

Control de la Hipertensión Arterial y función cognitiva

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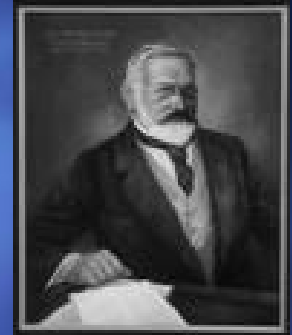
V Reunión Paciente Pluripatológico y Edad Avanzada



GERMANES HOSPITALÀRIES
del Sagrat Cor de Jesús
BENITO MENNI
Complex assistencial en Salut Mental



El inicio



- 1894 Biswanger
 - Describe patología cerebral:
 - Infartos pequeños subcorticales
 - Severa desmielinización de sustancia blanca y centros ovals
 - Infartos subcorticales

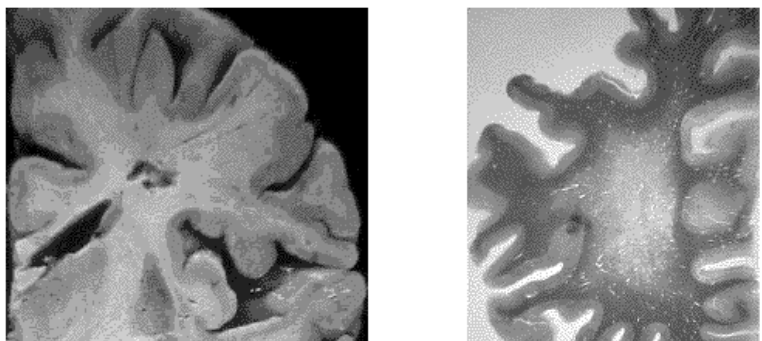
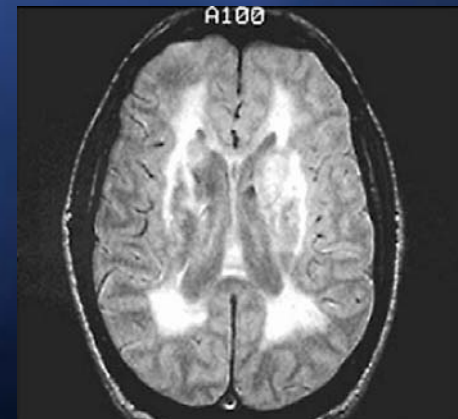


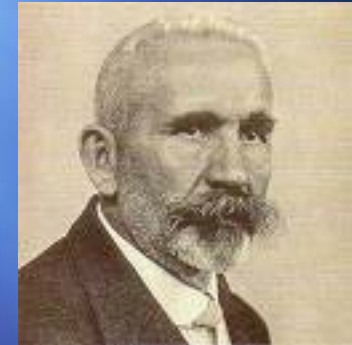
Figura 1. (A) Infarto lacunar en la sustancia blanca hemisférica, anatomía patológica macroscópica. (B) Leucoaraiosis, desmielinización en el centro semioval. (Cortesía de la Dra. T. Tuñón, Servicio de Anatomía patológica, Hospital de Navarra).



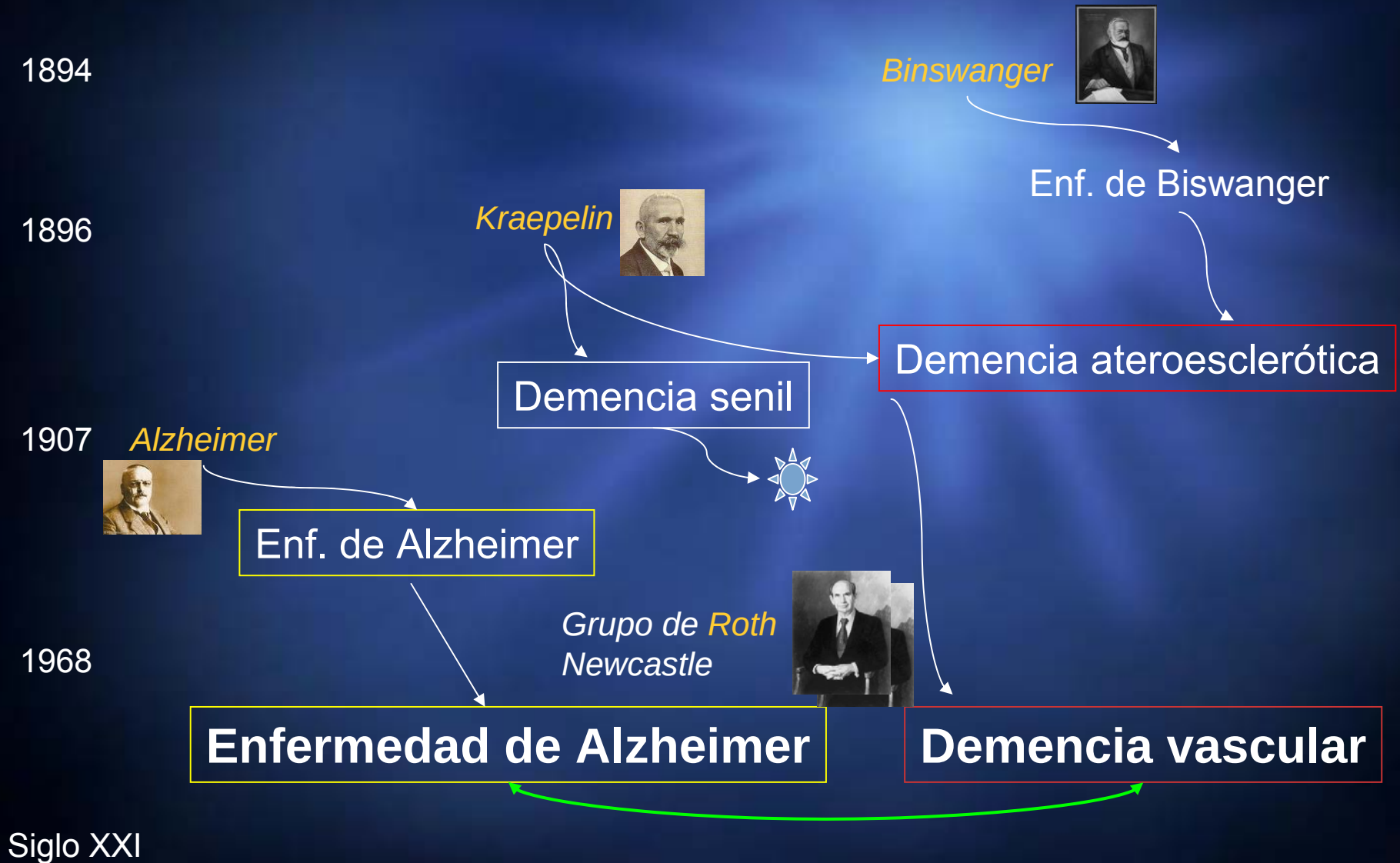
Witt D Journal für Neurologie, Neurochirurgie und Psychiatrie 2002; 3 (2): 59-62 ©

