VASCULAR DEMENTIA

Y. HIZEM, R. GOUIDER
RAZI HOSPITAL  LAMANOUBA
TUNIS-TUNISIA
Introduction

- **Cerebrovascular disease**: cause of cognitive impairment in later life, alone or in conjunction with Alzheimer disease (AD)

- **Vascular dementia (VaD)**: Dementia related to vascular disorders

- 8-15% of cognitively impaired aged subjects (>65y)

  (Jellinger 2008)
Thomas Willis, who studied well the cerebral vasculature led to his description of the circle of Willis in 1684.

Under the heading

“A palsie often succeeds stupidity, or becoming foolish,”

I have observed in many, that when, the Brain being first indisposed, they have been distempered with a dullness of mind, and forgetfulness, and afterwards with a stupidity and foolishness, after that, have fallen into a palsie, which I often did predict.
Historical Overview

“arteriosclerotic brain degeneration”
Most common form of senile dementia

Biswanger (1894)  Alzheimer (1895)

“Multi infarct dementia”

Hachinski (1974)
New concepts

“Vascular cognitive impairment : VCI”:

- Umbrella term
- Full spectrum of cognitive deficits due to cerebrovascular disease
- Includes
  - Cognitive deficits pre-dementia
  - Vascular dementia

(O’Brien et al 2003)
Prevalence and epidemiology

- Lack of clear and validated diagnostic criteria
- Complexity of brain pathologies, ethnic and geographic variations
- Considerable methodological differences

No agreement about epidemiology and prevalence
Prevalence and epidemiology

- Clinical studies: 4.5-39%
- Pathological studies: 0.03-35%
- Recent autopsy series (Japanese geriatric hospital): 23.6-35%

<table>
<thead>
<tr>
<th>Year</th>
<th>Setting</th>
<th>Studies</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962–1990</td>
<td>15 studies (Europe, USA, Canada)</td>
<td>2784</td>
<td>Prevalence 2.0–85.2% (mean 24.5%)</td>
</tr>
<tr>
<td></td>
<td>Markesbery 1998 [116]</td>
<td></td>
<td>Prevalence mean 11.3%</td>
</tr>
<tr>
<td>1991–2003</td>
<td>Riekse et al 2004 [139]</td>
<td>11 studies (USA, Scandinavia, Japan)</td>
<td>Prevalence 0.03–35% (mean 11.6%)</td>
</tr>
<tr>
<td>2004 Seattle, USA</td>
<td>Snowdon et al. 1999 [167]</td>
<td>20/170 cases</td>
<td>Prevalence 7%</td>
</tr>
<tr>
<td>2007 Austria</td>
<td>Jellinger: retrospective, dementia/AD</td>
<td>1600/870 cases</td>
<td>Prevalence 10.9/3.0%</td>
</tr>
<tr>
<td>Austria</td>
<td>Jellinger (unpubl.): prospective, dementias</td>
<td>180 cases</td>
<td>Prevalence 7.8%</td>
</tr>
<tr>
<td>Japan</td>
<td>Seno et al. 1999 [160], Akatsu et al 2002 [2]</td>
<td>122/270 cases</td>
<td>Prevalence 35.0/23.6%</td>
</tr>
</tbody>
</table>

Jellinger et al 2008
Razi Hospital Cohort
Distribution of subtypes of dementia by age

< 65 years

# P < 0.001

≥ 65 years
Razi Hospital’s Cohort
Prevalence of VD

- ≥ 65 ans : 2.76 %
  - 1.74 % : women
  - 3.71 % : men

p = 0.01
Pathogenic factors

1. Volume of brain destruction
2. Location of vascular lesions
3. Number of cerebrovascular lesions
Volume of Brain destruction

*Tomlinson 1970:*

- All patient with loss 100 ml brain volume: dementia
- Demented patients: more frequent infarcts > 20 ml than controls

- Small infarcts: possible contribution to dementia

- Concept of strategic sites of infarcts

- VaD: mean volume of infarcted brain loss: 39-47 ml
Pathogenic factors

1. Volume of brain destruction

2. Location of vascular lesions

3. Number of cerebrovascular lesions
Location of vascular lesions

- Dominant hemisphere
- Bilateral lesions
- Left angular gyrus
- Left or bilateral ACA and PCA territories
- Bilateral thalamic infarction
- Lacunar lesions in basal ganglia
- Head of the caudate nucleuc, inferior genu of the anterior capsule
- Hippocampal infarct
Pathogenic factors

