Infarct dementia



72 yr old man
presented with
sudden onset
confusion

Short term Memory Loss,
anomia and executive
dysfunction persisted

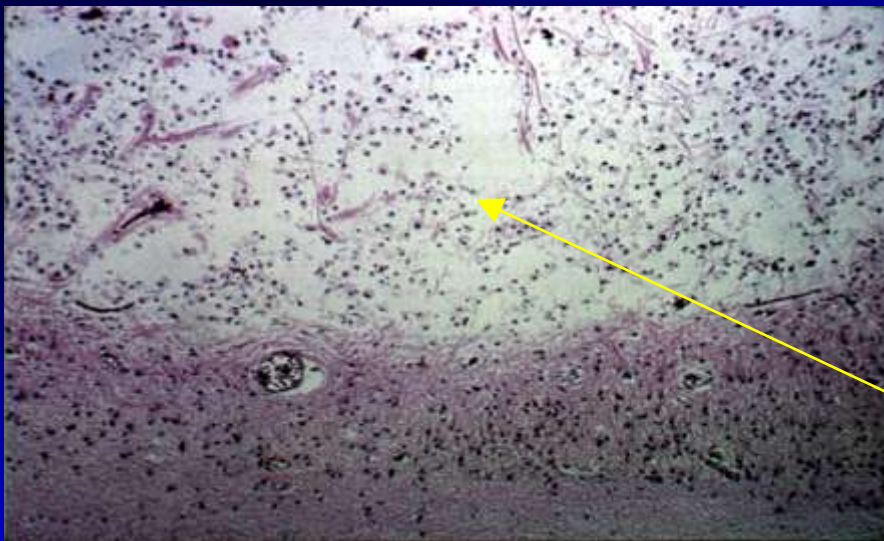
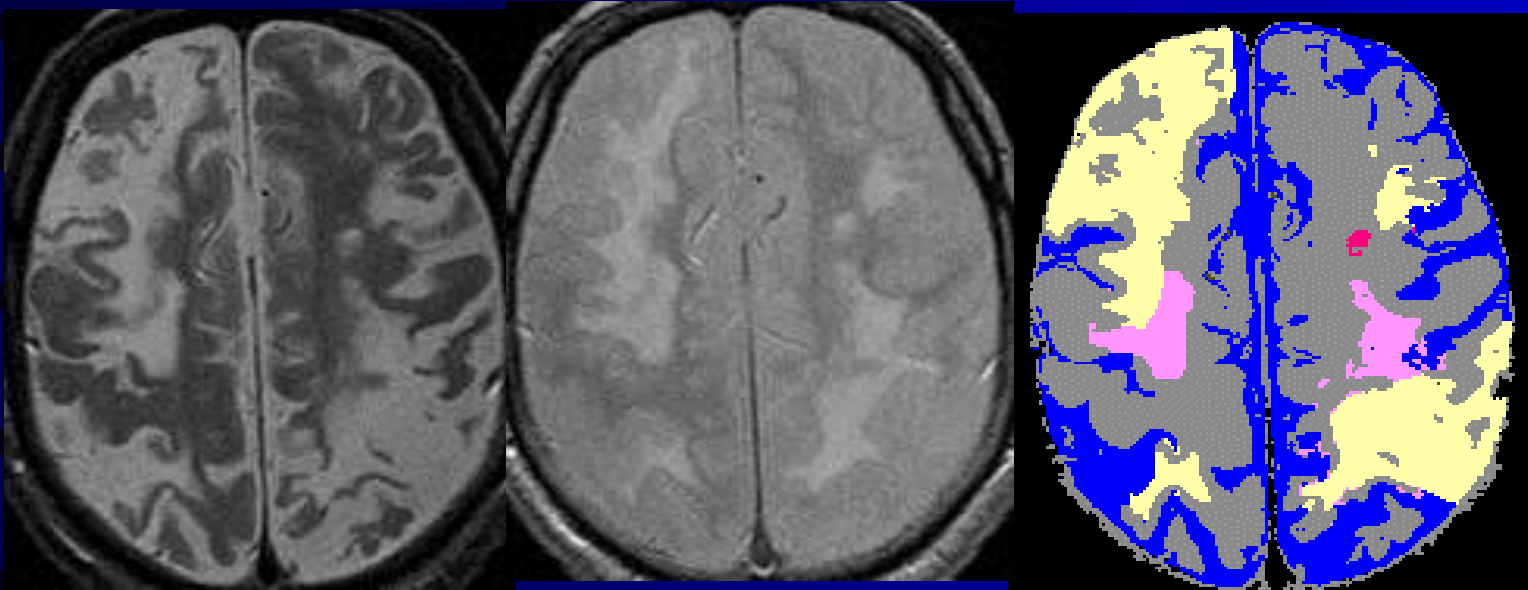


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Multi-Infarct dementia

- **Mailman at age 39 suffered**
 - Right and left hemisphere strokes.
 - Bilateral carotid occlusions, R vertebral and basilar stenosis on angiography.
- **At age 61** seen in memory clinic for forgetfulness, anomia, difficulty with comprehension
 - MMSE 23/30
 - good function in activities of daily living but unable to work
 - hospital volunteer 3x/week, bingo, shopping
 - developed seizures, partially controlled on meds and died in status epilepticus at age 64

Final Diagnosis



- **Above:** MRI shows watershed strokes
- **Left:** Autopsy shows ischemic infarcts: neuronal loss and gliosis. No Alzheimer's Disease

Subcortical Ischemic Vascular Disease – Cognitive Syndrome

EXECUTIVE DYSFUNCTION

- Impaired goal formulation, initiation, planning, organizing, sequencing, executing, set-shifting and maintenance, abstraction.

MEMORY DEFICIT (may be mild)

- Impaired recall, relative intact recognition, less severe forgetting, benefit from cues.

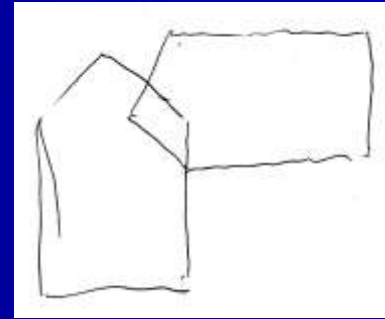
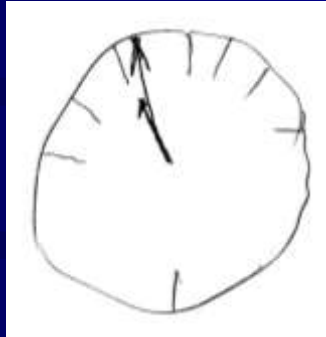
Clock Drawing (Set hands to 10 after 11)

81 y.o. man

23 y.o.e.

Dx: AD w CVD

MMSE: 27/30

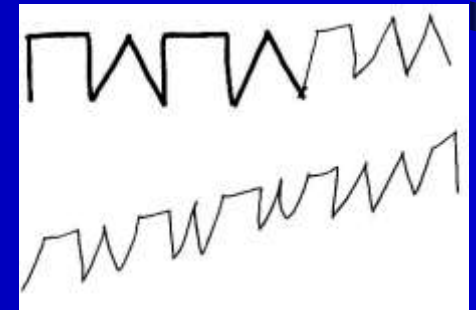
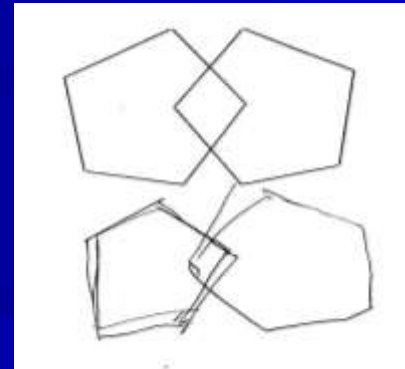
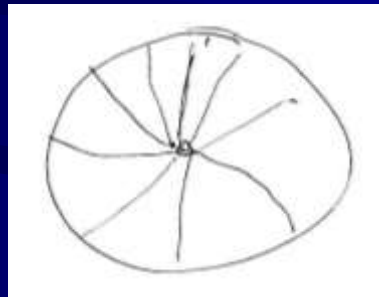


78 y.o. woman

12 y.o.e.

Dx: AD w CVD

MMSE: 25/30

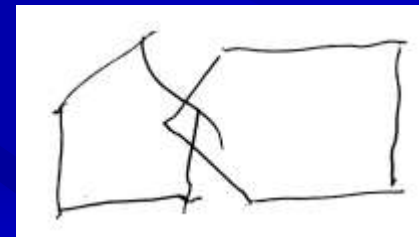
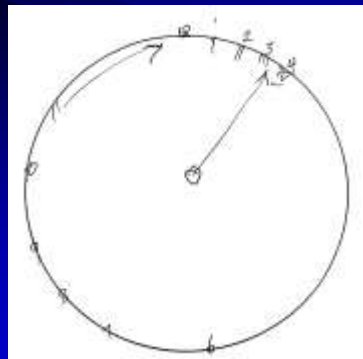


75 y.o. woman

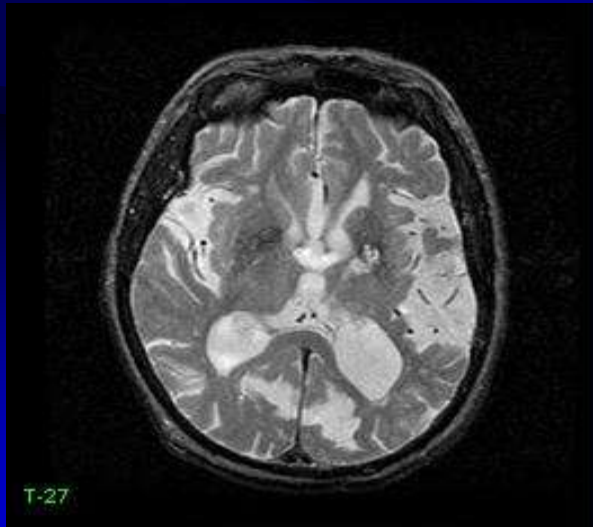
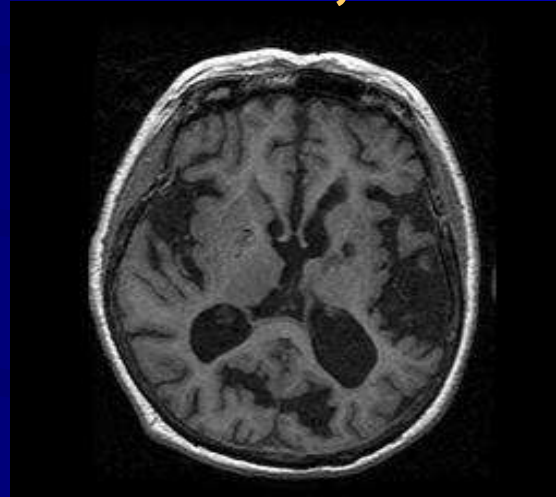
16 y.o.e.

Dx: VaD

MMSE: 26/30



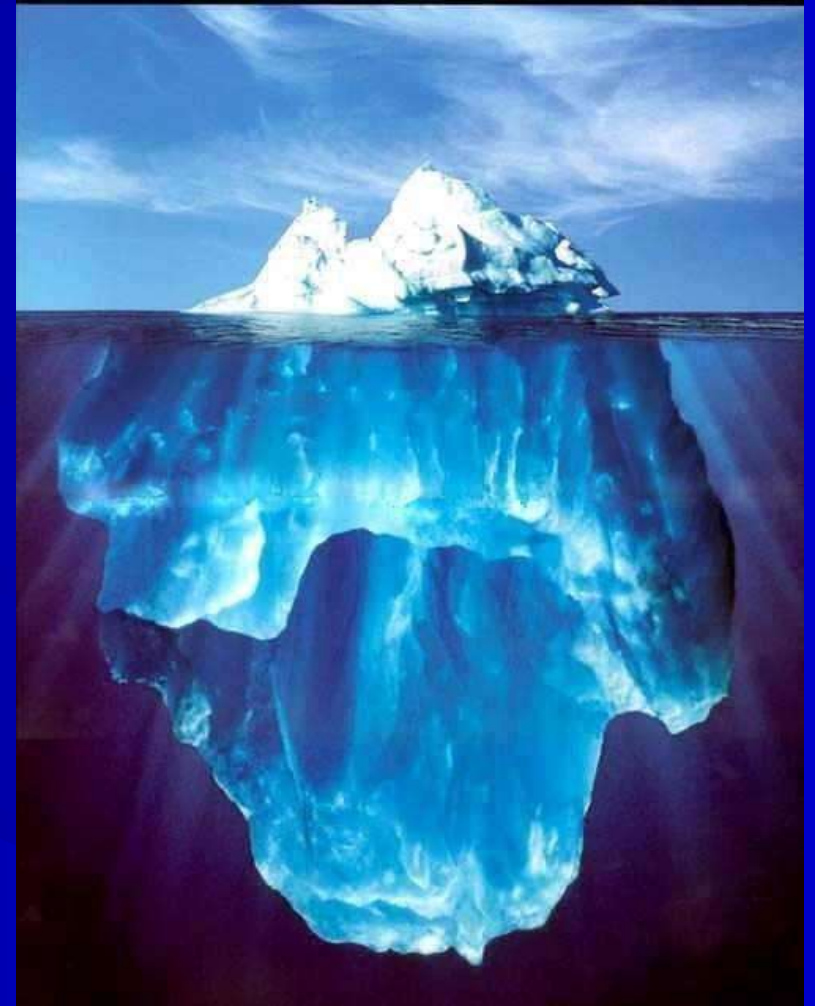
78 y.o. woman, MMSE 30/30



SIVD – Early Clinical Features

- Gait disorder, imbalance
- Urinary frequency and incontinence
- Dysarthria, dysphagia
- Emotional incontinence
- Extraparamidal signs (hypokinesia, rigidity)
- Depression and mood changes