El inicio

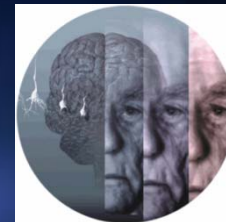
- 1896 **Kraepelin**
 - División de demencia:
 - Forma senil
 - Demencia aterosclerótica
- 1907 **Alois Alzheimer**
 - Descripción del 1 caso
 - Augusta E. (51 años)
 - Kraepelin la diferenció de la demencia senil



Evolución histórica



Factores de riesgo vascular y Enfermedad de Alzheimer



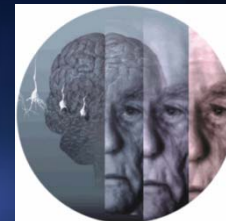
Luchsinger, J. A., Reitz, C., Honig, L. S., Tang, M. X., Shea, Steven, Mayeux, R. **Aggregation of vascular risk factors and risk of incident Alzheimer disease.** Neurology 2005 65: 545-551

- 1138 individuos sin demencia (edad media 76,2) durante 5,5 años.
- Diabetes*
- Hipertensión
- Tabaco*
- Enfermedad cardiaca

**Mayor riesgo de Enf. Alzheimer
(probable o posible)**

3 ó más factores de riesgo: OR 3,4 (1,8-6,3)

Factores riesgo vascular y enfermedad de Alzheimer



Kivipelto M et al. *Mildlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study*. BMJ 2001;322;1447-1451

- 1449 participantes de estudios poblacionales tras un estudio de 21 años. Edad entre 65-79 años. (Estudio FINMONICA)
- Se relacionaron los factores de riesgo en la edad media de la vida con la aparición de enf. Alzheimer
- HTA sistólica (≥ 160 mmHg) OR 2,3 (1.0-5.5)
- Hipercolesterolemia ($\geq 6,5$ mmol/l) OR 2,1 (1.0-4.4)
- AMBOS factores de riesgo: OR 3.5 (1.6-7.9)
- La TA diastólica no tenía un efecto significativo

Nun study

- Estudio longitudinal 678 monjas católicas miembros de la Congregación de las School Sisters of Notre Damn
- Entre 75 y 102 años al inicio del estudio
- FUENTES de DATOS
 - Archivos del convento
 - Exámenes anuales de salud y cognitivos anuales
 - Donación del cerebro

Snowdon



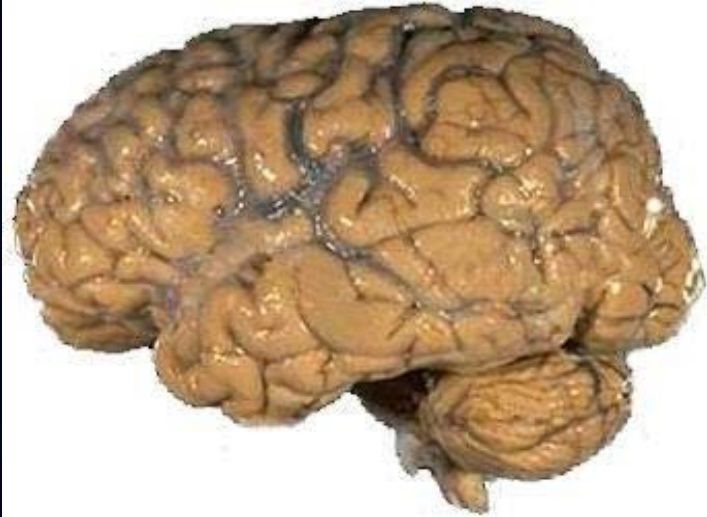


*“Now, regarding my long living,
It seems to be a special reward
From God”*

“En lo que respecta a mi
larga vida, parece ser una especial
recompensa de Dios”

Parte del Obituario escrito por ella misma
en 1996 (102 años de edad)

Hermana Matthia (1894-1998)
a los 104 años de edad



1180 gramos

No anomalías macroscópicas

Mínimo infarto en caudado derecho (0,2 por 0,1 mm)

Leve aterosclerosis en circulo de Willis (<25%)

Según la clasificación de *Braak and Braak*: 4 (de 1 a 5)

Nun study

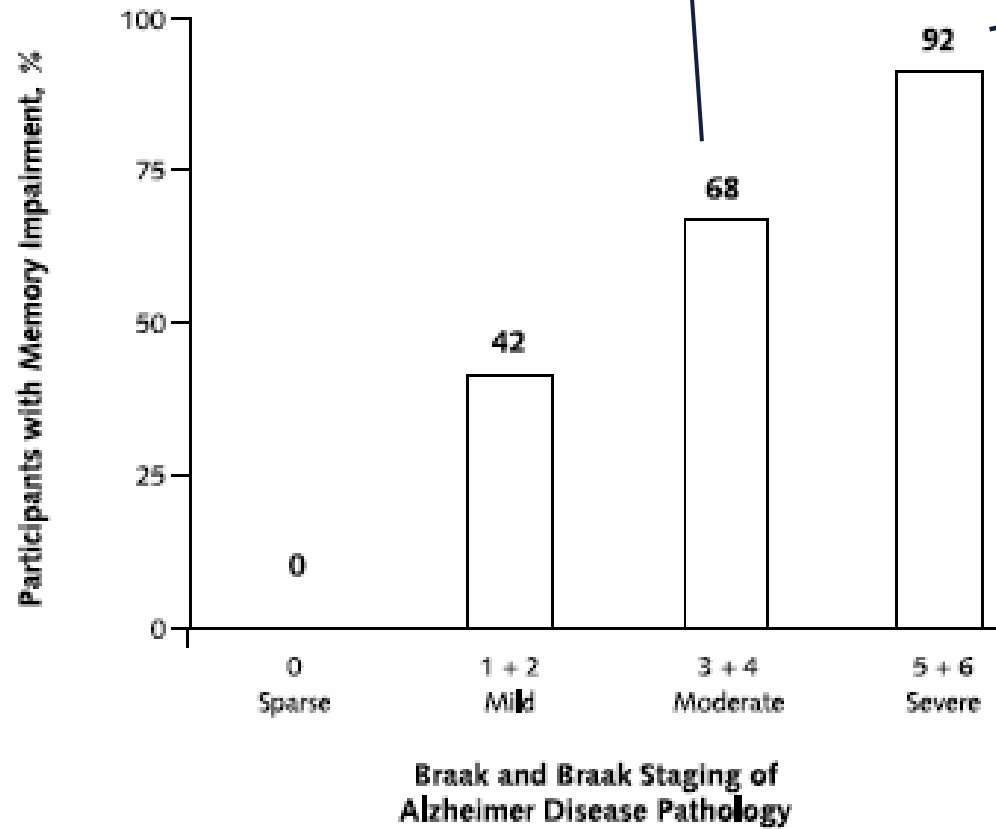
“The Nun study allows me to keep teaching, even after I die”



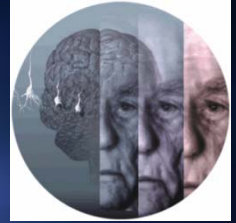
- Concepto de “Reserva cognitiva”
 - Igual número, tipo y localización de lesiones
 - Muy diferente expresión clínica
 - Un porcentaje muy importante de estadíos leves (1 y 2) y moderados (3 y 4) no mostraban alteración mnésica
- Puede deberse a diversos mecanismos
 - Cantidad de tejido cerebral y sinapsis
 - Entrenamiento cognitivo
 - Daño cerebral por traumatismos e isquemia
 - Déficits nutricionales

32% sin clínica
amnésica !!