1. Volume of brain destruction
2. Location of vascular lesions
3. Number of cerebrovascular lesions
Number of cerebrovascular lesions

- Basic concept: multiple small infarcts

- Mean number:
  5.8 - 6.7 VaD
  3.2 in non demented

- Additional factors (age, education level..) for intellectual decline
### Pathogenic Factors

- **Age**
- **Education**
- **Genetics**
- **Vascular risk factors**
- **ApoE...4**

#### Vascular causes
- Atherosclerosis
- Microvascular disease
- Reduced perfusion...

#### Additional pathologies

#### Neuronal synapse loss

#### Cognitive impairment
- Dementia

- Cerebral microinfarcts
- Lacunar state
- Withe matter lesions
- Multiple microinfarcts
- Neuronal synapse loss
- Cerebral atrophy
Pathogenic mechanisms

- Regional cerebral blood flow is reduced
- Oxidative stress including free radicals
- Damage of endothelial cells
- Chronic hypoperfusion
- Polioararoisis and leukoaroioisis
- Changes in the small penetrating arteries and arterioles in the white matter
Etiology and pathogenesis of vascular dementia

Ischemic vascular dementia (IVD)
Multi-infarct dementia (MID)

Microglial/astroglial proliferation
Secreted factors
Blood vessel-derived factors

Consequences for CNS parenchyma
(ischemia partial/complete)

Pathogenesis of vascular disease
macro/micro

Atheroma
FMD
?Vasculitis
Cardiogenic emboli
Others

AS/LH
CAA (spor/fam)
CADASIL
Others

Systematic factors
(hypotension, hypoxia)

Synapse and dendritic spine loss
Wallerian degeneration
Trans-synaptic degeneration
Retrograde cortical neuronal changes

Selnes et al 2006
Morphologic lesions

Pathologic changes in the brain related to VCI are multiple

Categorized:
- multifocal and/or diffuse disease and focal
- Large and small vessel disease
Major cerebrovascular lesions associated with cognitive impairment

1. **Gross large infarcts** in supply territories of large cerebral arteries, in particular ACM, ACM+ACP, unilateral or bilateral

2. **Lacunes** (lesions 0.5–15 mm (⌀) and multiple microinfarcts or small hemorrhages in basal ganglia, thalamus, hippocampus, basal forebrain (“strategic infarct dementia”))

3. **Multiple microinfarcts/scars** in cortical border zones (“granular cortical atrophy”) — rare

4. **Pseudolaminar cortical necrosis** (mainly arterial border zones)

5. **Hippocampal sclerosis**

6. **White matter lesions** /leukoaraiosis/Binswanger disease

7. **Combined cerebrovascular lesions**

(Jellinger 2008, JNS)
Newcastle categorization of the major cerebrovascular lesions associated with cognitive impairment

<table>
<thead>
<tr>
<th>VaD subtypes related to</th>
<th>Newcastle subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large infarct or several infarcts</td>
<td>I</td>
</tr>
<tr>
<td>(&gt;50 ml loss of tissue); multi-infarct dementia</td>
<td></td>
</tr>
<tr>
<td>Multiple small or microinfarcts</td>
<td>II</td>
</tr>
<tr>
<td>(&gt;3 with minimum diameter 5 mm);</td>
<td></td>
</tr>
<tr>
<td>small vessel disease (*); involving greater than three coronal levels;</td>
<td></td>
</tr>
<tr>
<td>hyalinisation, CAA, lacunar infarcts,</td>
<td></td>
</tr>
<tr>
<td>perivascular changes,</td>
<td></td>
</tr>
<tr>
<td>microhemorrhages</td>
<td></td>
</tr>
<tr>
<td>White matter lesions/leukoaraiosis/Binswanger disease</td>
<td>III</td>
</tr>
<tr>
<td>Strategic infarcts (e.g., thalamus, hippocampus, basal forebrain)</td>
<td></td>
</tr>
<tr>
<td>Cerebral hypoperfusion (hippocampal sclerosis, ischemic–anoxic damage, cortical laminar</td>
<td>IV</td>
</tr>
<tr>
<td>necrosis, borderzone infarcts involving three different coronal levels</td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhages (lobar, intracerebral, subarachnoidal)</td>
<td>V</td>
</tr>
<tr>
<td>Cerebrovascular changes with Alzheimer pathology (above Braak stage III); mixed dementia</td>
<td>VI</td>
</tr>
<tr>
<td>(according to the author’s experience stage IV would be appropriate)</td>
<td></td>
</tr>
<tr>
<td>Combined cerebrovascular lesions</td>
<td></td>
</tr>
</tbody>
</table>

