PREVALENCIA Y DETERMINANTES DE LAS LESIONES VASCULARES CEREBRALES DEFINIDAS POR RESONANCIA MAGNÉTICA Y ESTUDIO DE LA FUNCIÓN COGNITIVA EN POBLACIÓN ADULTA HIPERTENSA Y GENERAL

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"Prevalencia y determinantes de las lesiones vasculares cerebrales definidas por resonancia magnética y estudio de la función cognitiva en población adulta hipertensa y general"

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ABREVIACIONES

ABVD: Actividades Básicas de la Vida Diaria

ACA: Arteria Cerebral Anterior

ACM: Arteria Cerebral Media

ACP: Arteria Cerebral Posterior

AIVD: Actividades Instrumentales de la Vida Diaria

AIT: Accidente Isquémico Transitorio

CHS: Cardiovascular Health Study

Colesterol HDL: colesterol transportado por lipoproteínas de alta densidad

CSO: Centro Semioval

DE: Desviación Estándar

DCL: Deterioro Cognitivo Ligero

DM: Diabetes Mellitus

DVa: Demencia Vascular

EA: Enfermedad de Alzheimer

ECA: Ensayo Clínico Aleatorizado

ECN: Envejecimiento Cognitivo Normal

ECV: Enfermedad Cerebrovascular

EPVC: Enfermedad de Pequeño Vaso Cerebral

EPVD: Espacio Perivascular Dilatado

FLAIR: Fluid Attenuated Inversion Recovery

GGBB: Ganglios Basales

HSB: Hiperintensidades de Sustancia Blanca

HTA: Hipertensión Arterial

IC: Intervalo de Confianza

ICS: Infarto Cerebral Silente

IMC: Índice de Masa Corporal

LCR: Líquido Cefalorraquídeo

PA: Presión Arterial

PP: Presión de Pulso

RM: Resonancia Magnética (Cerebral)

RR: Riesgo Relativo

RESUMEN

Las enfermedades cerebrovasculares y la demencia están entre las primeras causas de muerte y discapacidad en el adulto en países desarrollados. Su coste sanitario es muy alto para los sistemas sanitarios de salud pública y su incidencia se espera que siga aumentando con el envejecimiento de la población.

Ambas enfermedades pueden pasar por etapas preclínicas, sin sintomatología aparente o con síntomas leves. Estudiar estas enfermedades en estos estadios facilita el entendimiento de la fisiopatología y evolución de la enfermedad y posibilita la prevención de futuros ictus o la progresión a demencia.

En esta tesis se describe la metodología del estudio ISSYS (Investigating Silent Strokes in hYpertensives, a magnetic resonance imaging Study) y sus resultados principales. El estudio ISSYS es un estudio comunitario en un grupo de hipertensos de edad media-avanzada y por tanto en alto riesgo de desarrollar ictus y demencia. En ellos hemos estudiado los estadios preclínicos de las enfermedades cerebrovasculares y el deterioro cognitivo y sus determinantes. Hemos usado RM cerebral para identificar las lesiones cerebrovasculares sublínicas y la evaluación cognitiva para el diagnóstico de Deterioro Cognitivo Ligero (DCL). También hemos estudiado la presencia y los determinantes (factores de riesgo vascular y función cognitiva) de los infartos corticales pequeños en población envejecida general no demencia (Estudio Rotterdam).

Hemos mostrado que la prevalencia de infartos cerebrales silentes es del 10% en hipertensos de estudio ISSYS (n=1037) y se asocia de manera independiente al sexo masculino, tener puntuaciones más altas en la escala de riesgo cardiovascular (REGICOR) y a tener presencia de marcadores de órgano diana para la hipertensión arterial (microalbuminúria). Los Espacios Perivasculares Dilatados son ubicuos en hipertensos y se asocian al envejecimiento y al resto

de lesiones radiológicas. El 17.5% de participantes del estudio ISSYS mostraron puntuaciones en la escala cognitiva de cribado DRS-2 por debajo de lo esperado por edad y años de escolaridad. El DCL se ha presentado en un 8.9% de los participantes con datos normativos y se ha asociado con tener baja educación, con la rigidez arterial nocturna (medida con presión de pulso de 24 horas) y con las hiperintensidades de sustancia blanca profundas en la RM cerebral.

