Predictive value of arterial stiffness for WHITE MATTER LESIONS AT BRAIN MRI and cognitive decline **the COVADIS-arterial stiffness study**

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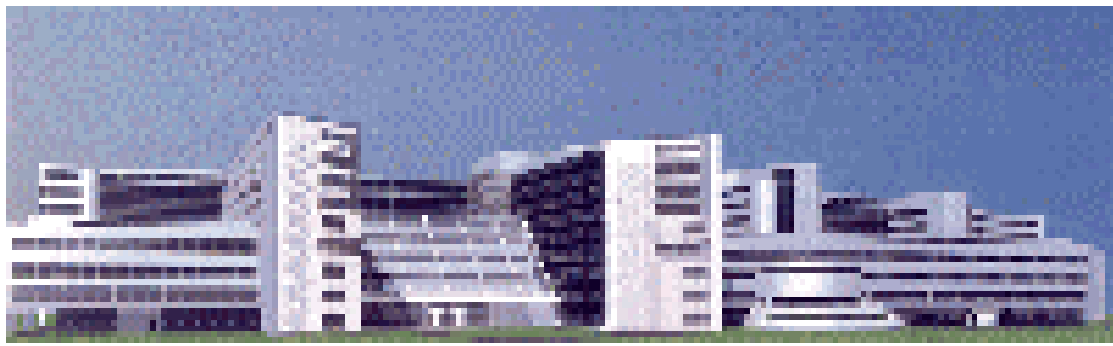
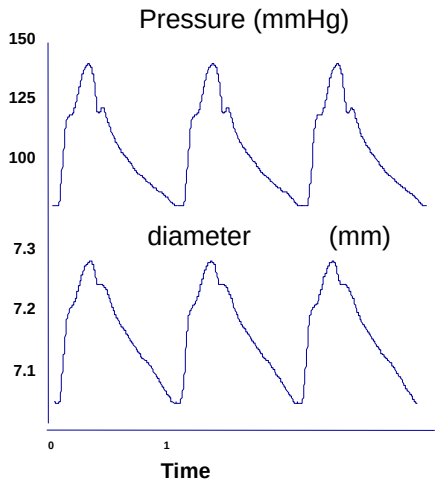
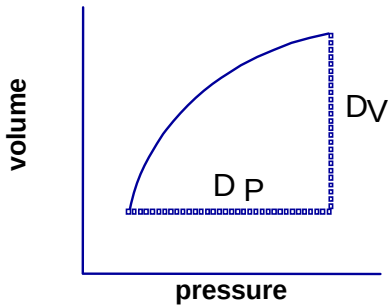