(Jellinger 2008, JNS)
Classification according to major morphologic lesions

**Small vessel disease**
- Ischemic white matter degeneration
- Cribriform atrophy of white matter
- Lacunar infarction in subcortical nuclei and WM
- Granular atrophy of cortex

**Large vessel disease**
- Very extensive or multifocal infarction
- Critically sited infarcts

**Hypoperfusion lesions**
- Hippocampal sclerosis
- Laminar cortical necrosis

**Rare local vascular disease**
- CADASIL
- Cerebral amyloidosis
- Cerebral vasculitis
- Antiphospholipid antibody syndrome
Diagnostic

1. Clinical evaluation
2. Cognitive assessment
3. Neuroimaging
4. Biomarkers
5. Neurpathology
Clinical evaluation

VCI is a clinical diagnosis:

- Cognitive complaint
- Information about vascular risk factors
- Others: migraine, depression: helpful
- Onset, progression, urinary incontinence, gait disturbance
- Focal neurological signs
- Cardio vascular system

No pathognomonic sign or symptom
Diagnostic Criteria

- Hachinski Ischemia scale
- Ischemic scale of Rosen
- DSMIII, DSMIII-R, DSMIV
- International classification of diseases ICD10
- State of California Alzheimer’s Disease Diagnostic and treatment Centers ADDTC (Chui et al 1992)
- National institute of Neurological Disorders and stroke-Association Internationale pour la Recherche et l’enseignement en Neurosciences (NINDS-AIREN)
# The Hachinski Ischemia Score

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>History of strokes</td>
<td>2</td>
</tr>
<tr>
<td>Evidence of associated atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurological symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurological signs</td>
<td>2</td>
</tr>
</tbody>
</table>

Score $\geq 7$ - VaD

Score $\leq 4$ – AD
The 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
The NINDS-AIREN criteria are currently most widely used in clinical drug trials on VaD.

Based on neuropathological series
- sensitivity was 58%,
- specificity was 80%,
- successfully excluded AD in 91% of cases,
- proportion of combined cases misclassified as probable VaD was 29%.

Compared to the CADDTC criteria, the NINDS-AIREN criteria were more specific, and they better excluded combined cases (54% vs. 29%)

<table>
<thead>
<tr>
<th>Nosology</th>
<th>HIS MID</th>
<th>IS-R MID</th>
<th>DSMIII MID</th>
<th>DSMIR MID</th>
<th>DSMIV VaD</th>
<th>ICD10 VaD</th>
<th>ADDC IVD</th>
<th>NINDS AIREN VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterograde amnesia</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Any deficit ≥ 2 domains</td>
</tr>
<tr>
<td>Retrograde amnesia</td>
<td>-</td>
<td>-</td>
<td>Or+</td>
<td>And+</td>
<td>Or+</td>
<td>Or+</td>
<td>Or+</td>
<td></td>
</tr>
<tr>
<td>Other cognitive impairment</td>
<td>-</td>
<td>-</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
<td>≥2</td>
<td>≥2</td>
<td></td>
</tr>
<tr>
<td>Focal neurological signs/symptoms</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+/+</td>
<td>+/-</td>
<td>+/-</td>
<td>-/+</td>
<td>+/+</td>
</tr>
<tr>
<td>Structural imaging</td>
<td>-</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>supportive</td>
<td>Or+</td>
<td>+</td>
</tr>
</tbody>
</table>
### Comparaison of cognitive syndrome and vascular causes