Los infartos corticales pequeños (<15mm) tienen baja prevalencia en la población general (1.1%, n=4905) y se encuentran en las zonas limítrofes anterior y posterior en la RM. Se asociaron con los factores de riesgo vascular (edad, género masculino y tabaquismo) y con una peor función cognitiva (peor memoria diferida y función ejecutiva) en la población general.

El estudio ISSYS pone las bases para seguir estudiando la historia natural de la enfermedad cerebrovascular y el deterioro cognitivo subclínicos y para el ensayo de terapias preventivas de ictus y demencia en hipertensos.

SUMMARY

Cerebrovascular disease (stroke) and dementia are first leading causes of death and disability in adults in developed countries. An important amount of public health budgets are spent in those diseases and their incidence is expected to grow with the aging population.

Both diseases might have a preclinical stage, without overt symptoms or with mild symptoms. Studying these diseases in these preclinical stages might help to understand the disease pathophysiology and evolution and might enable the prevention of future stroke and progression to dementia.

In this Thesis we describe the methodology of the ISSYS study (Investigating Silent Strokes in hYpertensives, a magnetic resonance imaging Study) and its main results. This study is a community-based study in hypertensive individuals, middle and older aged, and therefore at high risk of stroke and dementia. We studied the preclinical stages of stroke and dementia and their determinants in these participants. We used brain Magnetic Resonance Imaging to identify subclinical vascular lesions and cognitive evaluation to diagnose Mild Cognitive Impairment (MCI). Also we studied prevalence and determinants (vascular risk factores and cognitive function) of small cortical infarcts in a non-demented, aged, general community-based study (Rotterdam Study).

We showed that prevalence of silent brain infarcts is 10% in hypertensive individuals of ISSYS study (n=1037) and they are independently associated to male sex, higher cardiovascular risk score (assessed by REGICOR, Framingham calibrated equation for Spanish individuals) and other hypertension target organ damage (microalbuminuria). Enlarged Perivascular Spaces are ubiquitous in hypertensive individuals and are associated with ageing and other small vessel disease markers. 17.5% of the ISSYS participants had a score in a dementia screening scale (DRS-2) lower than expected by age and education years. MCI prevalence is 8.9% and is

associated with lower education, sleep arterial stiffness measured by ambulatory pulse pressure and extensive deep white matter hyperintensities.

Small cortical infarcts (<15mm) prevalence is low (1.1% in the general aging population, n=4905). We find them mostly in anterior and posterior external borderzone areas of big brain arteries. They are associated with vascular risk factors (aging, male sex and smoking) and worse cognitive function (worse delayed memory and executive function) than participants without any infarct in the general population.

ISSYS study will allow the study of the natural history of stroke and cognitive impairment subclinical phases and will permit the study of prevention therapies for stroke and dementia in hypertensive individuals.

A. INTRODUCCIÓN

A.1. LAS ENFERMEDADES CEREBROVASCULARES

A.1.1. DEFINICIÓN Y EPIDEMIOLOGÍA DE LA ENFERMEDAD CEREBROVASCULAR

Las **enfermedades cerebrovasculares (ECV o ictus)** se definen como el trastorno súbito de la función cerebral (transitorio o permanente) causado por la interrupción de la llegada de sangre a determinadas zonas del parénquima cerebral. En términos generales, el ictus se divide en isquémico y hemorrágico. El ictus isquémico es el que padecen la mayoría de los pacientes (un 80% aproximadamente) como consecuencia de una disminución (interrupción) de flujo circulatorio; el ictus hemorrágico (un 20% aprox.) se produce como consecuencia de la rotura y extravasación de sangre en el parénquima cerebral.

Las mejoras en el diagnóstico, tratamiento en fase aguda y prevención (control de los factores de riesgo vascular) de esta enfermedad han sido considerables en los últimos años, disminuyendo su incidencia en los países de renta alta en un 42% en las últimas cuatro décadas.(1) No obstante, a nivel global según la Organización Mundial de la Salud sigue habiendo 15 millones de ictus anuales que conllevan un resultado de muerte en un tercio de los casos y de discapacidad permanente en otro tercio. En España, el ictus es la segunda causa de muerte tras la enfermedad isquémica cardiaca siendo la primera causa de muerte en las mujeres y la tercera en hombres.(2) Además el ictus es la primera causa de discapacidad en el adulto tanto en hombres como en mujeres en nuestro país. Un 50% de los supervivientes tendrán algún grado de discapacidad y el 20% requerirán una hospitalización definitiva.