8 % sin clínica
amnésica!!!



Influencia de lesiones vasculares en Enfermedad de Alzheimer



Riekse G et al. ***Effect of Vascular Lesions on Cognition in Alzheimer's Disease: A Community-Based Study***. J Am Geriatr Soc. 2004 September ; 52(9): 1442–1448.

- 124 sujetos con valoraciones clínicas y neuropatológicas
 - 85 con lesiones de enf. Alzheimer
 - 38 con lesiones de enf. Alzheimer + lesiones vasculares (se excluyeron 20 por sufrir otras lesiones) =18
 - 47 solo lesiones enf. Alzheimer (se excluyeron 17)=30
 - No había diferencias en edad, sexo o educación
 - El MMSE era igual en ambos grupos
 - En cambio, el grupo alzheimer solo tenía lesiones mas graves que el grupo alzheimer + vascular
- Por lo tanto, ***LA PRESENCIA de LESIONES VASCULARES CONTRIBUYE a la GRAVEDAD del DETERIORO COGNITIVO en los pacientes con ENFERMEDAD de ALZHEIMER***

Table 1 Hypertension and cognitive decline. Cross-sectional studies.

References	n	Age (years)	Correlation
Wallace 1985 ⁹	2,433	>65	Positive correlation
Kuusisto 1993 ⁶	744	73	Positive correlation
Starr 1993 ⁷	598	70	Positive correlation
Gale 1996 ¹¹	973	>65	Positive correlation
Cacciatore 1997 ¹⁰	1,339	74	Positive correlation
Kilander 1997 ⁵	999	70	Positive correlation
Seux 1998 ⁸	2,252	70	Positive correlation
Farmer 1987 ¹²	2,032	55–89	No correlation
Desmond 1993 ¹⁴	249	71	No correlation
Scherr 1991 ¹³	3,809	>65	No correlation
Van Boxtel 1997 ¹⁵	936	24–81	No correlation
Guo 1996 ¹⁶	1,642	75–101	Negative correlation

	Study settings	Participants	Outcomes	Covariates*	Main results
Studies reporting no association with blood pressure					
Farmer et al, ⁸ 1987	Framingham Study, USA	2123 people (59% women) age 55–89 years	Performance on neuropsychological tests	Alcohol use, smoking, use of antihypertensive drugs	BP (continuous variable) was not related to performance on the tests
Scherr et al, ⁹ 1991	East Boston Study, USA	3627 people (62% women) age ≥65 years	Performance on neuropsychological test battery	Use of antihypertensive drugs	BP (continuous variable) was not a substantial contributor to cognitive status in elderly people
van Boxtel et al, ¹⁰ 1997	Maastricht Aging Study, Netherlands	936 healthy adults (49% women) age 24–81 years	Performance on neuropsychological test battery	Alcohol consumption, smoking, BMI	BP ≥140/90 mm Hg was not related to performance on memory, word fluency, or cognitive flexibility tests
Di Carlo et al, ¹¹ 2000	Longitudinal Study on Aging, Italy	3425 people (52% women) age 65–84 years	CIND; MMSE score <24 plus clinical evaluation	..	Hypertension (history, drug use, and BP ≥140/90 mm Hg) was unrelated to CIND
Studies reporting an association with high blood pressure					
Starr et al, ¹² 1993	Community survey in Edinburgh, UK	598 healthy people (60% women) age ≥70 years	Performance on MMSE	Predicted intelligence quotient	High BP (>181/95 mm Hg) was related to a lower MMSE score
Cacciatore et al, ¹³ 1997	Cross-sectional survey in Campania, Italy	1339 people (56% women) age 69–95 years	Cognitive impairment defined as MMSE score <24	Antihypertensive therapy, geriatric depression scale score	Each 10 mm Hg increase in DBP was related to OR 1.29 (95% CI 1.19–1.37) for cognitive impairment
Cerhan et al, ¹⁴ 1998	Atherosclerosis Risk in Communities, USA	13840 people (56% women, 25% African Americans) age 45–69 years	Performance on digit symbol subtest and word fluency	Ethnic origin, occupation, research centres	Hypertension (≥160/95 mm Hg) was related to lower scores on cognitive tests
Kilander et al, ¹⁵ 1998	A male cohort in Uppsala, Sweden	999 Swedish men age 69–75 years; BP was measured at age 70 years	Low cognitive function defined as MMSE score in the lowest quintile	Occupational levels, BMI, antihypertensive therapy, cholesterol, blood glucose	Each 1 SD increase in DBP was related to OR 1.45 (95% CI 1.20–1.75) for low cognitive function
Harrington et al, ¹⁶ 2000	Community primary care practices in Tyneside, UK	107 untreated hypertensive people, 116 controls (47% women) age 70–89 years	Performance on computerised cognitive test battery (8 tests)	MMSE score, free of stroke	Hypertensive group (BP 160–179/90–99 mm Hg) performed worse in three of eight tests and had slower speed in all tests
André-Petersson et al, ¹⁷ 2001	Men born in 1914 Study, Sweden	500 men age 68 years	Performance on neuropsychological test battery (5 tests)	Stroke, depression, use of antihypertensive drugs, ankle-brachial index	BP ≥180/110 mm Hg was related to poorer performance; BP of 140–159/90–99 mm Hg was related to better performance
Stewart et al, ¹⁸ 2001	Community primary care practices in London, UK	278 British African Caribbean people (57% women) age 55–75 years	Lower composite score derived from 11 neuropsychological tests	..	Clinically diagnosed hypertension was related to cognitive impairment, especially in less-educated people
Budge et al, ¹⁹ 2002	Oxford Project to Investigate Memory and Aging, UK	158 community dwelling volunteers (49% women) age 60–91 years	Performance on CAMCOG and MMSE	Plasma homocysteine, some interaction terms	High SBP (continuous variable) was related to lower scores on both tests
Kuo et al, ²⁰ 2004	Harvard Program on Aging, USA	70 very healthy people (44% women) age ≥65 years	Performance on neuropsychological tests	Ethnic origin, alcohol use, drug use, BMI, total cholesterol	SBP >145 mm Hg was related to impairment in executive function
Studies reporting an association with low blood pressure					
Launer et al, ²¹ 1995	Honolulu-Asia Aging Study, USA	3735 Japanese-American men, mean age 78 years	Poor cognitive function defined as CASI <82	..	SBP ≥160 mm Hg vs <110 mm Hg: OR 0.45 (95% CI 0.25–0.88); SBP 140–159 mm Hg vs <110 mm Hg: OR 0.45 (95% CI 0.25–0.88)
Guo et al, ²² 1997	Kungsholmen Project, Sweden	1736 people (76% women) age ≥75 years	Performance on MMSE	Stroke, heart disease, use of antihypertensive drugs	Each 10 mm Hg increase in BP was related to 0.41 unit increase in score
Pandav et al, ²³ 2003	Indo-US Cross National Epidemiological Study	4810 Indian people (47% women) age ≥55 years (12% ≥75 years); 636 US people (67% women) age ≥75 years	Cognitive impairment defined as MMSE <22 for Indian sample, or <24 for US sample	Stroke	Each 10 mm Hg increase in SBP or DBP was related to >10% reduction in cognitive impairment
Kähönen-Väre et al, ²⁴ 2004	Helsinki Aging Study, Finland	650 people (73% women) from three cohorts age 75, 80, and 85 years	Cognitive impairment defined as MMSE <24	..	Hypertension history was unrelated to cognitive impairment, but people with MMSE <24 had low BP
Studies reporting a U-shaped relation with blood pressure					
Morris et al, ²⁵ 2002	Chicago Health and Aging Project, USA	5816 people (61% women, 62% black) age ≥65 years	Performance on neuropsychological test battery	Ethnic origin	BP (continuous variable) had modest U-shaped relation with poorer performances
Waldstein et al, ²⁶ 2005	Baltimore Study of Aging, USA	847 people (44% women) age 60–96 years	Performance on neuropsychological test battery	Smoking, alcohol use, depressive score, use of antihypertensive drugs	Both high and low BP were related to poorer performance on the tests in less-educated people