Methods for large artery stiffness measurement

Local stiffness

Applanation tonometry





Echotracking

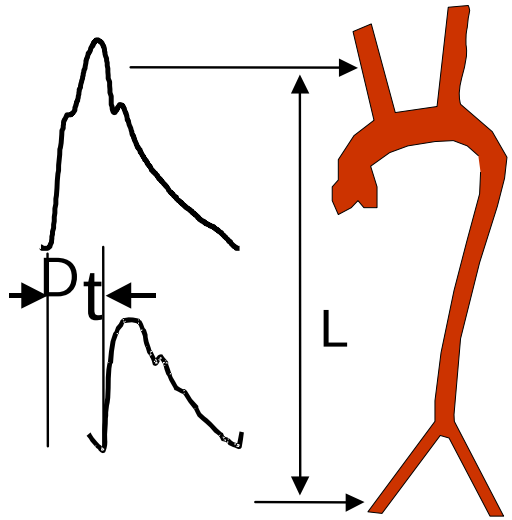
Dist = DV/ DP.V

Young's elastic modulus

$$E_{inc} = 3\left[1 + \frac{LCSA}{WCSA}\right]\frac{1}{Dist}$$

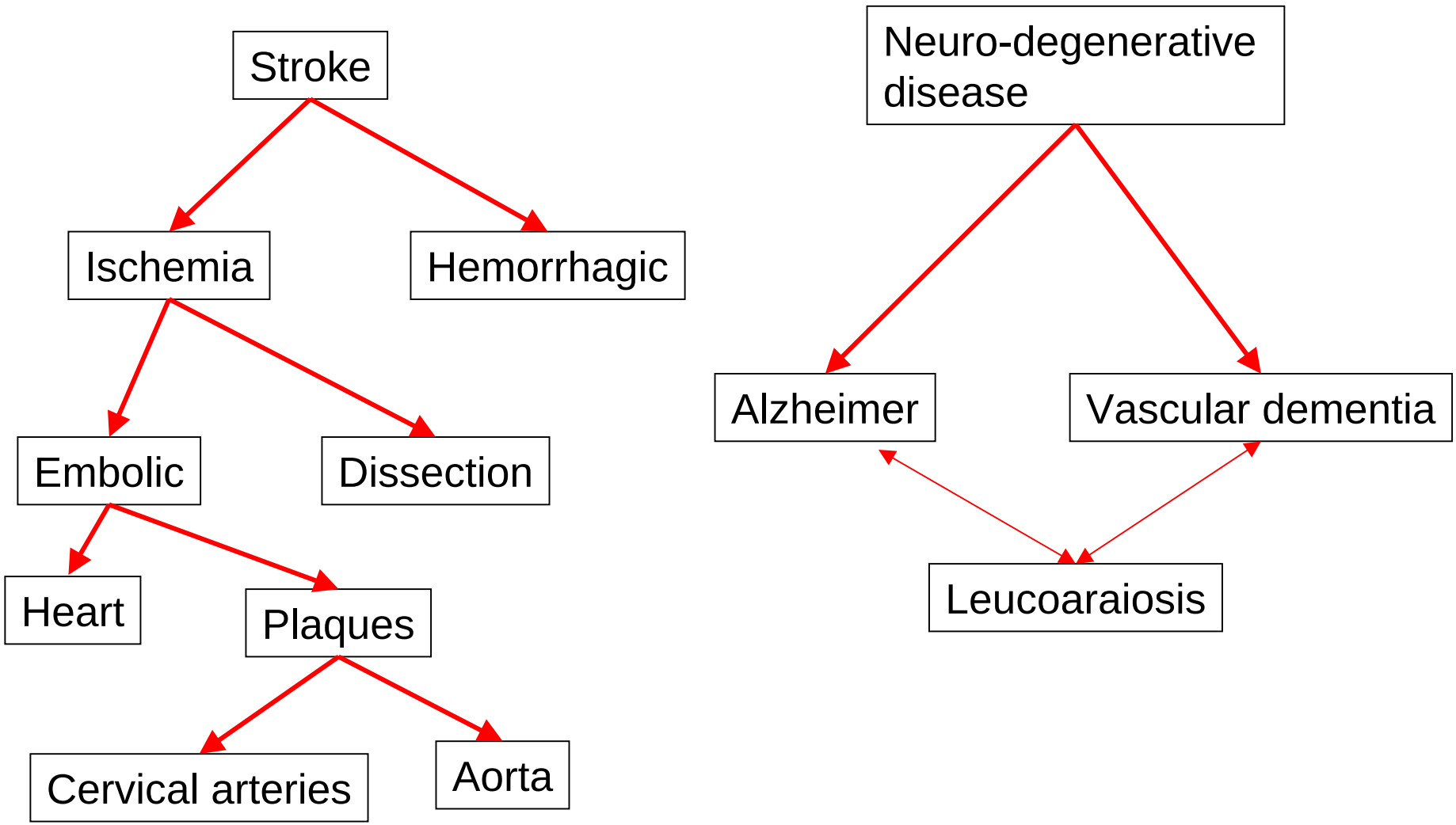
Aortic stiffness

Aortic pulse wave velocity



$$PWV = \frac{\Delta L}{\Delta t} = \sqrt{\frac{dP}{\rho.}\cdot\frac{V}{dV}} \approx \sqrt{\frac{1}{DIST}}$$