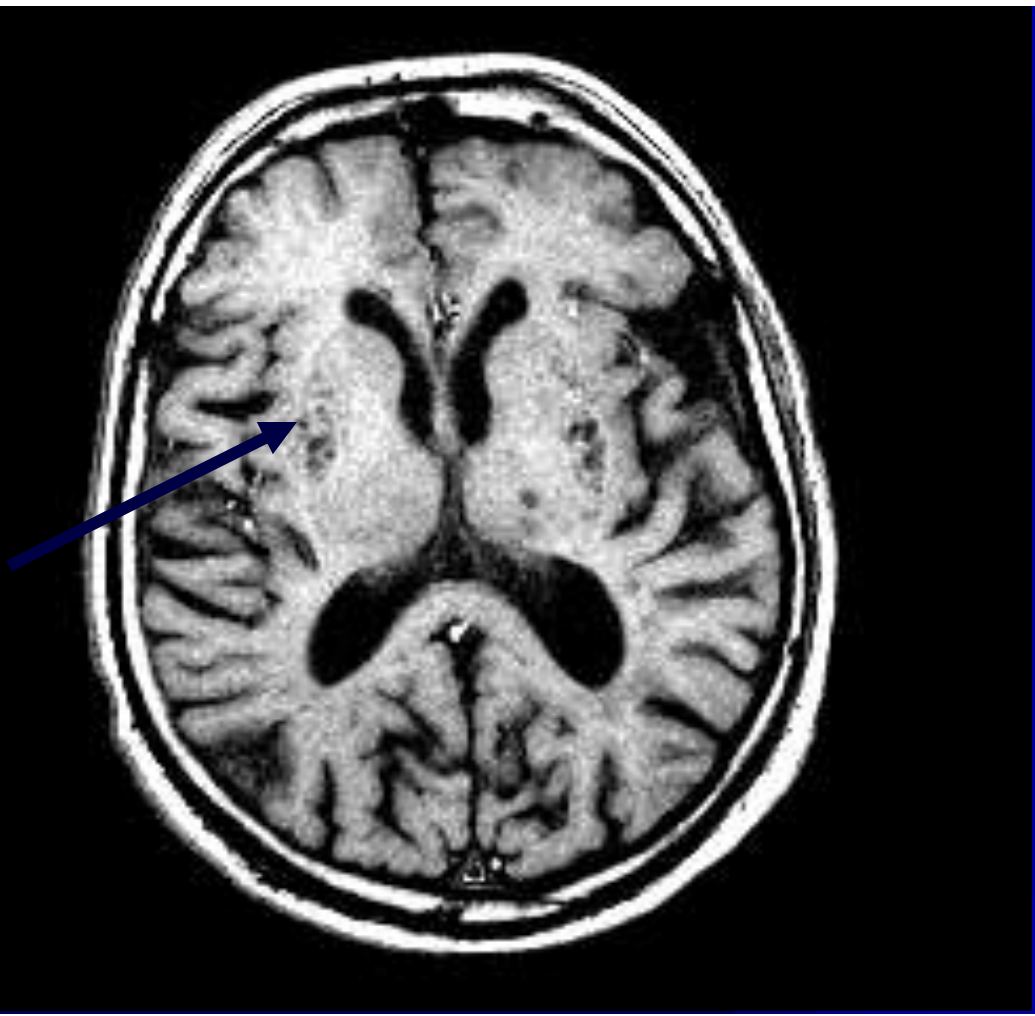
The Covert Disease



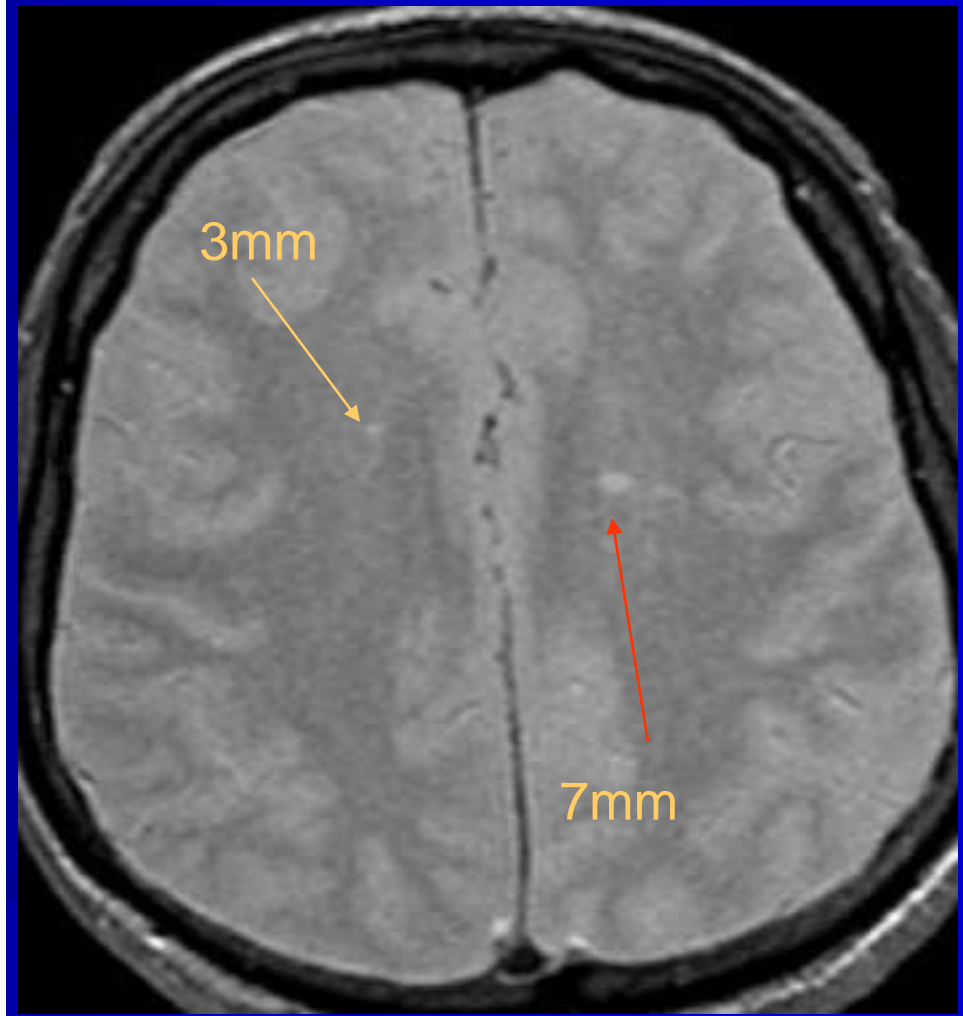
Small vessel disease

Silent Stroke Prevalence

- 3 mm diameter lesions (hypointense on T1, hyperintense on T2) potentially relevant even if “silent”, ie *covert infarcts*
- Baseline MRI shows silent infarcts in **28%** of seniors [3660 > 65, mean 75, in Cardiovascular Health Survey (CHS)] but frequency depends on age (12% seen in Framingham with mean age 62 yrs) (Longstreth et al, 1998; DeCarli et al Neurobiol Aging 2005)
- 10X as prevalent as overt infarcts (ie 15 million may have silent infarcts in the US)
- In the CVHS, in those with no baseline infarcts, **18 %** showed them on rescan **5 years later** (Longstreth et al 2002)

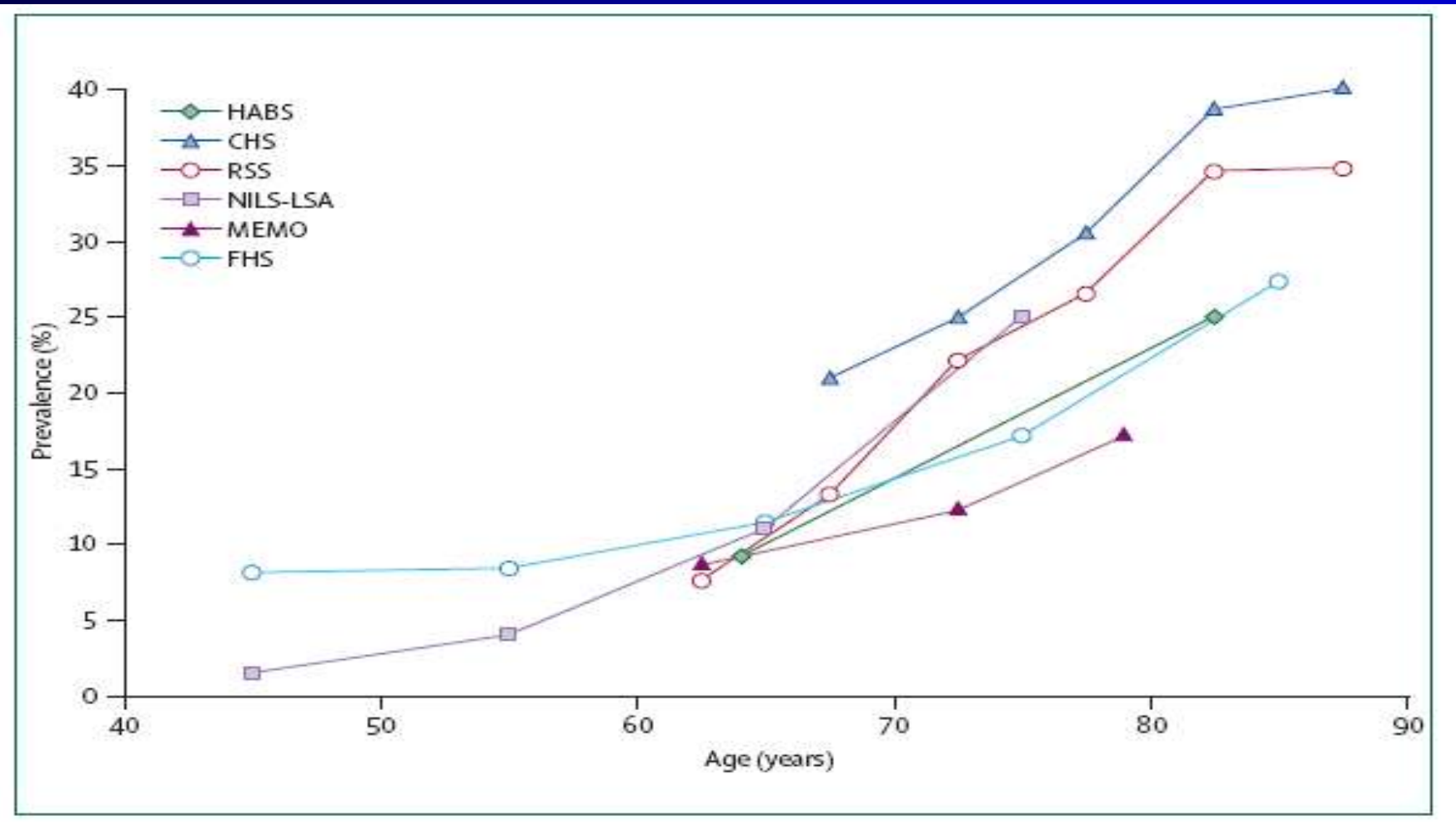


**Small lacunes on
T1 Weighted MRI**



**Focal Hyperintensity on
Proton Density MRI**

Prevalence is Linked to Age



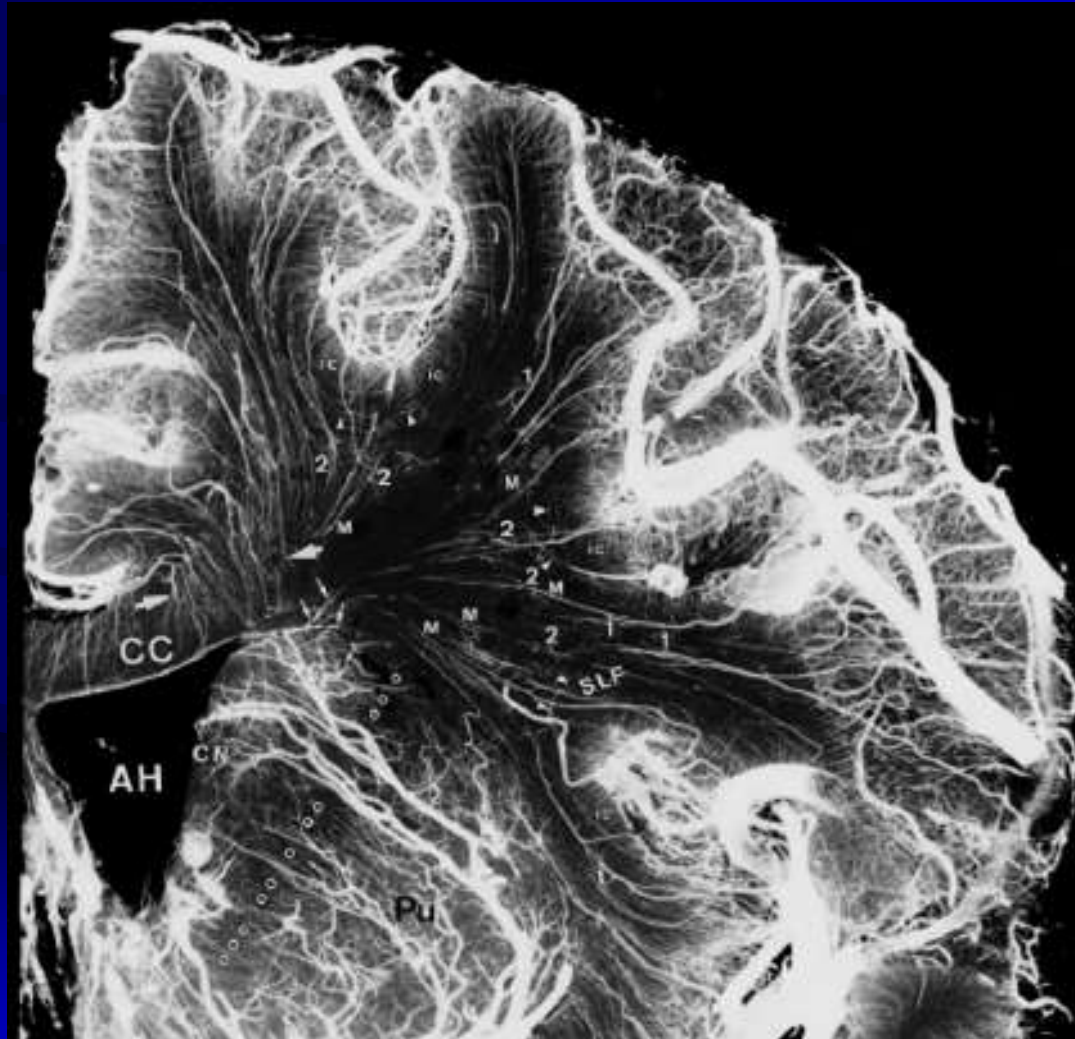
Covert is not benign

In > 1000 elderly aged 60-90 followed for 4 years in the Rotterdam Study, baseline silent infarcts on MRI meant:

- more rapid cognitive decline
- **2X** the risk of emergent dementia
- **5X** the risk of stroke
- **3X** stroke risk even after correcting for other vascular risk factors