*Demographic variables (ie, age, sex, education) were included as covariates in all studies. BP=blood pressure; BMI=body mass index; CIND=cognitive impairment, no dementia; MMSE=mini mental state examination; DBP=diastolic blood pressure; OR=odds ratio; CAMCOG=Cambridge examination for mental disorders of the elderly-cognitive section; SBP=systolic blood pressure; CASI=cognitive abilities screening instrument.

Table 1: Cross-sectional studies of late-life blood pressure in relation to cognition

	Study settings	Participants	Outcomes	Covariates*	Main results
Studies reporting no association with blood pressure					
Ueda et al, ³² 1992	Hisayama Study, Japan	887 people (60% women) age ≥65 years	Dementia, AD, VaD; DSM-III	Alcohol use, smoking, BMI, cholesterol, glucose, ECG	Hypertension (≥160/95 mm Hg) was related to VaD, but not to AD
Kuusisto et al, ³³ 1997	Kuopio Study, Finland	980 people (64% women) age 69–78 years	AD; NINCDS-ADRDA	APOE ε4, total cholesterol, fasting glucose, insulin	BP (continuous variable) was not significantly related to AD
Studies reporting an association with low blood pressure					
Guo et al, ³⁴ 1996	Kungsholmen Project, Sweden	1642 people (76% women) age ≥75 years	Dementia, AD; DSM-III-R	..	Low BP (≤140/75 mm Hg) was related to high prevalence of dementia and AD
Morris et al, ³⁵ 2000	Chicago Health and Aging Project, USA	709 people (61% women, 54% black) age ≥65 years	AD; NINCDS-ADRDA	Ethnic origin, use of antihypertensive drugs, BMI, vascular disorders	Low BP (<130/70 mm Hg) was related to high prevalence of AD
Petitti et al, ³⁶ 2002	Women's Memory Study, USA	3924 women age ≥75 years	Dementia; medical records	..	Self-reported hypertension was linked to low dementia prevalence
Kokmen et al, ³⁷ 1991	Rochester Epidemiology Project, USA	415 patients and 415 matched controls	AD; post-mortem and medical records	Residence	Documented hypertension: OR for AD 0.70 (95% CI 0.50–0.95)
Rockwood et al, ³⁸ 1996	Canadian Study of Health and Aging, Canada	204 patients and 511 controls (64% women) age ≥65 years	AD; NINCDS-ADRDA	Residence	Clinically diagnosed hypertension: OR for AD 0.38 (95% CI 0.25–0.58)

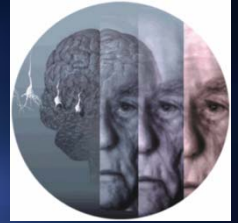
*Demographic variables (ie, age, sex, education) were included as covariates in all studies. BMI=body mass index; DSM-III (R)=Diagnostic and Statistical Manual of Mental Disorders, 3rd edn (revised); ECG=electrocardiogram; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; APOE=apolipoprotein E genotype; BP=blood pressure; OR=odds ratio.

Table 2: Cross-sectional studies of late-life blood pressure in relation to dementia

Estudios Transversales

- Hipertensión en edad avanzada
 - Hipertensión GRAVE, si no se trata empeora la cognición
 - La TA baja puede empeorar la demencia
 - TA baja “factor de riesgo” para demencia?
 - La mayoría de las personas con demencia tienen baja TA

Estudios longitudinales



En estudio de **Framingham**

- 1702 pacientes entre 55-82 años
- Incluidos entre 1956-1964
- Valoración neuropsicológica 1976-1978
- Controlando variables de confusión
- *El nivel y la cronicidad de la hipertensión empeoraban atención y memoria*
- Se comprobó en el total, en los que estuvieron sin tto durante la toma de TA y los que estaban sin tto todo el período

Elias et al. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. American Journal of Epidemiology (1993) vol. 138 (6) pp. 353-64E

Honolulu Heart Program



- 4638 supervivientes de la valoración inicial (1965-1968). Edad media 78 años.
- Cuarta evaluación (1991-1993)
- Controlando factores de confusión (edad, educación, ictus, enfermedad coronaria,
- *Relación inversa entre TA sistólica (pero no diastólica) en la mediana edad y función cognitiva en la vejez*

Launer et al. *The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study.* JAMA (1995) vol. 274 (23) pp. 1846-51

Launer et al. *Midlife blood pressure and dementia: the Honolulu-Asia aging study.* Neurobiol Aging (2000) vol. 21 (1) pp. 49-55