Understanding of Cerebrovascular diseases by a cardiologist-pharmacologist



Cerebral arterioles remodelling : experimental evidences

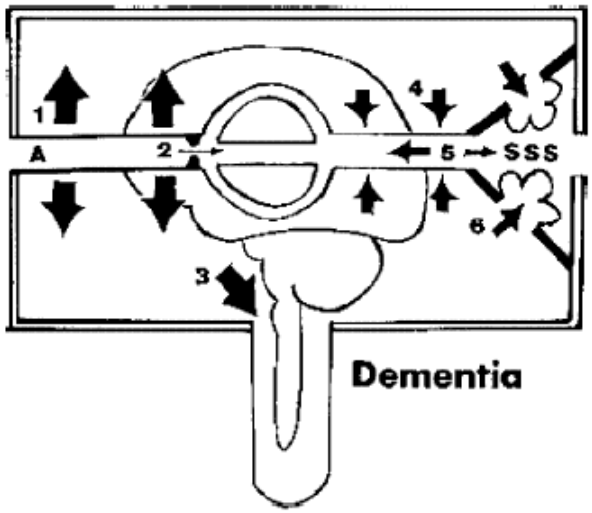
- Vascular hypertrophy of cerebral arterioles is related more closely to pulse pressure than to mean pressure
- Distensibility of pial arterioles is higher in SHRSP than in WKY
- Reduction of pial arteriolar pressure
  - prevents cerebral vascular hypertrophy
  - attenuates increases in passive distensibility of cerebral arterioles in SHRSP
- ACEi but not direct vasodilators prevent pulse pressure-induced remodeling of pial arterioles
- Endothelial dysfunction is related to increased central pulse pressure

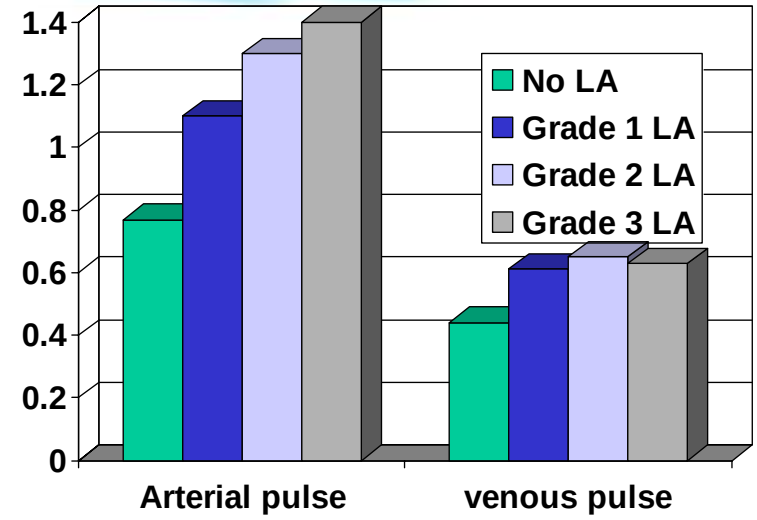
Baumbach, Circ Res 1991, Hypertension 1992, Stroke 1995

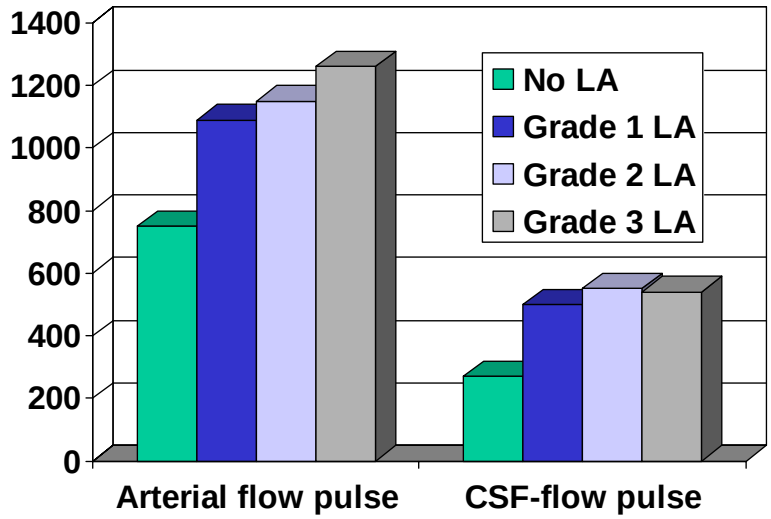
Pulse-wave encephalopathy :