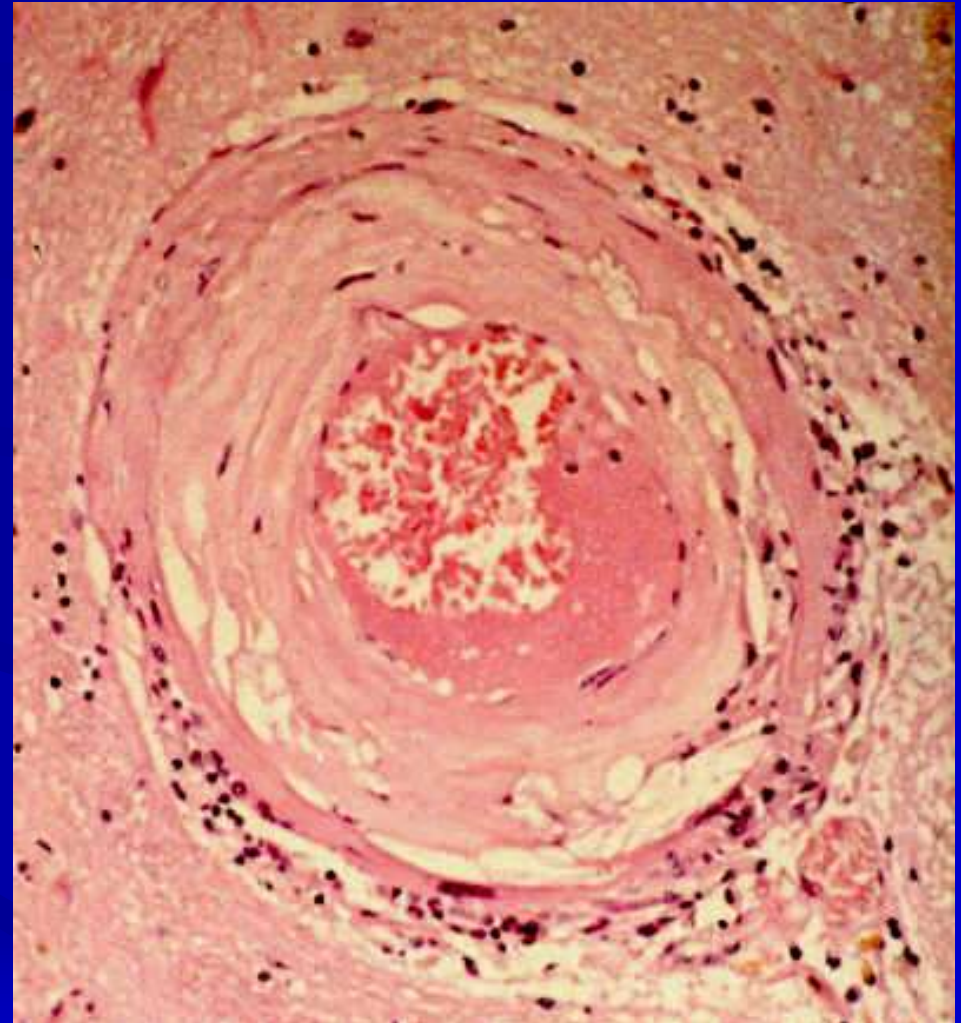
Vermeer et al, NEJM, 2003 & Stroke, 2003; CHS-Bernick et al, 2001

Arteries and Arterioles

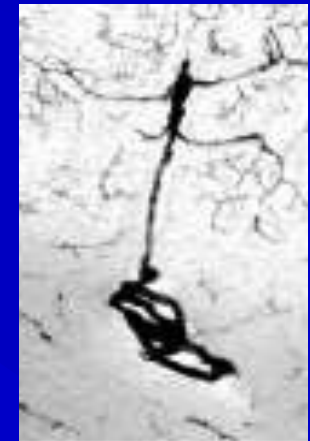
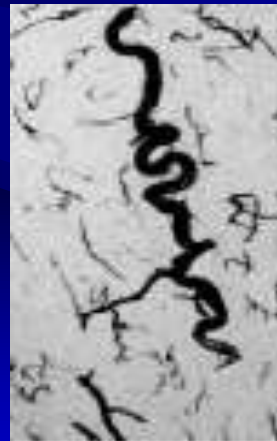
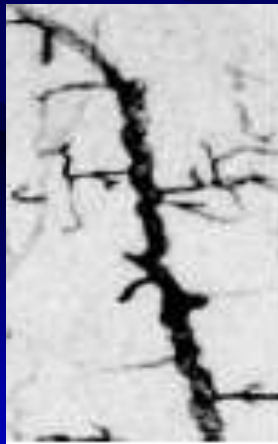
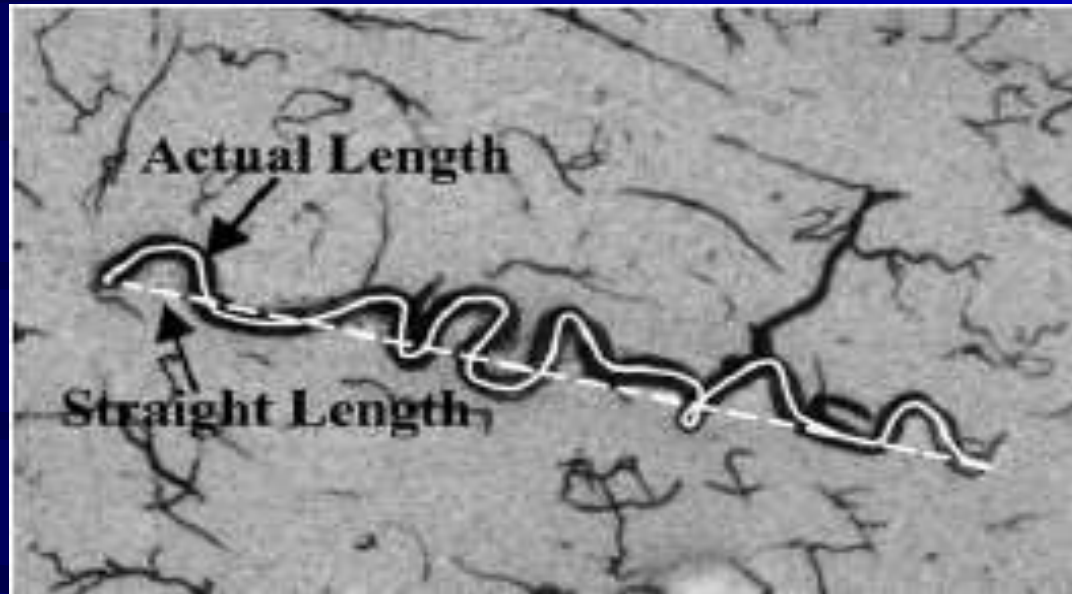


Small Vessel Disease

- Obliteration and occlusion
- Tortuosity, coiling
- Increased resistance
- Decreased autoregulation
- Endothelial changes
- BBB changes
- Perivascular changes
- CADASIL



Arteriolar Tortuosity

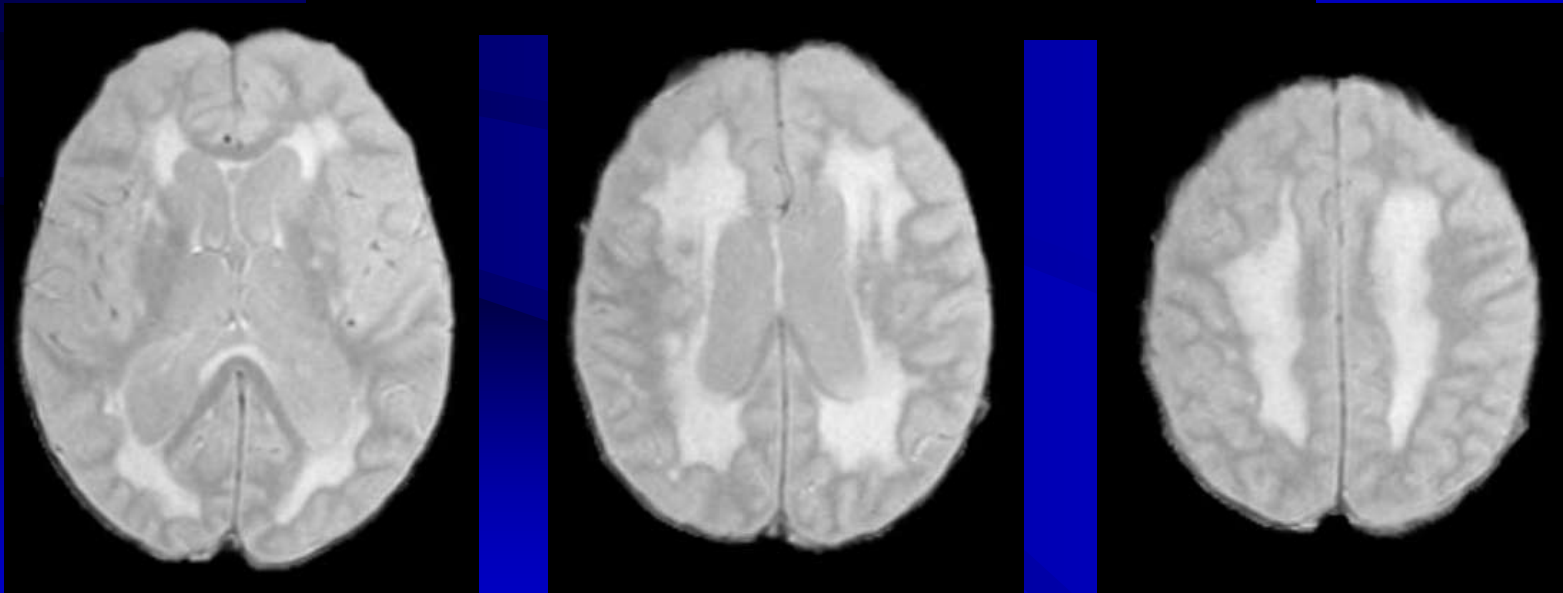
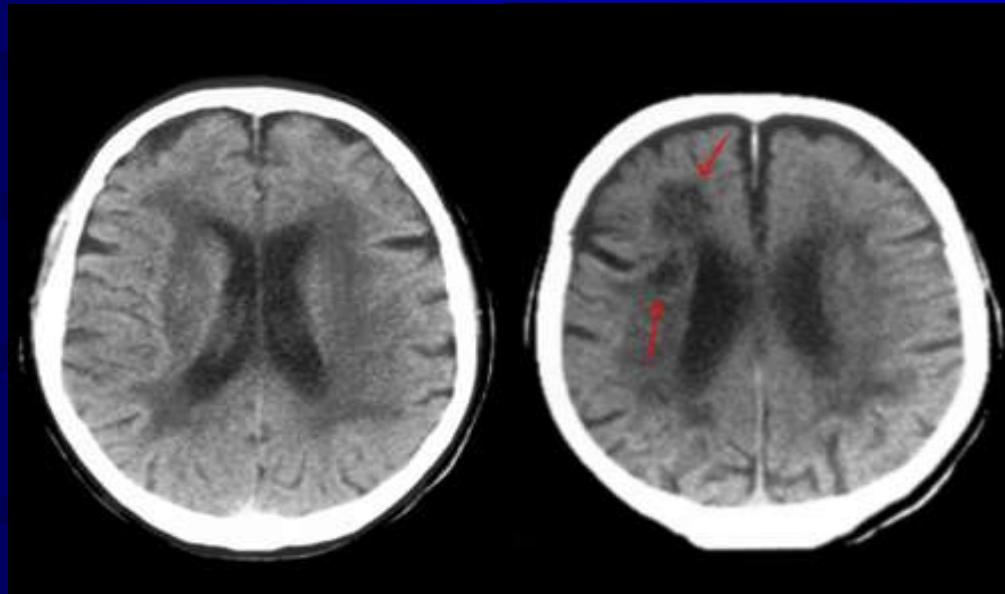


White Matter Hyperintensities in Aging

- In Cardiovascular Health Study (N= 3301 >65)
 - only 4.4% had no white matter lesions
 - 20% with extensive disease had poorer cognition, gait and dexterity ¹
- Decreased psychomotor speed and global cognitive function with severe white matter disease seen in Rotterdam Study²

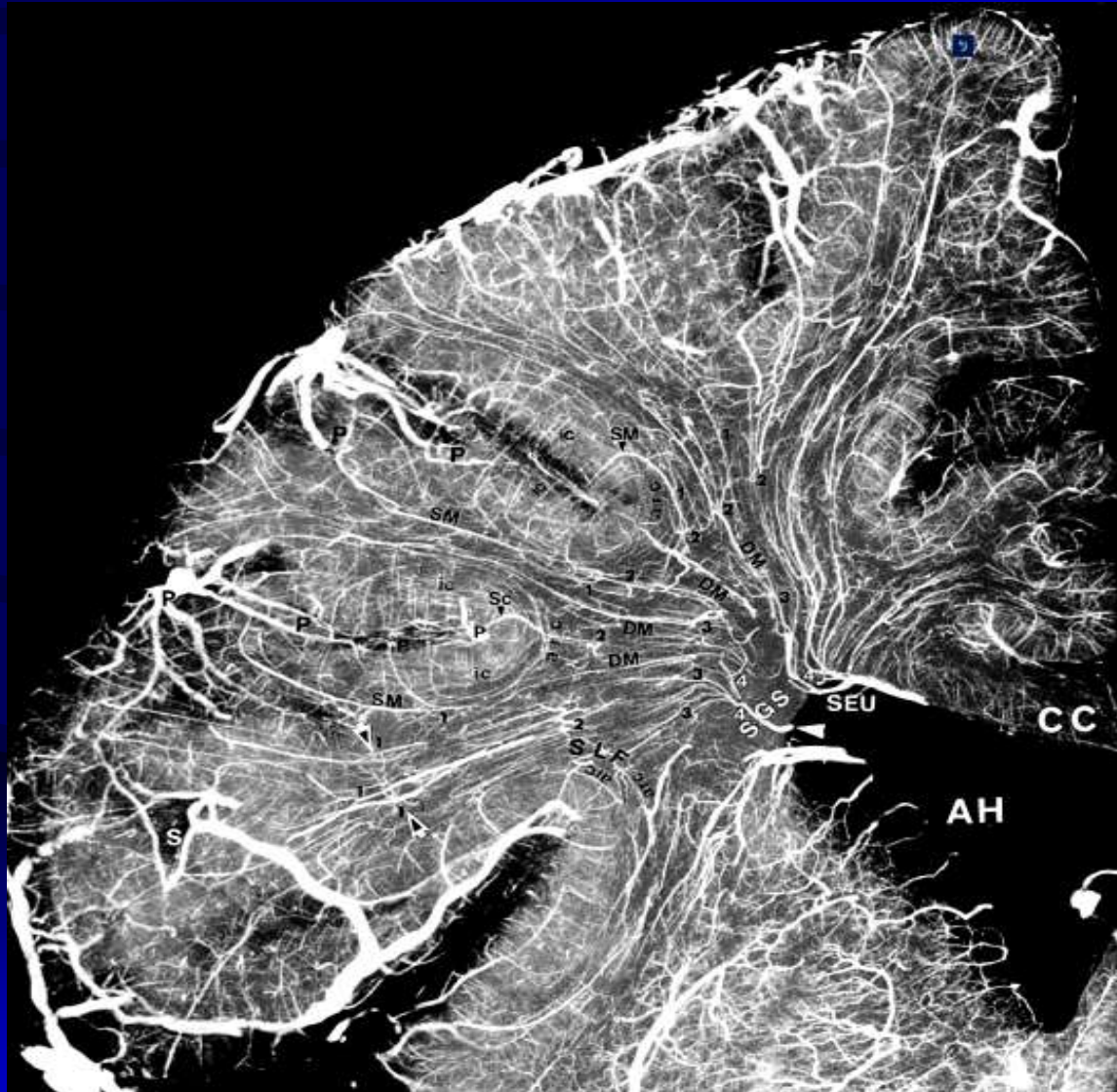
1 Longstreth et al,1996 2 DeGroot et al, 2000