	Study settings	Participants and follow-up	Outcomes	Covariates*	Main results
Studies reporting no association with blood pressure					
Hebert et al, ⁴¹ 2004	Chicago Health and Aging Project, USA	4284 people (62% women, 62% African American) age ≥ 65 years, follow-up 6 years	Changes in cognitive function; assessed with four cognitive tests	Ethnic origin	BP was not significantly related to cognitive changes
Tervo et al, ⁴² 2004	Population study in Kuopio, Finland	806 people (61% women) age 60–76 years, follow-up 3 years	MCI; defined as cognitive tests $<(\text{mean} - 1.5 \text{ SD})$	APOE	High BP ($\geq 160/95$ mm Hg) was unrelated to MCI; for medicated hypertension: OR 1.9 (95% CI 1.1–3.3)
Solfrizzi et al, ⁴³ 2004	Longitudinal Study on Aging, Italy	1445 people (49% women) age 65–84 years, follow-up 3.5 years	MCI defined as adjusted MMSE $<(\text{mean} - 1.5 \text{ SD})$	Smoking, heart disease, total cholesterol	Hypertension (ie, having a history, medically treated, or BP $\geq 140/90$ mm Hg): OR 1.2 (95% CI 0.8–1.9)
Studies reporting an association with high blood pressure					
Waldstein et al, ⁴⁴ 2005	Baltimore Longitudinal Study of Aging, USA	847 people (44% women) age 60–96 years, followed up to 11 years	Performance on neuropsychological tests	Smoking, alcohol use, depressive score, use of antihypertensive drugs	High SBP (continuous variable) was related to poorer cognitive performance, more cognitive decline
Tzourio et al, ⁴⁴ 1999	Epidemiology of Vascular Aging Study, France	1172 people (65% women) age 59–71 years, follow-up 4 years	Cognitive decline; MMSE dropped ≥ 4 points over 4 years	Income, depression, alcohol intake, baseline MMSE, APOE	High BP ($\geq 160/95$ mm Hg): OR 2.8 (95% CI 1.6–5.0); for non-treated people, high BP: OR 4.3 (95% CI 2.1–8.8)
Haan et al, ⁴⁵ 1999	Cardiovascular Health Study, USA	5888 Medicare recipients (69% women) age ≥ 65 years, followed up to 7 years	Performance on modified MMSE, digit symbol subtest	Ethnic origin, stroke	Each 1 SD increase (22 mm Hg) in SBP was related to 0.96 points decline in MMSE score over 7 years
Knopman et al, ⁴⁶ 2001	Atherosclerosis Risk in Communities, USA	10 963 people (56% women) age 47–70 years, follow-up 6 years	Performance on digit symbol subtest of WAIS	Ethnic origin, use of CNS drugs	Hypertension (BP $\geq 140/90$ mm Hg or use of antihypertensive drugs) was related to a greater decline on the score
Reinprecht et al, ⁴⁷ 2003	Men born in 1914 Study, Sweden	186 men, assessments were made at age 68 and 81 years	Changes in cognitive function; psychological test battery	Marital status, smoking, alcohol, physical activities, arteriosclerotic measure	DBP (as tertiles) at age 68 years was inversely related to verbal, spatial, and speed performance at 81 years
Piguet et al, ⁴⁸ 2003	Sydney Older Persons Study, Australia	377 people (47% women) age ≥ 75 years, follow-up 6 years	Changes in cognitive function; MMSE score	..	Individuals with clinically diagnosed hypertension had a greater decline in MMSE score over 6 years
Elias et al, ⁴⁹ 2003	Framingham Heart Study, USA	1423 people (61% women) age 55–88 years, follow-up 4–6 years	Neuropsychological test battery	Occupation, smoking, alcohol use, diabetes, total cholesterol	Hypertension (BP $\geq 140/90$ mm Hg) was related to a lower total test score in men, not in women
Studies reporting a U-shaped relation with blood pressure					
Guo et al, ²² 1997	Kungsholmen Project, Sweden	1736 people (76% women) age ≥ 75 years, follow-up 3 years	Cognitive impairment defined as MMSE < 24	Heart disease, stroke	SBP < 130 mm Hg vs 130–159 mm Hg: OR 1.9 (95% CI 1.0–3.5) in non-users of antihypertensive drugs; SBP ≥ 180 mm Hg vs 130–159 mm Hg: OR 1.6 (95% CI 0.9–3.0) in users
Glynn et al, ²⁰ 1999	East Boston cohort study, USA	3657 people (56% women) age ≥ 65 years, follow-up 9 years	Performance on a mental status questionnaire	Follow-up time	SBP < 130 mm Hg or ≥ 160 mm Hg was related to a higher rate of errors on the mental status questionnaire test
Bohannon et al, ²¹ 2002	Duke Population Studies of the Elderly, USA	3202 people (67% women, 55% black) age ≥ 65 years, follow-up 3 years	Performance on a short portable mental status questionnaire	Ethnic origin, diabetes, stroke, heart disease, smoking, depressive score, drug use	U-shaped relation between SBP and cognitive decline in white people; no association in African Americans

*Demographic variables (ie, age, sex, education) were included as covariates in all studies. BP=blood pressure; APOE=apolipoprotein E genotype; MCI=mild cognitive impairment; OR=odds ratio; WAIS=Wechsler adult intelligence scale.

Table 4: Longitudinal studies of late-life blood pressure in relation to cognition