Esta gran prevalencia y mal pronóstico del ictus conllevan además un importante gasto sanitario para el Sistema Nacional de Salud. En 2010 se estimó que los 644.025 afectados por la enfermedad consumían 8.584 millones de euros entre costes directos e indirectos de la

enfermedad (13.329 euros por enfermo y año).(3) Por lo tanto prevenir la enfermedad es una de las tareas más importantes a realizar para disminuir su incidencia.

La enfermedad cerebrovascular puede cursar también de forma diferente, sin síntomas clínicos que se presenten de forma aguda. En ese caso hablamos del **infarto cerebral silente (ICS) o encubierto** (del inglés, covert) el cual cursa de manera asintomática y se identifica con técnicas de imagen cerebral (TC o RM). No existen datos de su frecuencia en población española pero en un meta-análisis de datos de cohortes poblacionales internacionales se encontró que la prevalencia está en torno al 10-20%, mientras que la incidencia anual es del 2-4%.(4) Estas cifras son mayores que las de ictus clínico y aumentan todavía más en población que ha sufrido un ictus con manifestaciones clínicas. (5) De hecho, se estimó que eran cinco veces superiores a la prevalencia e incidencia del ictus clínico. En dos estudios epidemiológicos norteamericanos (Atherosclerosis Risk in Communities –ARIC-, Cardiovascular Health Study –CHS-) se extrapoló que de los 12 millones de personas que tuvieron un ictus en 1998, sólo 770.000 tuvieron un ictus clínico siendo el resto ICS.(6)

La prevención primaria en esta enfermedad es indispensable porque afecta a una amplia franja de la población y además también porque en la mayoría de personas (76% según un estudio reciente) la mayoría de los ictus cursan como un primer evento de enfermedad cerebrovascular.(7) Actuar en aquellos sujetos de alto riesgo es la manera más eficaz de luchar contra esta devastadora enfermedad.

A.1.2. FACTORES DE RIESGO DEL ICTUS

Los factores de riesgo (FR) son similares para los diferentes tipos de ictus (isquémico y hemorrágico) y también son similares para los ICS con algunas peculiaridades que se comentarán a continuación. En la **Tabla 1** se muestran los FR y su fuerza de asociación con los ICS. (4)

1.2.1. FR no modificables

La *edad* es el FR más importante tanto para el ictus que cursa clínicamente como para los ICS, el riesgo aumenta especialmente a partir de la 6ª década de vida. En el caso de los ICS el riesgo se dobla o triplica por década.(4)

La *raza o la etnia* se relacionan claramente con el ictus clínico, ya que las personas de raza negra y las de algunas comunidades de Hispánicos y Latinos tienen mayor incidencia y mayor tasa de mortalidad por ictus que los individuos de raza blanca.(8) En cuanto a los infartos silentes, en el estudio ARIC se encontró que los que no eran de raza blanca tenían aprox. un 64% más ICS que estos.(9)

En cuanto a los *factores de riesgo genéticos*, se estima que aumenta la probabilidad de ictus un 30% en aquellos que tienen antecedentes familiares.(8) En cambio, para los ICS existen menos estudios genéticos y los genes candidatos no consiguieron replicarse en los estudios de GWAS (del inglés Genome Wide Association Studies).(10)

En el caso del *sexo* no hay una mayor predisposición de un sexo comparado con el otro para el ictus ni para el ICS. (4)

En el caso del ictus clínico encontramos una asociación con el *bajo peso al nacer* (recién nacidos con peso<2500 gramos), esto no se ha descrito para los ICS.

A.1.2.2. FR modificables

Conjuntamente son la primera causa de ictus tal y como mostró un estudio de casos y controles internacional en 6000 participantes en el que se vio que 10 factores de riesgo modificables son la causa del 90% de los ictus.(11)

De entre todos los factores de riesgo, enfatizaremos el papel de la hipertensión arterial, por estar una parte de esta tesis especialmente dedicada a la presencia de lesiones vasculares cerebrales y deterioro cognitivo en los sujetos hipertensos.