Leukoariosis

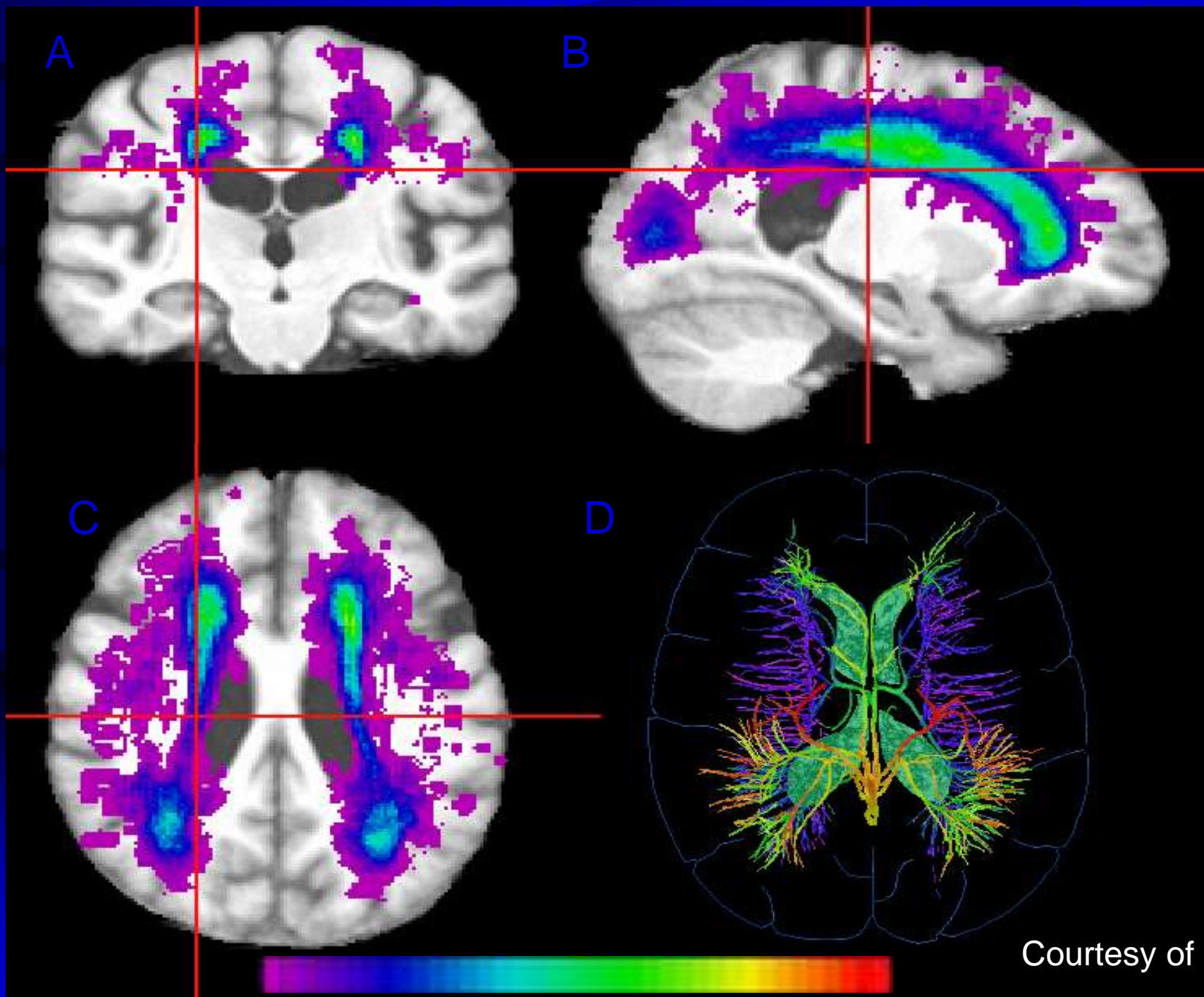


SEBlack, SHSC, UT

Veins

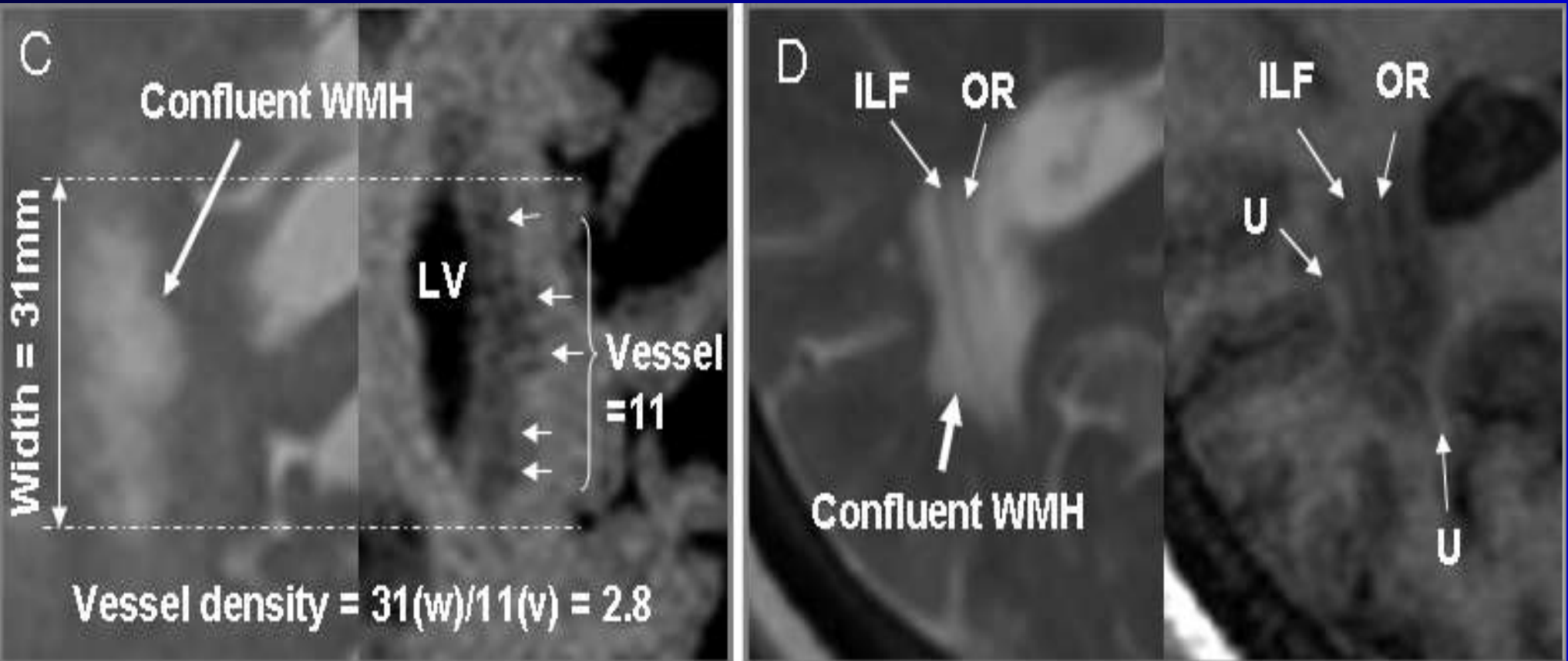


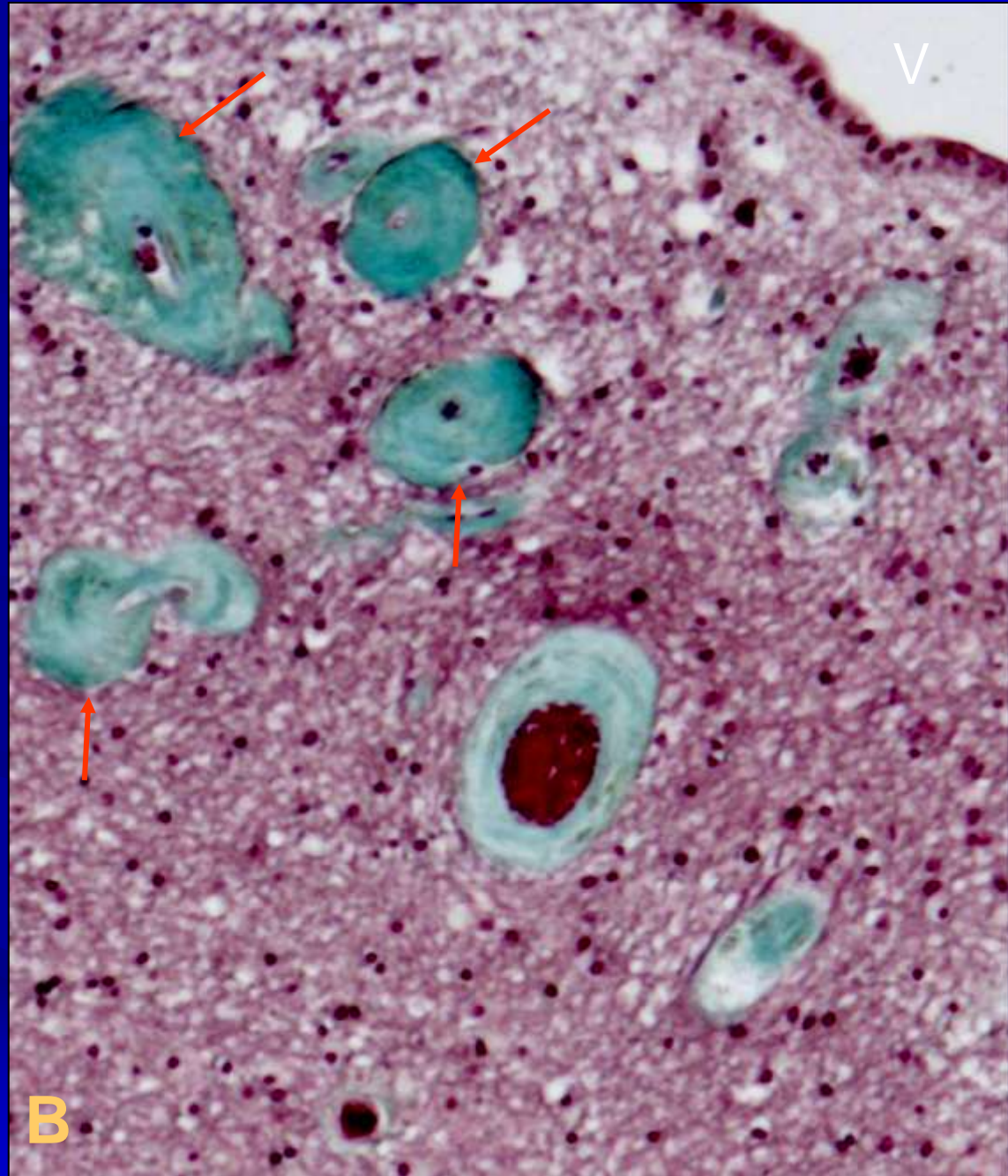
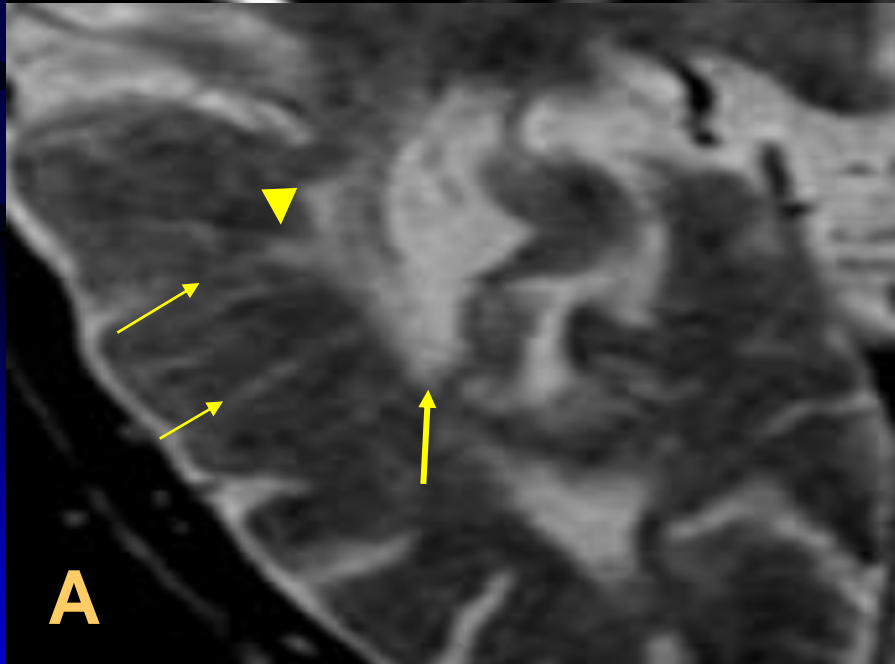
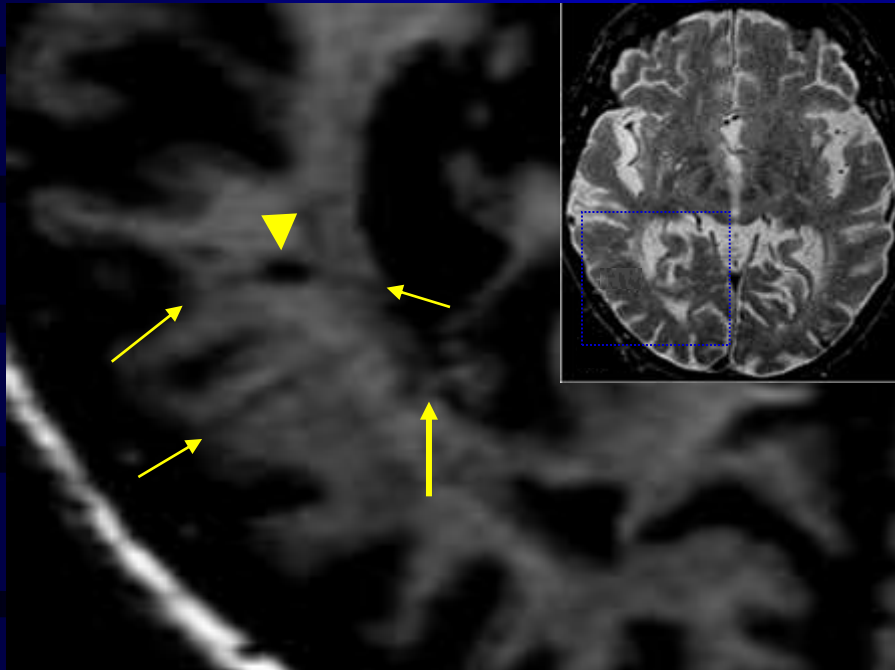
SEBlack, SHSC, UT