<table>
<thead>
<tr>
<th>Nosology</th>
<th>HIS MID</th>
<th>IS-R MID</th>
<th>DSMIII MID</th>
<th>DSMIR MID</th>
<th>DSMIV VaD</th>
<th>ICD10 VaD</th>
<th>ADDC IVD</th>
<th>NINDS AIREN VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple large vessel infarcts</td>
<td>NS</td>
<td>NS</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>≥2</td>
<td>+</td>
</tr>
<tr>
<td>Strategic infarct</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Temporal relationship</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>≤6m</td>
<td>+</td>
<td>≤3m</td>
</tr>
<tr>
<td>Type of onset</td>
<td>abrupt</td>
<td>abrupt</td>
<td>abrupt</td>
<td>abrupt</td>
<td>Abrupt/insidious</td>
<td>Abrupt/insidious</td>
<td>NS</td>
<td>Abrupt or gradual</td>
</tr>
<tr>
<td>stepwise</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>NS</td>
<td>+</td>
</tr>
</tbody>
</table>
Neuropsychological impairment

- Profile of memory with better preservation of recognition memory performance
- Greater executive impairment than AD
- CADASIL (younger, less AD pathologic changes): less pronounced dysexecutive function and attention
- Large cortical infarcts: cognitive profile variable with location and volume of lesion
## Strategic infarct syndrome

<table>
<thead>
<tr>
<th>Vascular territory</th>
<th>Structures affected</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>anterior cerebral artery</td>
<td>medial frontal cortex</td>
<td>frontal behaviours (apathy, disinhibition, hyperorality, inappropriate sexuality, emotional lability); memory changes</td>
</tr>
<tr>
<td>middle cerebral artery</td>
<td>angular gyrus</td>
<td>Alexia, agraphia, fluent aphasia, memory changes, abnormal spatial awareness</td>
</tr>
<tr>
<td>middle cerebral artery</td>
<td>cerebral convexity cortical &quot;watersheds&quot;</td>
<td>Amnesia, apraxia, aphasia agnosia, hemi-neglect, visual disturbances</td>
</tr>
<tr>
<td>Boundary regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>posterior cerebral artery</td>
<td>hippocampus</td>
<td>Amnesia, anoma, visual field disturbances, confusion</td>
</tr>
<tr>
<td>posterior cerebral artery</td>
<td>medial thalamic nuclei</td>
<td>memory impairment (especially memory acquisition); inattention</td>
</tr>
</tbody>
</table>
Neuropsychological impairment

- Specificity of cognitive profile: debated

  Overlap with AD / ≠ AD?

- No correlation between extent of ischaemic lesion and severity or pattern of neuropsychological impairment

- Neuropsychological pattern:
  not adopted as a diagnostic feature
Diagnostic Brain Imaging of VaD

Multiple large vessel infarcts

Strategic thalamic infarct
Diagnostic Brain Imaging of VaD

CADASIL

Biswanger’s Disease
Diagnostic Biomarkers

- CSF-albumin index: blood-brain barrier integrity
- Matrix metalloproteinases: MMP2, MMP9
- Light neurofilament subunit
- CSF tau and phospho tau concentration: negative biomarker

(Moorehouse 2008, Lancet Neurol)
Diagnostic Neurpathology

Deep white matter demyelination

Lacunar infarct

Thalamic lacunes

Multiple cortical microinfarcts

Small arteries with marked ‘onion skin’-type thickening
Clinical Subtypes

Vascular dementia

- Vascular dementia construct: post stroke dementia, multi-infarct dementia, subcortical dementia, leukoariosis

VCI no dementia

- Subcortical ischemia + cognitive impairment of presumed vascular cause
- Risk of progression to dementia, mixed or vascular dementia

Mixed dementia

- Clinical and neuropathological features of Alzheimer’s disease and vascular dementia
Relationship between cognitive impairment and cerebrovascular disease
### AD vs. VaD: “Classical” Clinical Features