Study settings		Participants and follow-up	Outcomes	Covariates*	Main results
Studies on cognition					
Kilander et al, ⁴⁵ 1998	A male cohort in Uppsala, Sweden	999 Swedish men age 69–75 years; BP was measured at age 50 years	Performance on MMSE	Stroke, occupational levels	DBP (categorised as quintiles) at age 50 years was inversely related to global cognitive function at age 70 years
Launer et al, ²¹ 1995	Honolulu-Asia Aging Study, USA	3735 Japanese-American men, mean age 78 years; BP was measured 25 years ago	Poor cognitive function defined as CASI <82	Stroke, heart disease, and ankle-brachial index	SBP ≥160 mm Hg vs <110 mm Hg; OR 2.11 (95% CI 1.22–3.66)
Elias et al, ⁴⁶ 1993	Framingham Study, USA	1702 people (60% women) age 55–88 years; BP was measured 20 years ago	A composite score of neuropsychological tests	Stroke, smoking, alcohol drinking, and occupation	High BP (continuous variable) and chronicity of hypertension was related to lower cognitive functioning
Swan et al, ⁴⁴ 1998	A cohort of male twins, USA	392 men age 68–79 years; BP was measured at age 43–53 years	Performance on MMSE and other neuropsychological tests	Stroke	High SBP (≥140 mm Hg) was related to a greater decline in cognitive function over 10 years
Swan et al, ⁴⁷ 1998	Western Collaborative Group Study, USA	717 white men, mean age 75 years; BP was measured at mean age 45 years	Performance on six neuropsychological tests	Stroke, depression, use of antihypertensive drugs	Persistent high SBP (≥140 mm Hg) was related to reduced verbal learning and memory function
Kilander et al, ⁴⁸ 2000	A male cohort in Uppsala, Sweden	502 Swedish men age 69–74 years; BP was measured at age 50 years	Performance on 13 neuropsychological tests	Stroke, occupational levels	Low DBP (≤70 mm Hg) was related to better performance on tests assessing the subcortical-frontal cognitive functions
Elias et al, ⁴⁶ 2004	Maine-Syracuse Longitudinal Study, USA	529 people (52% women) age 18–83 years; BP was measured up to 20 years ago	Performance on WAIS	Smoking, alcohol intake, occupation, psychotropic drugs, BMI, depression	BP (continuous variable) was inversely related to visualisation/fluid composite score
Kivipelto et al, ⁵⁰ 2001	Kuopio and Joensuu Study, Finland	1449 people (62% women) age ≥65 years, follow-up 21 years	MCI defined with Mayo Clinic Criteria	BMI	SBP ≥160 mm Hg vs <140 mm Hg; OR 1.2 (95% CI 0.7–2.2); no association with DBP
Studies on dementia					
Launer et al, ⁵¹ 2000	Honolulu-Asia Aging Study, USA	3703 Japanese-American men age 65 years; BP was measured at age 45–68 years	Dementia, DSM-III-R; AD, NINCDS-ADRDA	Stroke, heart disease, smoking, alcohol use, ankle-brachial index, APOE	Midlife high BP (≥160/95 mm Hg) increased risk of dementia in later life in men not treated with antihypertensive drugs
Kivipelto et al, ⁵² 2001	Kuopio and Joensuu Study, Finland	1449 people (62% women) age ≥65 years, follow-up 21 years	AD, DSM-IV and NINCDS-ADRDA	BMI, stroke, myocardial infarct, smoking, alcohol use	SBP ≥160 mm Hg vs <140 mm Hg; OR 2.8 (95% CI 1.1–7.2); DBP ≥95 mm Hg vs <90 mm Hg; OR 1.7 (95% CI 0.8–3.6)
Wu et al, ⁵³ 2003	Linxian County, China	602 people (60% women) age ≥65 years; BP was measured over 15 years ago	AD; DSM-IV	Smoking, alcohol intake, diet habits, anaemia	Hypertension (≥160/95 mm Hg) in midlife was related to a higher risk of prevalent AD in later life; OR 2.0 (95% CI 1.1–3.5)
Yamada et al, ⁵⁴ 2003	Adult Health Study in Hiroshima, Japan	1774 people (73% women) aged ≥60 years; BP was recorded over 25 years ago	AD, VaD; DSM-IV	Milk, salt, or soy sauce intake	High SBP was related to VaD (OR per 10 mm Hg 1.33; 95% CI 1.14–1.56), but not to AD
Whitmer et al, ⁵⁵ 2005	Kaiser Permanente Medicare Program of Northern California, USA	8845 people (54% women) mean age 69 years; midlife hypertension was defined at mean age of 42 years	Dementia; ICD-9-CM codes 2900.0, 2900.1, 29040.1, 3310.0, and 7809.3	Ethnic origin (73% white, 16% black, and 11% others)	Hypertension (self-reported, use of drugs, or measured BP ≥140/90 mm Hg) was related to a HR of 1.24 (95% CI 1.04–1.48) for dementia

*Demographic variables (ie, age, sex, education) were included as covariates in all studies. BP=blood pressure; CASI=cognitive abilities screening instrument; OR=odds ratio; WAIS=Wechsler adult intelligence scale; BMI=body mass index; MCI=mild cognitive impairment; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3rd edn (revised); NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; APOE=apolipoprotein E genotype; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edn; HR=hazard ratio; ICD-9-CM=International Classification of Diseases, 9th revision, clinical modification.

Table 3: Longitudinal studies of midlife blood pressure in relation to late-life cognition and dementia

	Study settings	Participants and follow-up	Outcomes	Covariates*	Main results
Studies reporting no association with blood pressure					
Yoshitake et al, ⁷³ 1995	Hisayama Study, Japan	828 non-demented people (60% women) age 65–98 years, follow-up 7 years	AD, NINCDS-ADRD; VaD, NINDS-AIREN	Alcohol use, physical activity, diabetes, stroke, baseline cognition	BP $\geq$ 160/95 mm Hg was not related to AD, but to VaD (OR per 1 SD increase in SBP 1.6; 95% CI 1.2–2.2)
Brayne et al, ⁷⁴ 1998	Cambridge Cohort Study, UK	376 people (64% women) age $\geq$ 75 years, follow-up 2–4 years	Dementia, AD; similar to ICD-10	..	History of hypertension was not related to dementia: OR 1.1 (95% CI 0.4–2.6)
Tyas et al, ⁷⁵ 2001	Population study in Manitoba, Canada	694 people (62% women) age $\geq$ 65 years, follow-up 5 years	AD; NINCDS-ADRD	..	Self-reported high BP was not related to AD: OR 1.14 (95% CI 0.53–2.45)
Posner et al, ⁷⁶ 2002	Washington Heights–Inwood Columbia Aging Project, USA	1259 Medicare recipients (69% women) age $\geq$ 65 years, follow-up 7 years	AD, NINCDS-ADRD; VaD, NINDS-AIREN	Ethnic origin, heart disease	Hypertension history was related to a higher risk of VaD, but not to AD and cognitive changes
Lindsay et al, ⁷⁷ 2002	Canadian Study of Health and Aging	3566 people (58% women) age $\geq$ 65 years, follow-up 5 years	AD; DSM-IV	..	Self-reported high BP was not related to AD: OR 0.88 (95% CI 0.62–1.27)
Kuller et al, ⁷⁸ 2003	Cardiovascular Health Study, USA	3275 Medicare recipients in four clinical centres, age $\geq$ 65 years, follow-up 7 years	Dementia, AD; diagnosed by an expert committee	Ethnic origin	History of hypertension was not significantly associated with dementia: RR 1.1 (95% CI 0.9–1.4)
Borenstein et al, ⁷⁹ 2005	Kame Project, USA	1859 Japanese Americans (56% women) age $\geq$ 65 years, mean follow-up 6 years	AD, NINCDS-ADRD	APOE	Self-reported hypertension was not related to AD
Petitti et al, ⁸⁰ 2005	Women's Memory Study, USA	1133 women from prepaid health plan, age $\geq$ 75 years, follow-up 9 years	Dementia; diagnosed by telephone interview and medical record review	..	SBP and DBP measured 9 or 5 years before dementia diagnosis were not significantly different between demented and unimpaired groups
Studies reporting an association with high blood pressure					
Skoog et al, ⁸¹ 1996	Göteborg H-70 Study, Sweden	382 people (58% women) age 70 years, followed up to 15 years	Dementia, DSM-III-R; AD, NINCDS-ADRD	BMI	SBP and DBP levels at baseline were higher in individuals who developed dementia than those who did not
Studies reporting an association with low blood pressure					
Ruitenberg et al, ⁸² 2001	Göteborg H-70 and Rotterdam studies	6985 people (60% women) age $\geq$ 55 years, follow-up 3 years	Dementia, VaD, AD; DSM-III-R	Study population	BP (continuous variable) was inversely related to dementia risk in users of antihypertensive drugs
Morris et al, ⁸³ 2001	East Boston Study, USA	378 people (63% women) age $\geq$ 65 years, follow-up 13 years	AD; NINCDS-ADRD	Follow-up interval, stratified sampling	SBP $\geq$ 160 mm Hg vs 130–139 mm Hg: OR 0.3 (95% CI 0.1–0.9); DBP $<$ 70 mm Hg vs 80–89 mm Hg: OR 1.8 (95% CI 0.8–4.3)
Verghese et al, ⁸⁴ 2003	Bronx Aging Study, USA	488 community volunteers (women 64%) age $\geq$ 75 years, mean follow-up 6.7 years	Dementia, AD; diagnosed at consensus conferences	Medical problems (eg, diabetes, hypertension)	SBP 140–179 mm Hg vs 111–139 mm Hg: RR for dementia 0.6 (95% CI 0.3–4.1); DBP $<$ 70 mm Hg vs $\geq$ 90 mm Hg: RR for dementia 2.1 (95% CI 1.1–3.8)
Studies reporting an association with both high systolic and low diastolic pressure					
Qiu et al, ⁸⁵ 2003	Kungsholmen Project, Sweden	1270 people (75% women) age $\geq$ 75 years, follow-up 5 years	Dementia, AD; DSM-III-R	MMSE score, vascular disease, antihypertensive drug use	SBP $>$ 180 mm Hg vs 141–180 mm Hg: RR for dementia 1.4 (95% CI 0.9–2.4); DBP $<$ 70 mm Hg vs 70–89 mm Hg: RR of dementia 1.8 (95% CI 1.2–2.6)