Courtesy of FQ Gao

Confluent WMH, veins & sparing of u&long-fiber tracts





Courtesy of FQ Gao, J Bilbao



Vascular Cognitive Impairment:

***Overt and covert
stroke disease
often co-exist
with Alzheimer's
Disease
in the aging brain***

Common Risk Factors for Cognitive Impairment (AD and VaD)

Age

Midlife hypertension (Kivipelto et al, 2001; Launer et al, 2001)

Elevated cholesterol (Kivipelto et al, 2001)

APOE E4 (Slooter et al, 1998)

Diabetes (Arvanitikas et al, 2004)

Homocysteinemia (Seshradi et al, 2002)

Stroke and CAD

The Nun Study



- 102 sisters, aged 76 to 100 years, prospectively studied
- 61 met pathological criteria for AD, but only 57% met clinical criteria for dementia at autopsy
- Less AD pathology was needed for clinical dementia if infarcts present
- If AD and small strokes, **93%** were demented
- Synergistic effect: if small vessel strokes, **20x** risk of dementia (Snowdon et al JAMA 1997)

Community autopsy series: coexisting AD and CVD is common

In US population autopsy series:

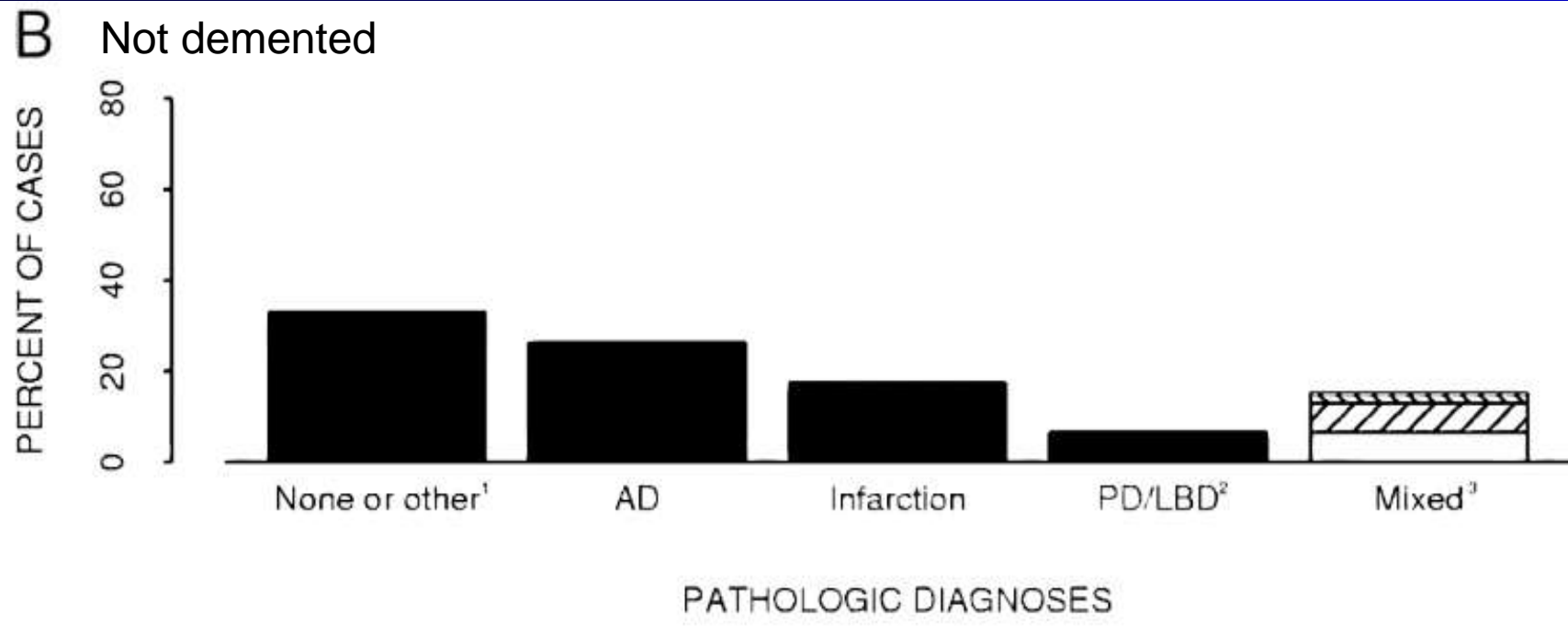
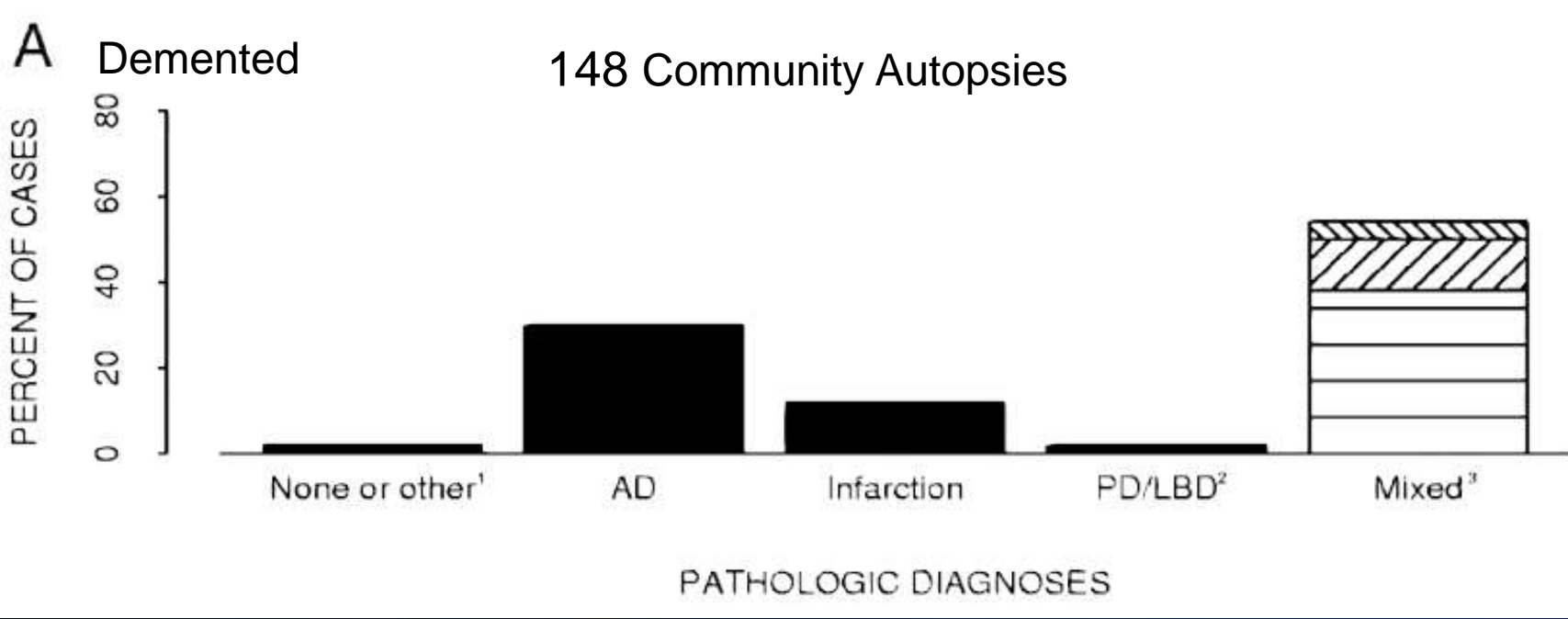
- AD: 24-36%
- AD+CVD: 36-45%
- VaD: 3-13%

(Lim et al, JAGS,1999; Snowdon et al, JAMA, 1997)

In a British population (median age 85):

- 70% had AD and 78% had CVD
- Small vessel disease was most common (69%)

(Neuropath Group, Lancet, 2001)

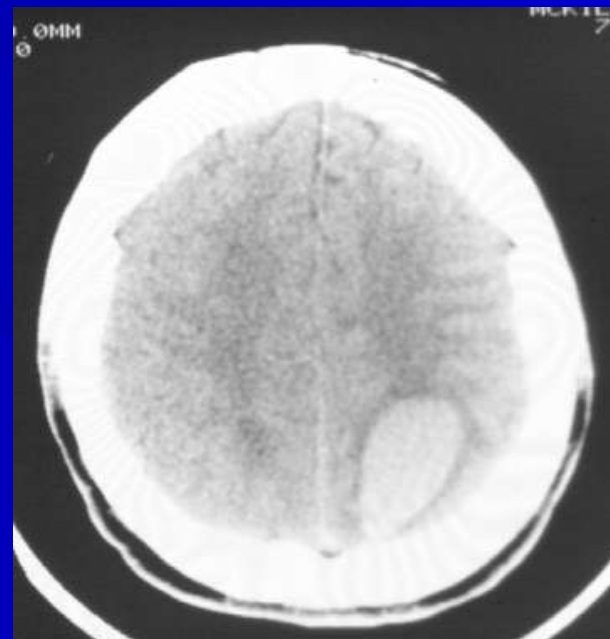
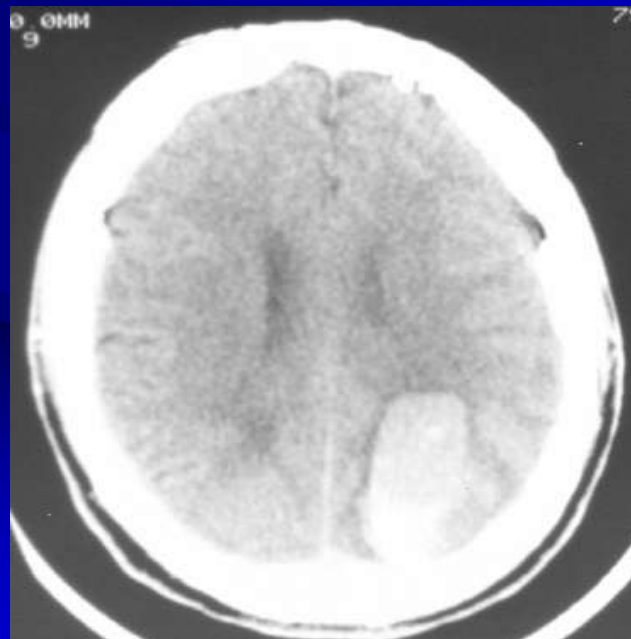
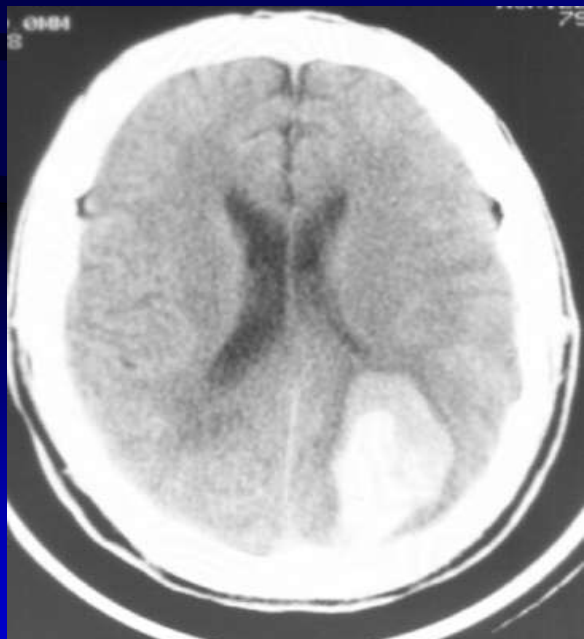
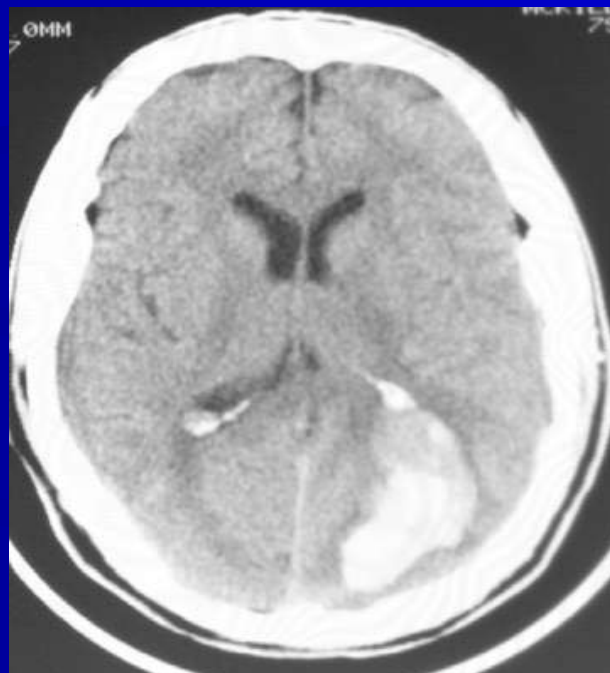
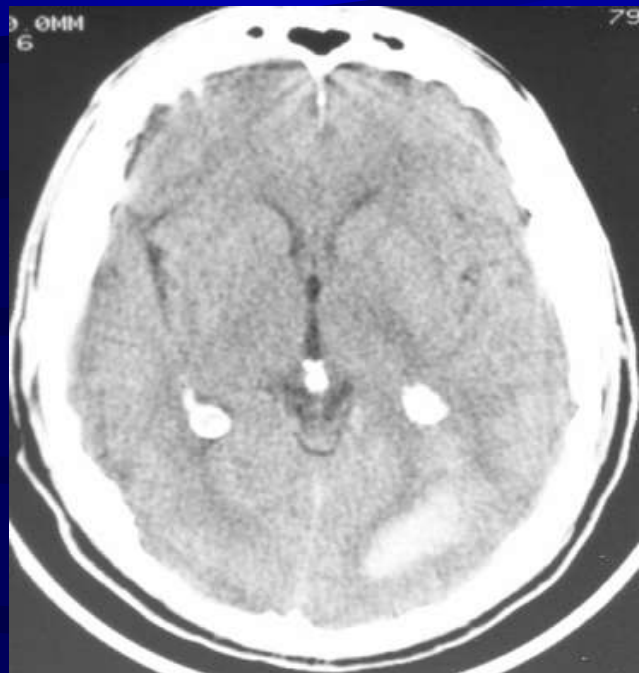