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Insidious</td>
<td>Abrupt</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Slow, gradual</td>
<td>“Stepwise”</td>
</tr>
<tr>
<td><strong>Focal neurological signs or symptoms</strong></td>
<td>Usually absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Vascular risk factors</strong></td>
<td>May be present</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>Present (linked to genes on various chromosomes)</td>
<td>Present (CADASIL, autosomal dominant 19q12)</td>
</tr>
<tr>
<td><strong>Cognitive profile</strong></td>
<td>Memory, naming – with typical progression</td>
<td>“Spotty deficits”, executive dysfunction often prominent</td>
</tr>
</tbody>
</table>
Razi Hospital’s Cohort

MEAN AGE AND MMSE AT THE FIRST CONSULTATION
VD PATIENTS vs AD PATIENTS

**MEAN AGE**
- AD Patients: 72.65
- VD Patients: 71.83

**MEAN MMSE**
- AD Patients: 10.77
- VD Patients: 12.87

p = 0.61

p = 0.024
Razi Hospital’s Cohort

INITIAL CLINICAL STAGE
VD PATIENTS vs AD PATIENTS

p = 0.028
Common causative mechanisms of AD and VaD

Alzheimer’s dementia

Mixed dementia

Vascular dementia

Aβ

Release of free radical and glutamate

Activation of L-VSCC, NMDAR and AMPA/KAR

Disruption of Ca²⁺ homeostasis

Translocation and activation of cPLA2

Up-regulation of COX2

Excess of PGD2 generation

Elevation of 15dΔ¹²,¹⁴-PGJ2

Apoptosis and neuronal cell loss

Yagami 2006
Overlap Between Alzheimer’s Disease and VaD

Cholinergic deficit

AD

Probable  Possible  Mixed  Possible  Probable

Amyloid plaques
Genetic factors
Neurofibrillary tangles

Mixed

VaD

Stroke/TIA
Hypertension
Diabetes
Hypercholesterolemia
Heart disease

Amyloid plaques
Genetic factors
Neurofibrillary tangles
Stroke/TIA
Hypertension
Diabetes
Hypercholesterolemia
Heart disease
## Risk Factors

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Stroke factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Previous/recurrent cerebrovascular accident (CVA)/TIA</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
</tbody>
</table>

## Vascular risk factors

- Hypertension
- Atherosclerosis
- Diabetes mellitus
- Low blood pressure
- Coagulopathies
- Peripheral vascular disease
- ApoE4
- Cigarette smoking
- Hypercholesterolemia
- Ischemic heart disease
- Atrial fibrillation
- Elevated homocysteine
- Myocardial infarction (MI)/angina
  systemic inflammation
Razi Hospital’s Cohort
VASCULAR RISK FACTORS IN VD GROUP (1)

SMOKING

HYPERTENSION

DIABETES MELLITUS

HYPERCHOLESTEROLEMIA
Razi Hospital’s Cohort
VASCULAR RISK FACTORS VD vs OTHER DEMENTIA

HYPERTENSION

- VD: 26
- Other Dementia: 68
- p < 0.001

STROKE

- VD: 35
- Other Dementia: 228
- p < 0.001

CARDIOPATHY

- VD: 45
- Other Dementia: 220
- p < 0.001

HYPERCHOLESTEROLEMIA

- VD: 48
- Other Dementia: 220
- p = 0.014
Primary prevention

Treatment of vascular risk factors

1. Treat HTA optimally
2. Treat diabetes
3. Control hyperlipidaemia
4. Tobacco + alcohol
5. Anticoagulants for atrial fibrillation
6. Antiplatelet therapy
7. Carotid endarterectomy for severe (> 70%) stenosis
8. Dietary control
9. Lifestyle (stress, weight…)
10. Stroke + TIA: NMDA, ca++, antioxidants
11. Rehabilitation
## Antihypertensive Treatment and Cognitive Decline

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Change in BP (mm Hg)</th>
<th>Drugs</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYST-EUR 2, 2002</td>
<td>2902</td>
<td>-7/3.2</td>
<td>CCB ± ACE inhibitors ± Diu</td>
<td>4y</td>
<td>↓ dementia</td>
</tr>
<tr>
<td>Stroke patients</td>
<td></td>
<td></td>
<td></td>
<td>55%</td>
<td>(24-73%)</td>
</tr>
<tr>
<td>PROGRESS, 2003</td>
<td>6105</td>
<td>-9/4</td>
<td>ACE inhibitors ± Diu</td>
<td>4y</td>
<td>↓ cognitive decline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19%(4-32%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ dementia w/recurrent stroke</td>
</tr>
<tr>
<td>HOPE, 2002</td>
<td>9297</td>
<td>-3.8/2.8</td>
<td>ACE inhibitors</td>
<td>4.5y</td>
<td>↓ cognitive decline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34%(3-55%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>decline relative to stroke</td>
</tr>
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<td></td>
<td></td>
<td>41%(6-63%)</td>
</tr>
</tbody>
</table>