Unifying link between neurodegenerative diseases and arterial stiffness

- Leucoaraiosis
  - ↑ arterial pulsatility
  - ↓ cerebrospinal compliance
  - fibrosis of periventricular veins







Bateman, Neuroradiology 2002
Feugeas Magnetic resonance imaging 2005

High blood pressure (SBP) is the major determinant of white matter lesions

- 10 european cohorts, 1805 non demented patients (65-75 years)

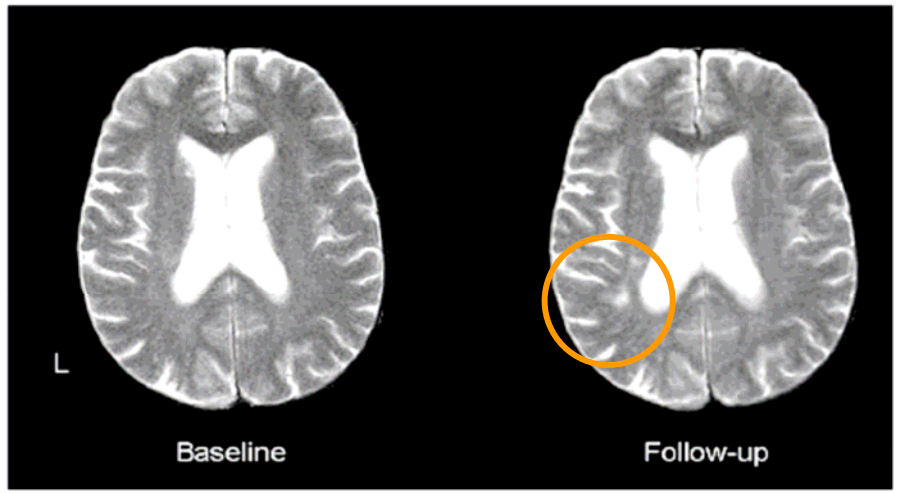
Severe White Matter Lesions	No Hypertension (n=814)	Hypertension All (n=811)	Hypertension Treatment Status: Untreated (n=267)	Treated Successfully (n=336)	Poorly Controlled (n=208)
Periventricular	1.0 (ref)	1.6 (1.3–2.2)	1.5 (1.0–2.2)	1.4 (1.0–2.0)	2.3 (1.6–3.4)
Subcortical	1.0 (ref)	1.4 (1.1–1.8)	1.1 (0.8–1.7)	1.3 (0.9–1.8)	2.0 (1.4–2.9)

Van Dijk, Hypertension 2004

Effect of BP lowering on cerebral white matter lesions in patients with stroke : a PROGRESS substudy