Schneider
et al
Neurology
2007



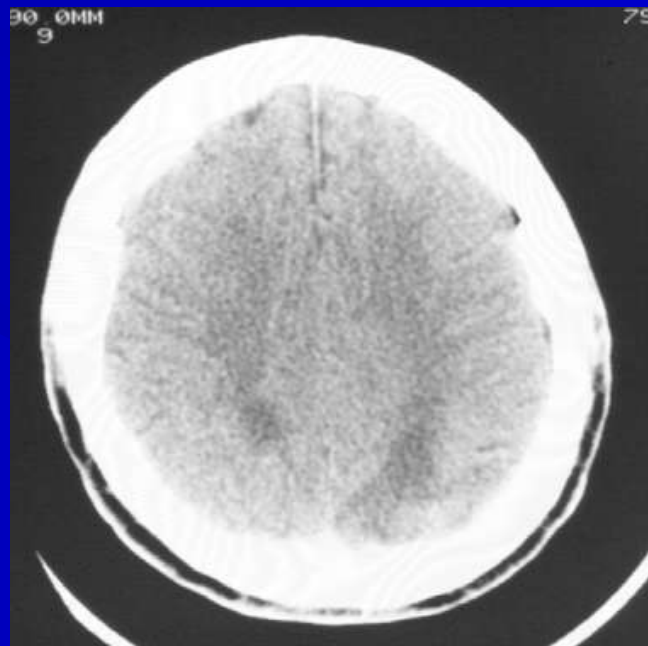
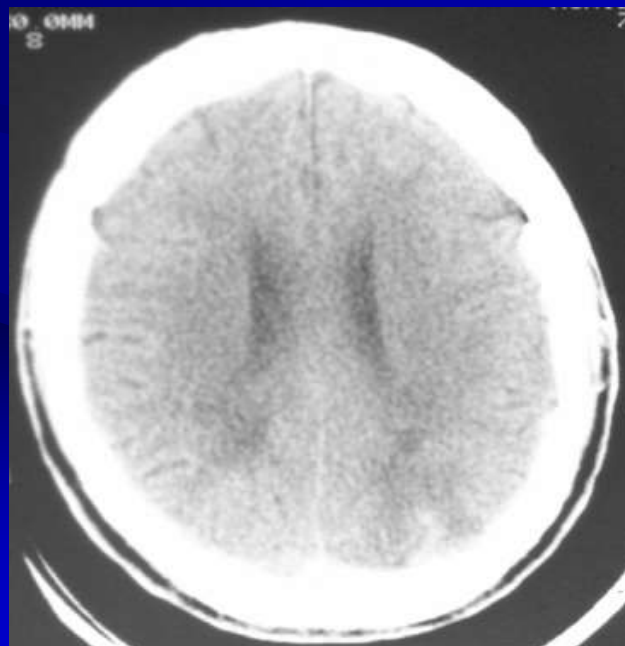
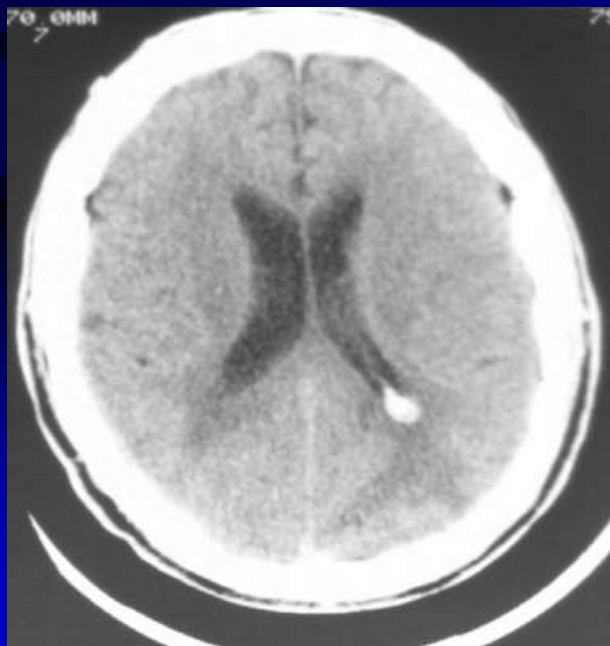
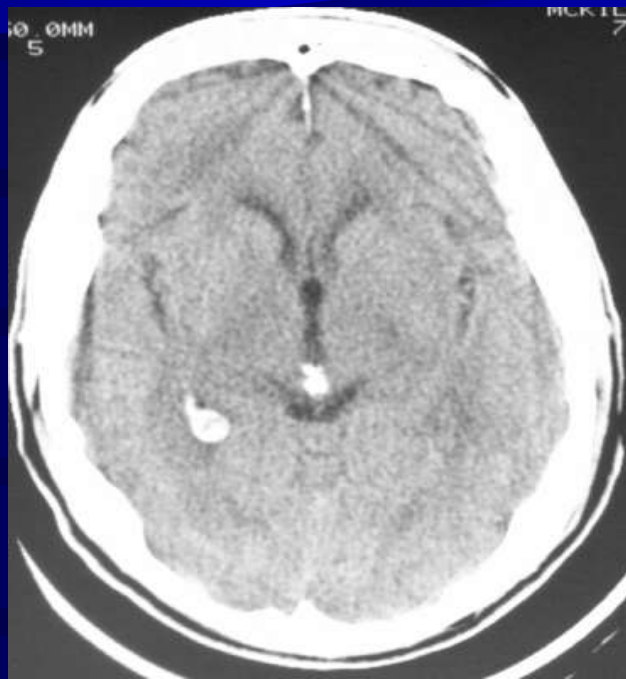
Vascular Cognitive Impairment

***Co-morbidity:
Case in Point***

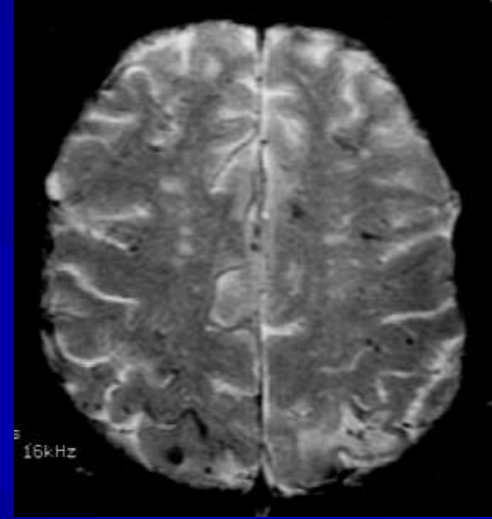
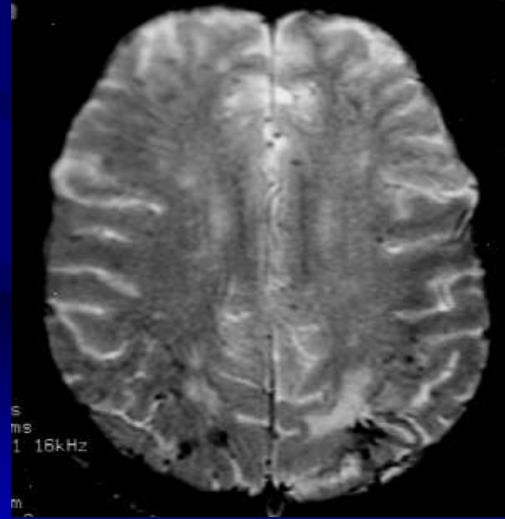
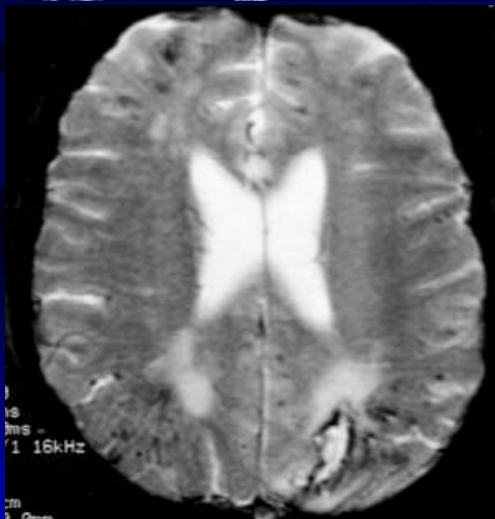
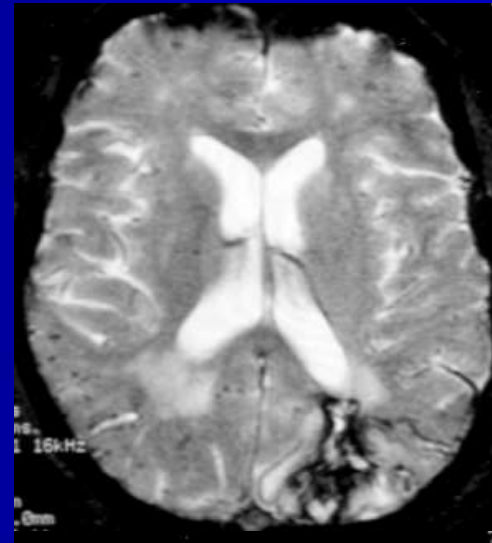
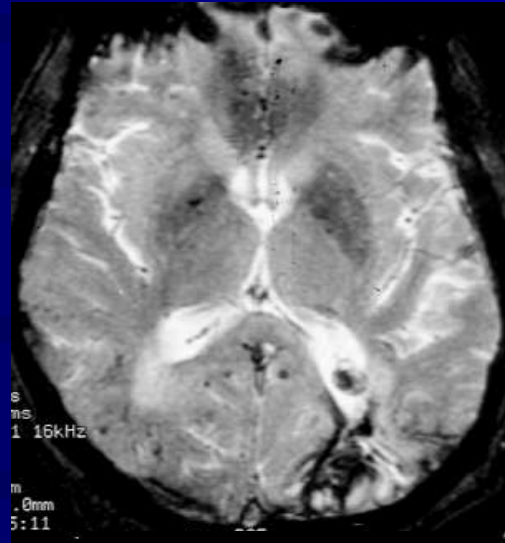
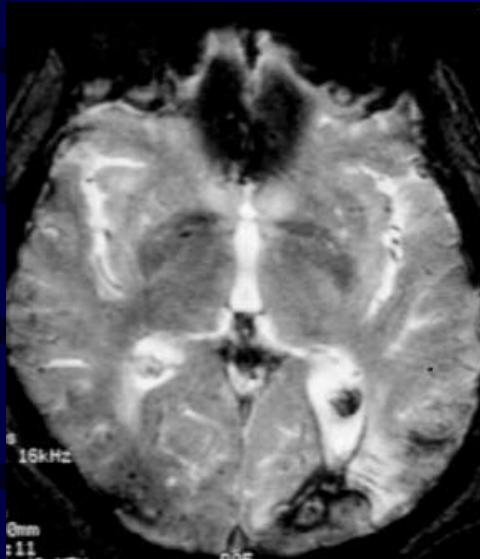


M.D. – 61 y.o. lawyer

- Became confused at work, bumping into objects
- Findings:
 - R hemianopsia & hemineglect
 - R sensory extinction
 - R pronator drift
 - Transcortical sensory aphasia (fluent speech), alexia & apraxia
- Angiography : no secondary cause



Gradient Echo

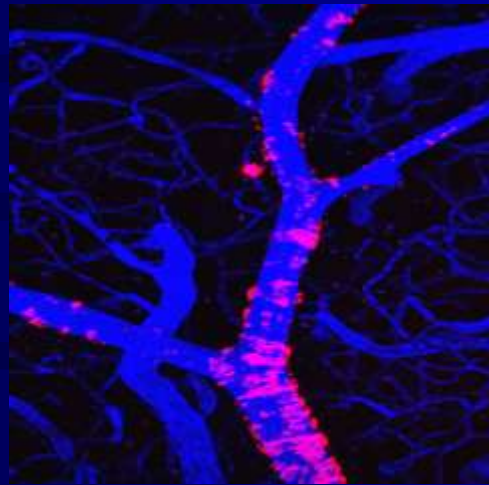
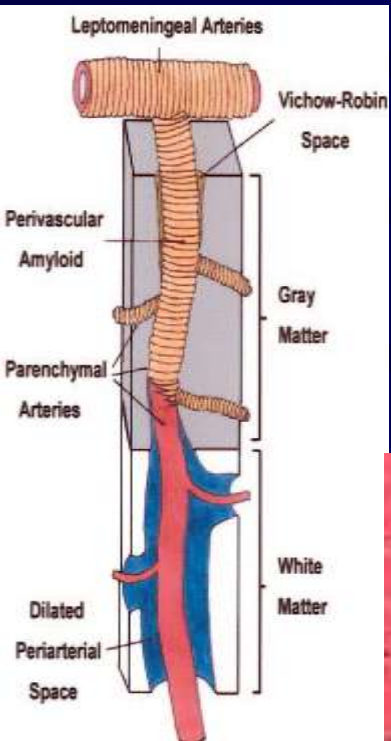


Microbleeds:
*Hemosiderin
Deposits*

M.D. - Course

- Unable to drive or work
- Persistent reading and calculation difficulties, but okay in other ADL's
- Lost to follow-up and then reappeared 7 years later gradual onset memory loss (MMSE 16/30)
- Progressive decline in cognition and behaviour over 2 years with some initial response to donepezil
- Found without vital signs in nursing home 9 yrs post-hemorrhage
- Autopsy results: confirmed old hemorrhages, amyloid angiopathy and ?