Modified from Hanon and Forette, Alzheimer’s and Dementia 2005, 1:30-37
**Prevention Regimen For Effectively avoiding Second Strokes – The PRoFESS® Trial**

<table>
<thead>
<tr>
<th></th>
<th>ER-DP + ASA (400 mg/50 mg)</th>
<th>Clopidogrel* (75 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telmisartan (80 mg)</td>
<td>ER-DP + ASA + Telmisartan</td>
<td>Clopidogrel* + Telmisartan</td>
</tr>
<tr>
<td></td>
<td>(5,000 pts)</td>
<td>(5,000 pts)</td>
</tr>
<tr>
<td>Placebo</td>
<td>ER-DP + ASA + Placebo</td>
<td>Clopidogrel + Placebo</td>
</tr>
<tr>
<td></td>
<td>(5,000 pts)</td>
<td>(5,000 pts)</td>
</tr>
</tbody>
</table>

Donepezil in Vascular Dementia: Combined Analysis of Two Large-Scale Clinical Trials


Dement Geriatr Cogn Disord 2005;20:338–344

- Combined analysis of 2 randomized, doubleblind, placebo-controlled, 24-week studies (307, 308)
- 1219 patient
- NINDS-AIREN criteria
- Donepezil 5mg/10mg/placebo
Donepezil in VaD: Cognition

Benefit in Cognition: improvement in ADAS-cog and MMSE scales (5mg)

Efficacy of galantamine in probable vascular dementia and Alzheimer’s disease combined with cerebrovascular disease: a randomised trial

Timo Erkinjuntti, Alexander Kurz, Serge Gauthier, Roger Bullock, Sean Lilienfeld, Chandrasekhar Rao Venkata Damaraju

Lancet 2002; 359: 1283–90

GAL-INT-6

24 weeks
Galantamine 24mg daily
592 patients
NINDS-AIREN
MMSE 10-24
MRI or CT evidence of VD
ADAS-cog Scores (6 Months)

**Cognition**: improvement in scores on the ADAS-cog scale versus placebo

- **Mixed D Placebo (n = 87)**
- **Probable VaD Placebo (n = 67)**

Mean change +/- SE in ADAS-cog/11

Time (months): 0, 1, 2, 3, 4, 5, 6

- Baseline
- Improved
- Deteriorated

\[ \Delta = 2.2 \]
\[ p = 0.013 \]
Efficacy and Safety of Memantine in Patients With Mild to Moderate Vascular Dementia

A Randomized, Placebo-Controlled Trial (MMM 300)

Jean-Marc Orgogozo, MD; Anne-Sophie Rigaud, MD, PhD; Albrecht Stöffler, MD; Hans-Jorgen Möbius, MD; Françoise Forette, MD

28 weeks
Memantine 24 mg daily
321 patients
NINDS-AIRNS
MMS 12-20
MRI or CT evidence of VD

Stroke 2002, 33:1834-1839
**ADAS-cog**

Significant Benefit on Cognition: improvement of ADAS-cog

![Graph showing mean change from baseline with ADAS-cog score difference on the y-axis and week on the x-axis. The graph compares Memantine (20 mg/day) and Placebo treatments. The graph indicates a significant benefit on cognition with improvement of ADAS-cog.](image)

Orgogozo et al., Stroke 2002
CONCLUSION

- Vascular dementia: evolving concept VCI
- Epidemiology not exactly determined but real impact
- Diagnosis: no specific marker but a mix of arguments
- Several classifications: NINDS-AIREN
- No Cure but prevention and symptomatic treatment
Acknowledged ignorance is a form of knowledge (courtesy of Vladimir HACHINSKI)

THANK YOU