- WML dependent on SBP at baseline

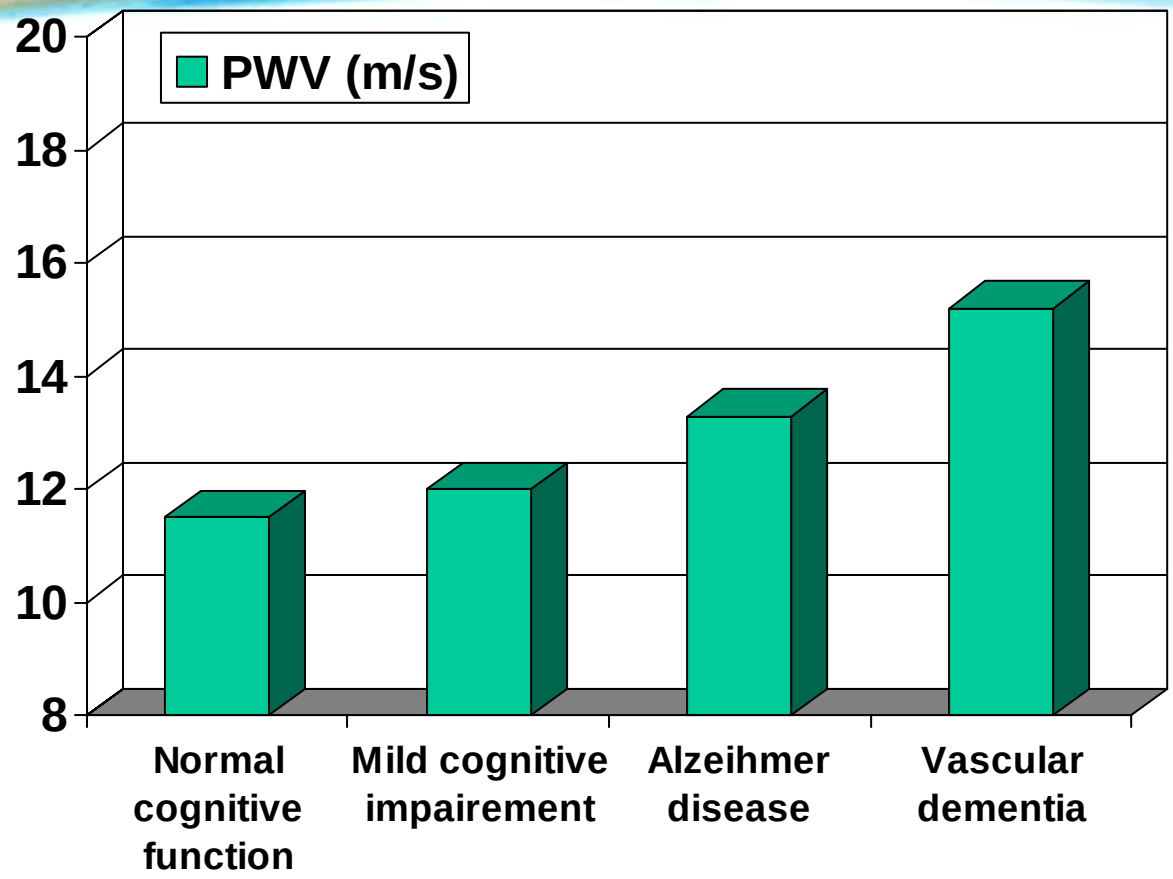
↘ 43% new high grade WMH



	Total (n=192)	Placebo (n=103)	Active (n=89)	*P* Value, Model 1*	*P* Value, Model 2†
Incident WMH, n (%)	24 (13)	16 (16)	8 (9)	0.17	0.10
Mean volume of incident WMH, mm^3 (SE)	1.8 (0.5)	2.0 (0.7)	0.4 (0.8)	0.012	0.009
Volume of incident WMH by initial grade of WMH, mm^3 (SE)					
No WMH	0.05 (0.8)	0	0.09 (0.8)	0.76	0.81
Mild to moderate WMH	1.2 (1.2)	1.3 (1.0)	0.9 (1.0)	0.58	0.71
Severe WMH	6.5 (2.0)	7.6 (1.0)	0	<0.0001	<0.0001

Dufouil C, Circulation 2005

Arterial stiffness and cognitive decline



N=308 elderly patients

Adjusted on
Age,
Sex
SBP
Education
CV disease
Treatments

PWV correlated with MMSE ($r=-0.27$, $p<0.0001$)

Hanon, Stroke 2005

Arterial stiffness and further cognitive decline

- Increased arterial stiffness is predictive of further cognitive decline during longitudinal follow-up

Hypertension 2007

Evidence for association between blood pressure and neurodegenerative diseases

(Alzheimer, vascular dementia, leucoaraiosis)

- Association with white matter lesions
  - Dufouil C, Neurology 2001
  - VanDijk, Hypertension 2004
- Cross-sectional studies : NDD➔ low blood pressure
- Longitudinal studies : BP at midlife ➔ strongest predictor of NDD

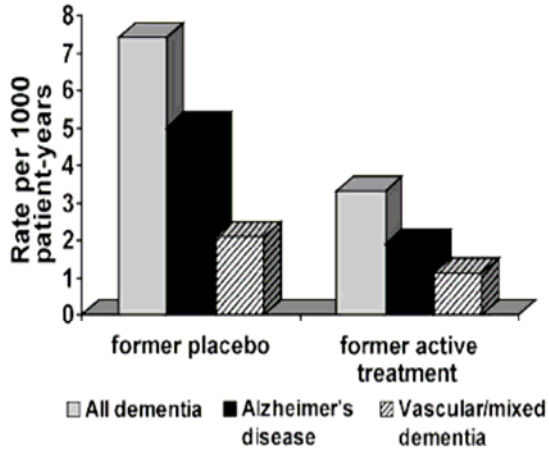
  •Qiu, Lancet Neurol 2005 (review)
- Treatment of hypertension
  - Prevents progression of white matter lesions