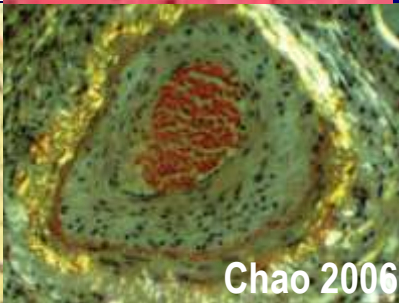
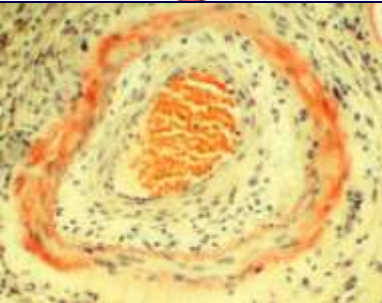
Amyloid Angiopathy



Prada 2007



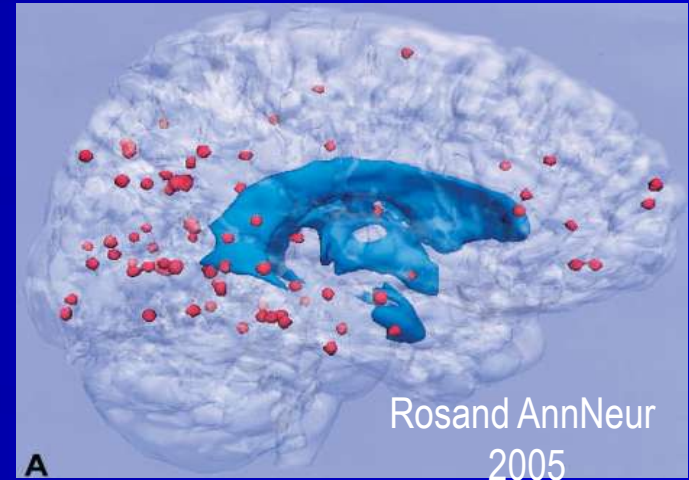
Vinters 2007



Chao 2006

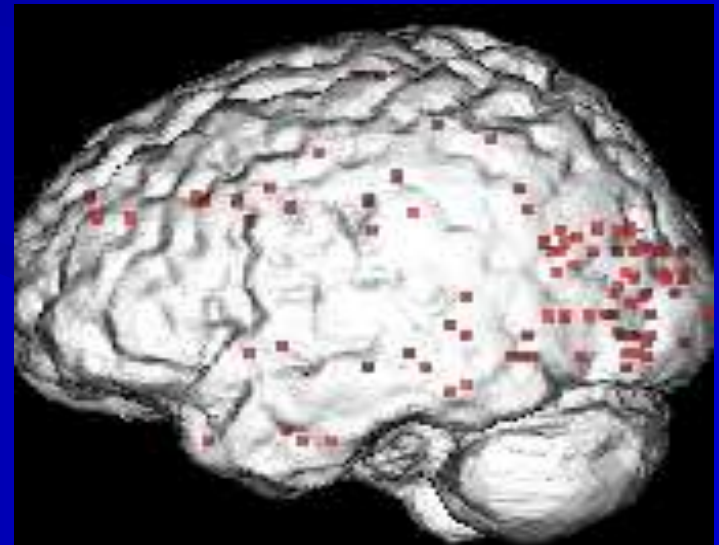
Alzheimer's Disease

SEBlack,SHSC,UT



Rosand AnnNeur 2005

Lobar Hemorrhage

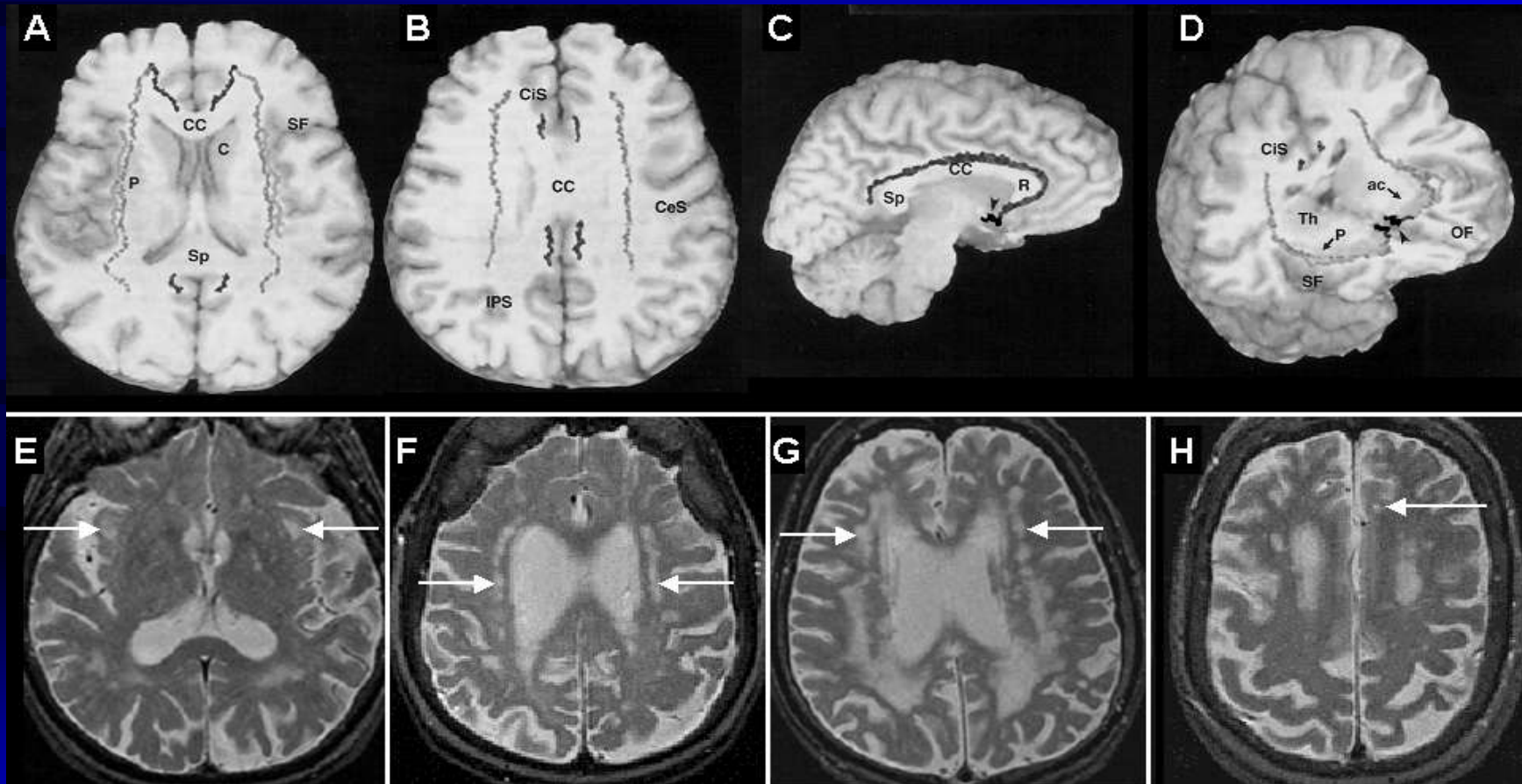


Pettersen et al Arch Neur 2008



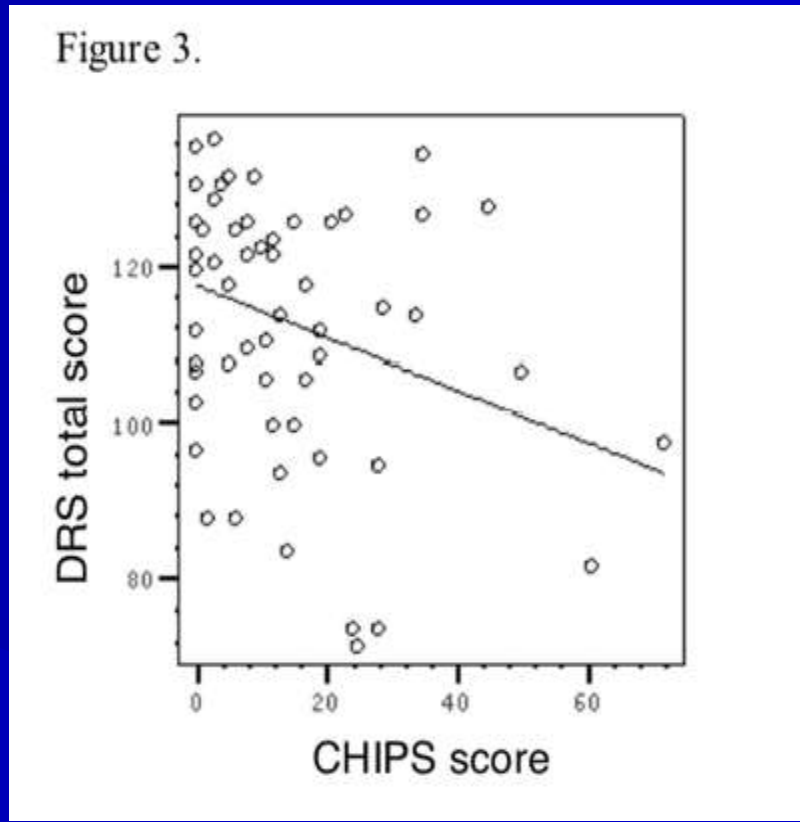
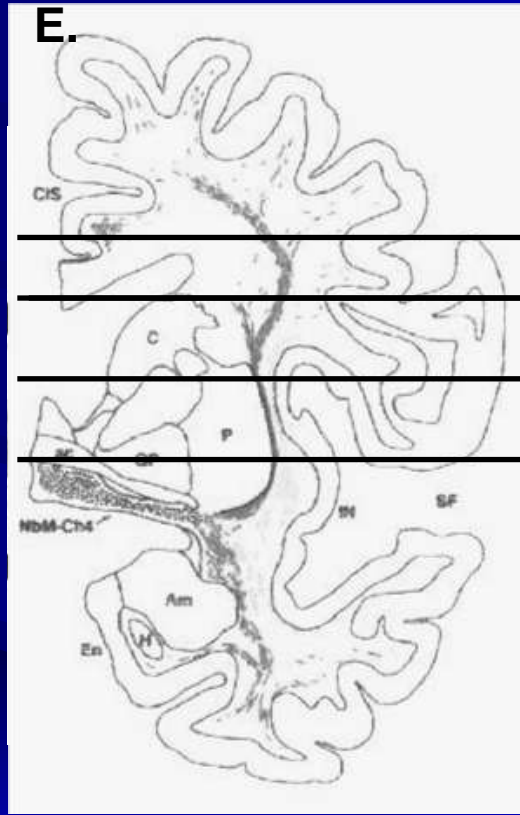
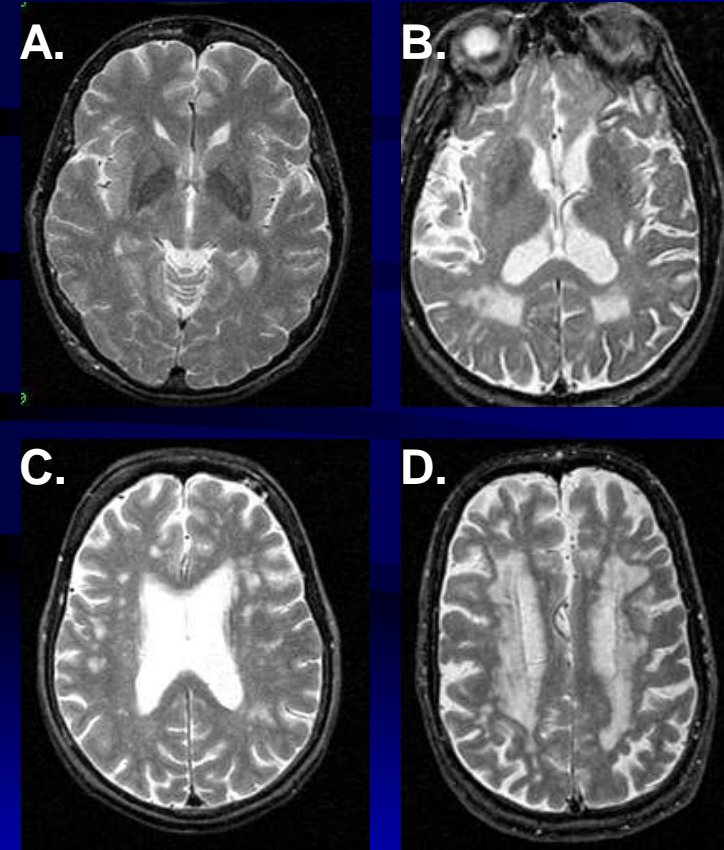
Cognitive Enhancers

Trajectories of cholinergic pathways



(Selden et al. 1998)

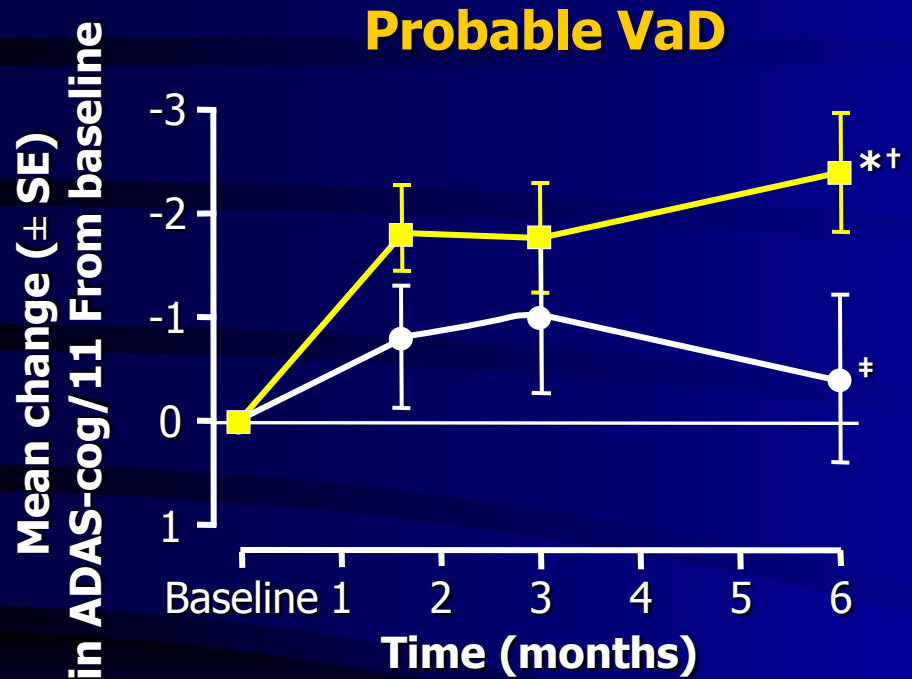
Cholinergic Hyperintensity Pathway Scale (CHIPS)