*Demographic variables (ie, age, sex, education) were included as covariates in all studies. NINCDS-ADRD=National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; NINDS-AIREN=National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences; BP=blood pressure; OR=odds ratio; ICD-10=International Classification of Diseases, 10th revision; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edn; RR=risk ratio; APOE=apolipoprotein E genotype; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3rd edn (revised); BMI=body mass index.

Table 5: Longitudinal studies of late-life blood pressure in relation to dementia



Estudio de cohortes de Upsala Suecia

- 999 hombres seguidos desde los 50 años para estudiar los factores de riesgo vascular
- A los 70 años, entre otras medidas, registro amb de 24 h de TA y evaluación cognitiva
- *La elevación de la TA diastólica a los 50 años predecía el deterioro cognitivo, incluso tras excluir AVCs*

Kilander et al. *Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men.* *Hypertension* (1998) vol. 31 (3) pp. 780-6



Longitudinal Population Study of 70-year-olds

(Göteborg, Suecia)

- Estudia la relación de la TA a los 70 años y la incidencia de demencia a los 70-75, 75-79 y 79-85
- Seguimiento durante 15 años
- En medición basal, tanto demencia vascular como Alzheimer tenían mayores TA sistólica y diastólica
- En cambio en mediciones previas al inicio de la demencia TA menor
- Parece que hipertensión es factor de riesgo para AMBOS tipos de demencia
- No queda claro si la hipoTA previa a demencia es CAUSA o CONSECUENCIA

Skoog et al. 15-year longitudinal study of blood pressure and dementia. Lancet (1996) vol. 347 (9009) pp. 1141-5



Longitudinal – Curva en J

- Okumiya K, Matsubayashi K, Wada T *et al.* J-curve relation between blood pressure and decline in cognitive function in older people living in community, Japan. *J Am Geriatr Soc* 1997;45:1032-3.
- Glynn et al. Current and remote blood pressure and cognitive decline. *JAMA* (1999) vol. 281 (5) pp. 438-45

Estudios longitudinales

- La HTA en la mediana edad aumenta el riesgo de enf. De Alzheimer y demencia vascular
 - Se ha comprobado por autopsia (aumento de placas, de ovillos fibrilares y de atrofia del hipocampo)
- En edad avanzada la HTA solo parece ser factor de riesgo si es muy extrema
- LA TA baja es marcador de demencia en edad avanzada

	Study description	Outcomes	Medications	Covariates*	Main results
Lindsay et al, ⁷⁷ 2002	A Canadian national sample of 3238 people (58% women) age ≥65 years, follow-up 5 years	AD; DSM-IV	Antihypertensive agents	..	RR 0.91 (95% CI 0.64–1.30)
Morris et al, ⁴³ 2001	A random sample of 634 people (63% women) from East Boston age ≥65 years, follow-up 4 years	AD; NINCDS-ADRDA	Diuretics and β-blockers	..	No association
Qiu et al, ⁷⁶ 2003	1270 people (75% women) from dementia-free community age ≥75 years, median follow-up 5 years	Dementia, AD; DSM-III-R	Antihypertensive drugs	BP, MMSE score, vascular disorders	Dementia: RR 0.8 (0.6–1.0); similar for AD
in't Veld et al, ³⁷ 2001	A community cohort of 6416 non-demented people (59% women) in Rotterdam suburb age ≥55 years, mean follow-up 2.2 years	Dementia, DSM-III-R; AD, NINCDS-ADRDA; VaD, NINDS-AIREN	Antihypertensive drugs	BMI, MMSE, stroke, atherosclerosis, BP, diabetes, smoking	Decreased risk of dementia and VaD, but not AD
Yasar et al, ⁵⁸ 2005	1092 dementia-free community volunteers (37% women) age ≥60 years, followed up to 19 years	AD; NINCDS-ADRDA	DHP-CCB	BP, smoking, heart disease	RR 0.30 (95% CI 0.07–1.25)

*Demographic variables (ie, age, sex, education) were included as covariates in all studies. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edn; RR=risk ratio; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; BP=blood pressure; NINDS-AIREN=National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences; BMI=body mass index; DHP-CCB=dihydropyridine type calcium channel blockers; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3rd edn (revised).

Table 6: Population-based longitudinal studies of antihypertensive medication use in relation to dementia