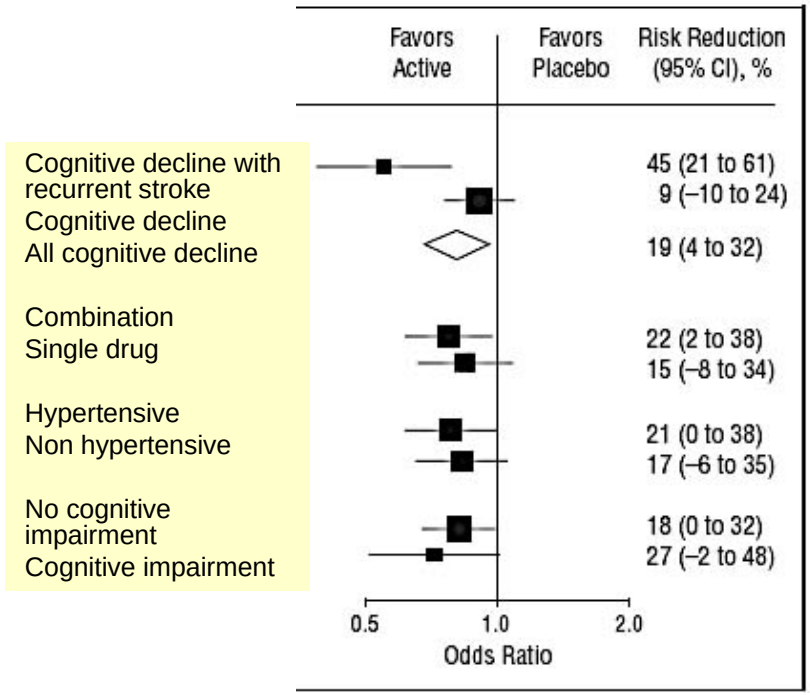
    •Dufouil C, PROGRESS trial, Circulation 2005
  - most potent prevention of dementia

    • Forette F, Syst-Eur, Lancet 1998, Arch Intern Med 2002
    • Tzourio et al, PROGRESS trial, arch intern med 2003