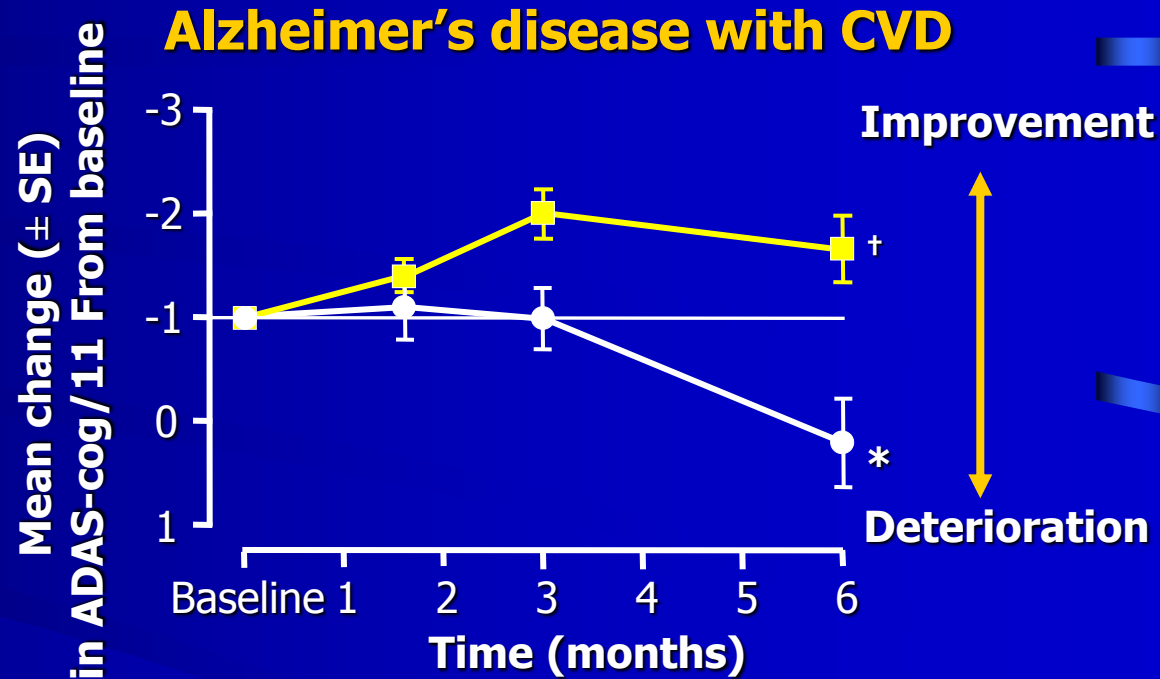
Correlation of CHIPS and Dementia Rating Scale ($r^2=.12$, $p=.02$)

Swartz et al, JStr CVD, 2002;
Bocti et al, Stroke, 2008

Galantamine: Cognitive Function: Subgroup Analysis

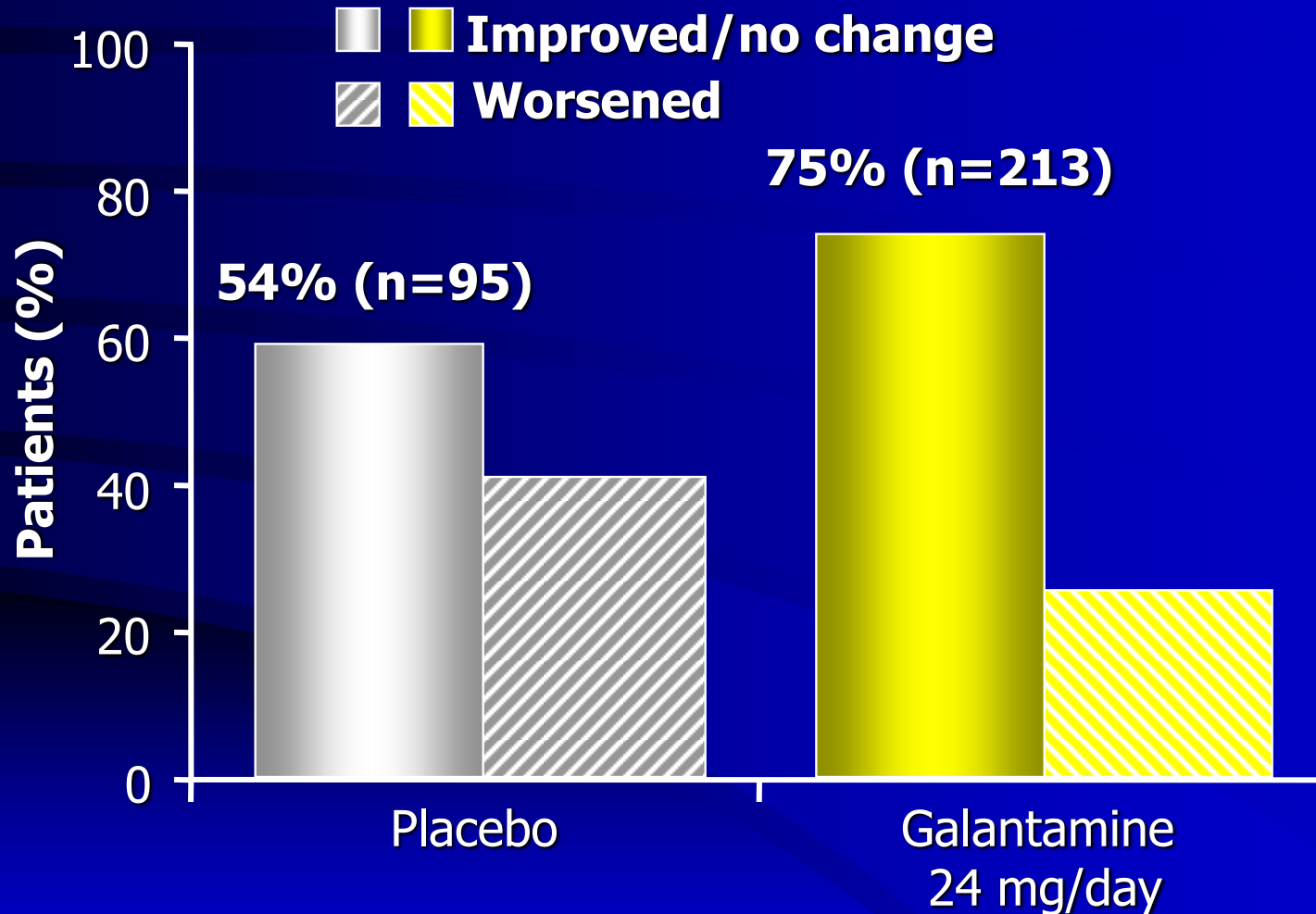


- Galantamine 24 mg/day (n=121)
- Placebo (n=67)
- * $P = .06$ vs placebo



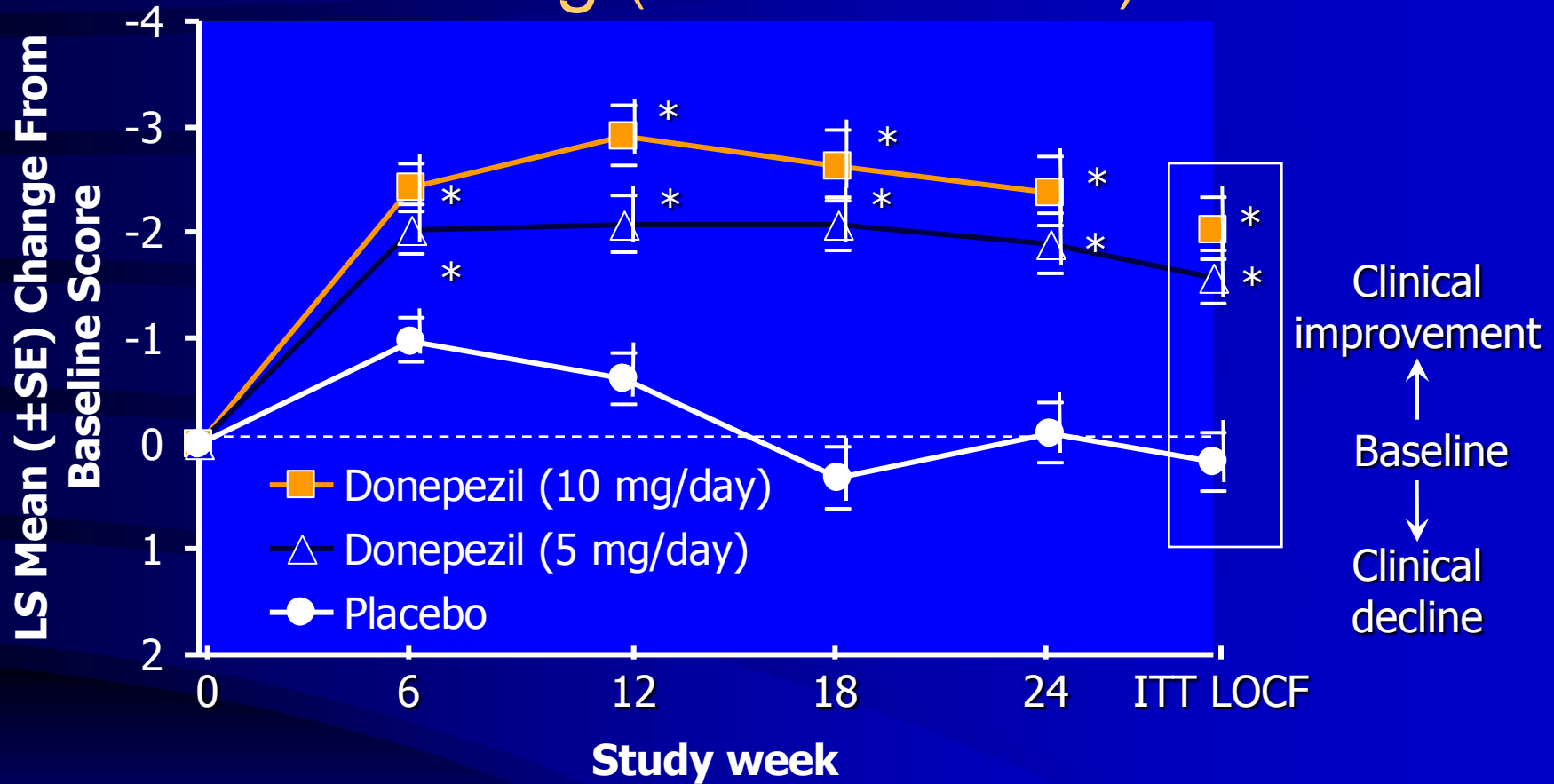
- Galantamine 24 mg/day (n=152)
- Placebo (n=87)
- † $P < .001$ vs placebo and baseline

Galantamine Benefits Overall Global Functioning at 6 Months



Donepezil: Cognitive Function

ADAS-cog (Prob/Poss. VaD)



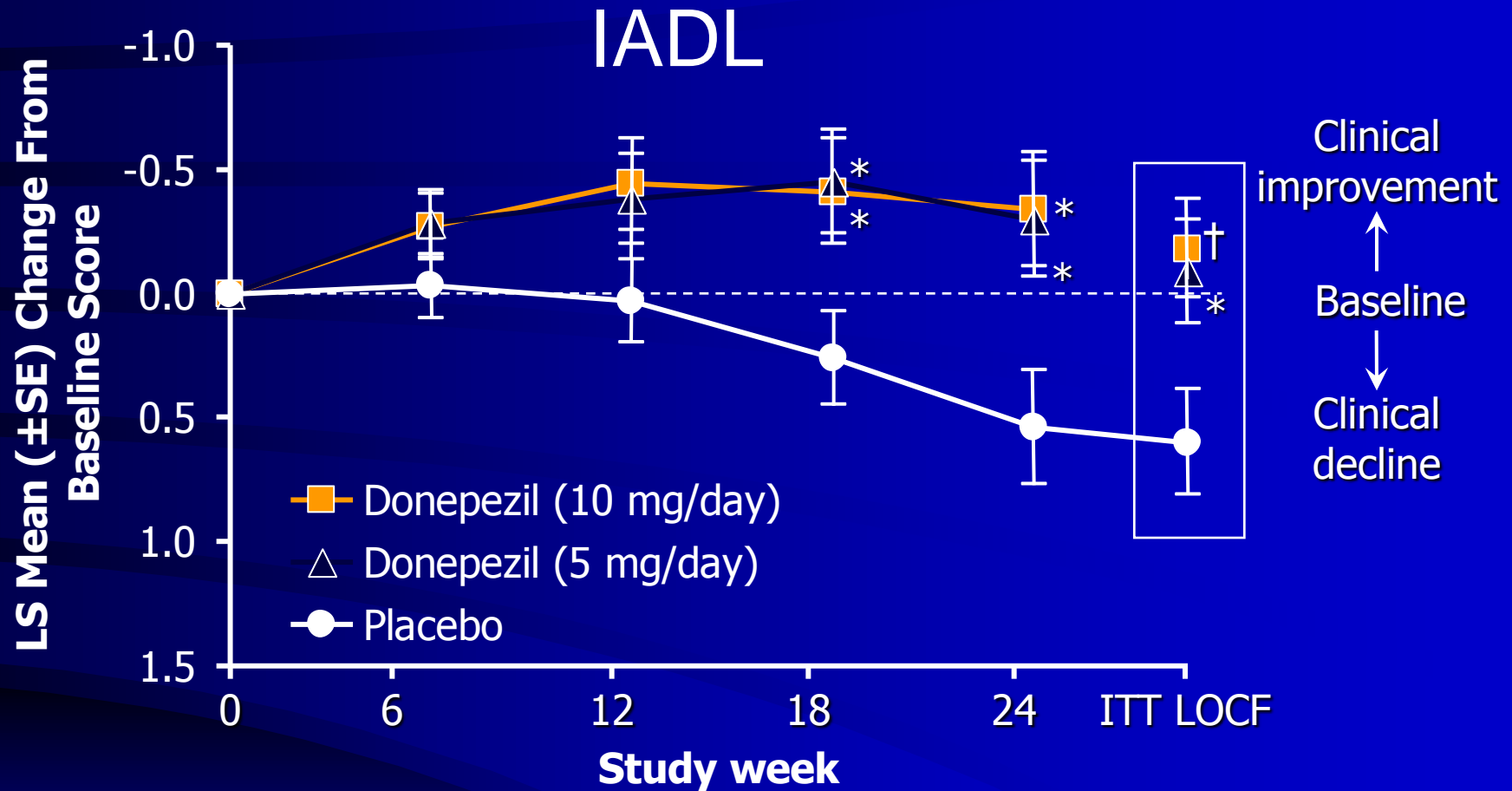
	0	6	12	18	24	ITT LOCF
Don 10 mg n=	380	370	334	309	298	380
Don 5 mg n=	387	372	354	327	317	384
Placebo n=	369	367	341	328	310	368

* $P < 0.001$ versus placebo.

Wilkinson et al. *Neurology*. 2003; Black et al. *Stroke* 2003.

SEBlack, SHSC, UT

Donepezil: Functional Outcomes



Don 10 mg	n= 382	373	334	305	297	382
Don 5 mg	n= 371	357	339	316	308	370
Placebo	n= 362	359	334	322	306	361

Wilkinson et al. *Neurology*. 2003; Black et al. *Stroke* 2003

* $P < 0.001$; † $P < 0.01$.

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Summary

- Best Practice suggests screening for VCI in all phases of **overt** stroke disease, when **silent stroke** disease is uncovered, and even with **vascular risk factors** (including age)
- Standardized testing recommended-consider the harmonization criteria
- Small Vessel disease is ubiquitous in our aging population, often co-exists with AD and is not benign
- Executive functioning and speed of processing are important to assess if you suspect VCI
- Cholinesterase inhibitors are a potential (off-label) option for cognitive enhancement in VaD

Key Take Homes

- Post-stroke dementia can occur in 25% and VCI is common in elderly stroke patients
- Mixed AD/CVD is likely the commonest substrate for dementia
- A major goal for vascular medicine is risk factor control not just to prevent heart attack and stroke, but also dementia!

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