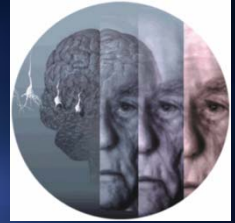
	Study description	Outcomes	Medications	Covariates*	Main results
SHEP Cooperative Research Group, ²²⁵ 1991	4736 patients (57% women, 14% black) from 16 clinical centres (USA) with SBP 160–219 mm Hg and DBP <90 mm Hg, age ≥60 years, mean follow-up 4.5 years	Dementia; diagnosed through expert evaluations	Chlorthalidone or plus atenolol or reserpine	Balanced BMI, BP, smoking, alcohol use, stroke, diabetes	Treatment 1.6% vs placebo 1.9%, no statistical difference
Forette et al (Syst-Eur I), ²²⁶ 1998	2418 patients (66% women) from 19 European countries, with SBP 160–219 mm Hg and DBP <95 mm Hg, age ≥60 years, median follow-up 2.0 years	Dementia, AD, mixed or VaD; DSM-III-R	Nitredipine or plus enalapril, hydrochlorothiazide	Balanced BMI, BP, MMSE score, atrial fibrillation	Reduced dementia risk by 50% (3.8 vs 7.7 per 1000 PY; p=0.05)
Forette et al (Syst-Eur II), ²²⁵ 2002	Extension of Syst-Eur I: 2902 treated patients and placebo controls received antihypertensive therapy after end of Syst-Eur I, median follow-up 3.9 years	Dementia, AD, mixed or VaD; DSM-III-R	Nitredipine or plus enalapril, hydrochlorothiazide	Entry DBP	Reduced dementia risk by 55% (3.3 vs 7.4 per 1000 PY; p<0.001); for AD, 1.9 vs 5.0 per 1000 PY
Tzourio et al, ²²⁶ 2003	6105 people (30% women) from 19 countries, with previous stroke or transient ischaemic attack in 5 years, mean age 64 years, mean follow-up 3.9 years	Dementia or dementia with recurrent stroke; DSM-IV	Perindopril or plus indapamide	Balanced BMI, APOE, alcohol, smoking, MMSE	RR 0.88 (95% CI 0.72–1.08), OR 0.66 (95% CI 0.45–0.97)

*Demographic variables (ie, age, sex, education) were included as covariates in all studies. SHEP=Systolic Hypertension in the Elderly Program; BMI=body mass index; BP=blood pressure; Syst-Eur=Systolic Hypertension in Europe; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, 3rd edn (revised); PY=patient years; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edn; APOE=apolipoprotein E genotype.

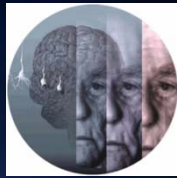
Table 7: Randomised clinical trials of antihypertensive therapy in relation to dementia

Qiu et al. [The age-dependent relation of blood pressure to cognitive function and dementia](#). Lancet neurology (2005) vol. 4 (8) pp. 487-99

FÁRMACOS y RIESGO



- **Inhibición del sistema renina-angiotensina**
 - El sistema renina-angiotensina cerebral está implicado en la cognición y en la memoria
 - Captopril, perindopril: lipofílicos, atraviesan la barrera hematoencefálica
 - *Syst-Europ, Progress y Hyvet*
 - Mecanismos posibles:
 - Modulación del flujo cerebral
 - Efectos pleiotrópicos en sistema nervioso y muscular
 - Efectos sobre la inflamación y radicales libres
 - Disminución de las lesiones en sustancia blanca



Bloqueadores de los canales del Ca⁺⁺

- Nimodipino

Lopez-Arrieta, J.M. and Birks, J. (2002) **Nimodipine for primary degenerative, mixed and vascular dementia**. Cochrane Database Syst Rev CD000147

- Podrían corregir la hipoperfusión que precede a la demencia Alzheimer y Vascular, quizás antagonizando la vasoconstricción provocada por la presencia de beta-amiloide
- Control de los niveles de calcio intracelular que provocan muerte celular

Beta-bloqueantes

- Lipofílicos asociados con EMPEORAMIENTO de la COGNICIÓN en algunos estudios
- Inervación adrenérgica del hipocampo
- No demostrado

Systolic Hypertension in the Elderly Programme (SHEP)



- Aleatorizado y doble ciego. 4736 pacientes con edad media de 72 años
- **Clortalidona +/- atenolol o reserpina**
- *Bajó la tensión pero NO redujo la demencia*
- Sólo 5 años, análisis posterior sobre los pacientes perdidos

Di Bari et al. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. American Journal of Epidemiology (2001) vol. 153 (1) pp. 72-8

Medical Research Council treatment trial of hypertension study (MRC)

- Aleatorizado y doble ciego. 2584 pacientes con edades entre 65-74 años
- **Diurético y/o beta-bloqueante**
- *Bajó la tensión pero NO redujo la demencia*
- Seguimiento durante 54 meses
- También problemas metodológicos, pero en estudio posterior (Cervilla et al.) cuanto mayor disminución de la TA, mejor cognición (tras seguimiento entre 9 y 12 años)

Prince et al. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ (1996) vol. 312 (7034) pp. 801-5



Study on Cognition and Prognosis in the Elderly (SCOPE)

- 4964 pacientes hipertensos con una edad media de 76 años
- Candesartan +/- diurético
- Era doble ciego y aleatorizado, pero el grupo control estaba muy tratado para la hipertensión, sobre todo con diuréticos y betabloqueantes
- Se convirtió en COMPARACIÓN de 2 TRATAMIENTOS
- NO DIFERENCIAS después de 3,7 años

Lithell et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens (2003) vol. 21 (5)



Hypertension in the Very Elderly Trial –cognitive function assessment (HYVET-COG)

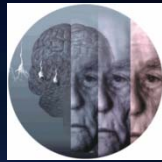
- 3336 pacientes > de 80 años con hipertensión
- Aleatorizado y doble ciego
- Indapamida retard +/- perindopril
- *Solo 2,2 años de seguimiento* (se paró porque se vió gran beneficio en mortalidad)
 - *RR de declive cognitivo 0,93*
 - *RR de demencia Alzheimer 0,85*
 - *RR de demencia vascular 0,87*



Systolic Hypertension in Europe study (Syst-Eur)

- Aleatorizado y doble ciego
- 2418 pacientes >60 años con hipertensión sistólica aislada
- Nitrendipino (60%) +/- enalapril +/- hidroclorotiacida
- Seguimiento de sólo 2 años (se redujo un 42% los AVC)
- *Reducción de los 3 tipos de demencia (vascular, Alzheimer y mixta)*
 - Un 50%!!: de 7,7 casos por 100 a 3,7 casos por 100
 - Después de 4 años; de 7,4 a 3,3 por 100

Forette et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med (2002) vol. 162 (18) pp. 2046-52



Perindopril Protection Against Recurrent Stroke Study (PROGRESS)

- 6105 pacientes de 19 países con una edad media de 64 años
- Perindopril +/- indapamida
- Seguimiento de 3,9 años
- *Reducción del riesgo de “declive cognitivo” (reducción de 3 pts en MMSE) del 19% y de demencia del 12% (ambos fármacos 23%)*
- El efecto fue mayor en los pacientes con AVC previo y fue similar en pacientes hipertensos y normotensos

Chalmers y MacMahon. *Perindopril Protection Against Recurrent Stroke Study (PROGRESS): interpretation and implementation*. Journal of hypertension Supplement : official journal of the International Society of Hypertension (2003) vol. 21 (5) pp. S9-14

Tzourio et al. *Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease*. Arch Intern Med (2003) vol. 163 (9) pp. 1069-75

CONCLUSIONES

- Límites nada claros entre Enfermedad de Alzheimer y demencia vascular
- Probable efecto de HTA a lo largo de toda la vida (acumulativo)
- Probable efecto negativo de la hipoTA en edad avanzada
- Se necesita más investigación sobre TA ideal en cada momento
- Primera ocasión para prevención EFICAZ de demencia

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