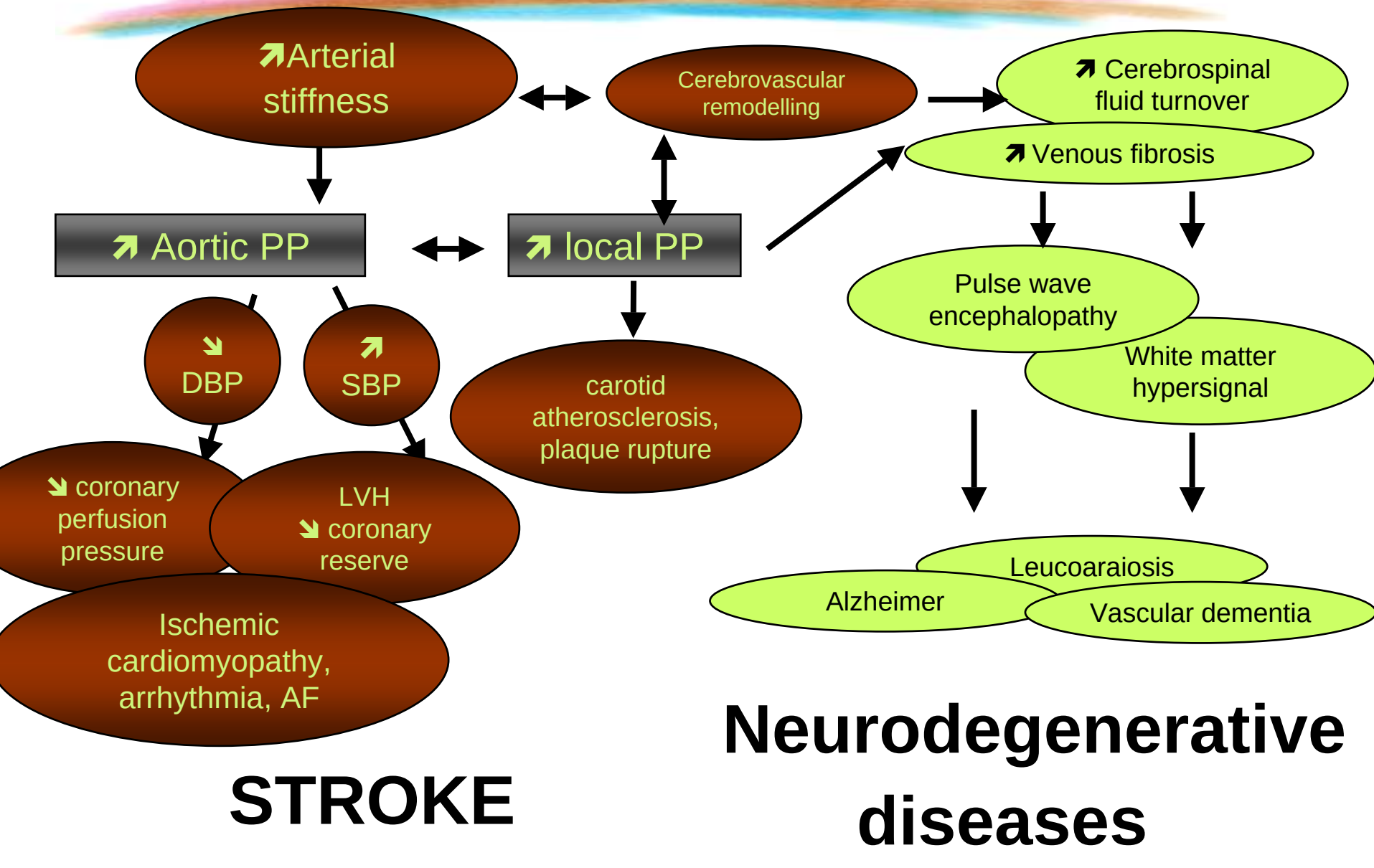
Effect of blood pressure reduction on further incidence of dementia

- SYST-EUR trial
  - ↘ risk of dementia by 55%, from 7.4 to 3.3 cases per 1000 patient-years (43 vs 21 cases, P<.001)
  - – Adjusted RR of dementia with nitrendipine was 0.38 95% CI [0.23-0.64]; P<.001)
- PROGRESS trial
  - ↘ risk of dementia by 34% in patients with recurrent stroke
  - ↘ cognitive decline by 19% in whole population and 45% in patients with recurrent strokes





Arterial stiffness, central pressure and cerebrovascular diseases



COVADIS study

- French prospective cohort study started in 1999 and
  - 3500 non-institutionalized persons aged 65 to 79 years, recruited from the electoral rolls of a French City (Dijon).

The primary aim of the COVADIS study is to evaluate **the risk of cognitive impairment and dementia** attributable to vascular factors.

  - Baseline (1999-2000) and 4 year follow up (2003-2004)
    - face-to-face interviews using standardized questionnaires on health-related data
    - blood pressure measurement
    - cognitive testing
    - assessment of vascular risk factors, measurement of biological parameters
    - magnetic resonance imaging (MRI) examinations.

The ancillary COVADIS-ARTERIAL STIFFNESS STUDY

- 2 000 subjects from the COVADIS cohort
  - During the 8-year follow-up (2007-2008)
    - arterial stiffness and central pressure measurements (carotid to femoral pulse wave velocity and pulse wave analysis, respectively; Sphygmocor ®).
  - Arterial measurements will be done only once (2007-2008) into the COVADIS-Arterial stiffness study
  - 2 MRI examinations will be available: the first has been performed in 2003-2004 and the second will be performed in 2010.
  - Objectives :
    - (1) Cross-sectional relationships between arterial stiffness, central pressure with white matter lesions and cognitive status
    - (2) Longitudinal relationships between arterial stiffness and changes in MRI data (new white matter lesions and significant progression of the WML total volume (≥30%) on follow up MRI) and cognitive function will be studied