La hipertensión arterial (HTA) se define como la elevación de las cifras de presión arterial (PA) por encima de 140/90 mmHg, su etiología es variada pero la mayoría de casos se deben a HTA esencial (primaria).

La HTA es un factor de riesgo vascular (FRV) mayor tanto para ictus isquémico y hemorrágico, AIT (Accidente Isquémico Transitorio) como para ICS. Es el más común de los FRV modificables para la enfermedad cerebrovascular, dos terceras partes de los >65 años son hipertensos y su relación con el ictus aumenta a medida que aumentan las cifras de PA. En el caso de los ICS se encontró que la razón de probabilidad fue hasta cuatro veces superior para los hipertensos que para los no hipertensos.(4)

Así, el cerebro se considera un órgano diana para el daño hipertensivo, pudiendo producirse eventos clínicos (ictus), daño silente o subclínico (ICS, Hiperintensidades de Sustancia Blanca o HSB) u otro tipo de manifestaciones clínicas, como las relacionadas con el deterioro cognitivo. Esto sucede de forma similar en otros órganos como el riñón, el corazón o las arterias y para algunos de ellos también existen marcadores de lesión subclínica,(12, 13) como se muestran en la siguiente **Tabla 2**.

Tabla 2: Principales órganos diana de la hipertensión y sus marcadores de lesión subclínica.

Órgano diana	**Marcador subclínico**
Corazón	- *Hipertrofia del ventrículo izquierdo* medido por electrocardiograma (índice Sokolov-Lyon>3.5 mV, onda R en aVR>1.1mV, producto voltaje por duración de Cornell>244 mVxseg) - *Hipertrofia del ventrículo izquierdo* medido por ecocardiografía (masa del

	ventrículo izquierdo en hombres>115g/m^2, en mujeres>95g/m^2 de superficie corporal)
Riñón	- *Filtrado glomerular* 30-60 ml/min/1.73m2 (medido por CKD-Epi) - *Microalbuminúria* de 24 horas de 30-300 mg - *Cociente albúmina/creatinina* de 30-300 mg/g
Arterias	- *Velocidad de la onda de pulso entre carótida y femoral*>10 m/s - *Índice tobillo-brazo*<0.9 - *Grosor íntima-media carotideo*>0.9 mm o placa carotidea - En ancianos, *Presión de Pulso* (PP)≥60 mmHg
Cerebro	- Presencia de *infartos cerebrales silentes, microsangrados e hiperintensidades de sustancia blanca*

El tratamiento de la HTA previene la aparición de ictus, coronariopatía, insuficiencia cardiaca y renal. Un meta-análisis con 23 Ensayos Clínicos Aleatorizados (ECA) mostró que el tratamiento de la HTA reducía el riesgo de ictus en un 32% (IC95% 24-39). Reducir las cifras de PA en pre-hipertensos (PA 120-139/80-89) también se asocia a una disminución del riesgo de ictus en un 22%. Igualmente el control de la HTA sistólica aislada (Presión Arterial Sistólica o PAS >160 y Presión Arterial Diastólica o PAD<90 mmHg), típica del anciano, es importante ya que los ECA han mostrado reducciones de ictus total y fatal. Reducir las cifras de PA (tanto sistólica como diastólica) es probablemente más importante que la clase farmacológica usada y se recomienda para todos los hipertensos, los pre-hipertensos deben recibir recomendaciones dietéticas.(8) En el caso de los ICS no se han realizado ECA con fármacos hipotensores por lo tanto no sabemos si disminuir la PA reduce también la nueva aparición de ICS.

La *diabetes mellitus* (DM) es un FRV independiente para ictus y se estima que un 20% de diabéticos fallecerán a causa de esta enfermedad, a demás los diabéticos tienen más

frecuentemente otros FRV (HTA, dislipemia, obesidad y ateroesclerosis) que se relacionan con la aparición del ictus. (8) No obstante, los ECA individuales no han mostrado una reducción del riesgo de ictus con el control estricto de la glucemia y tampoco un reciente meta-análisis de 9 estudios mostró un beneficio con el control glucémico estricto pero sí hubo menos ictus en aquellos diabéticos con índice de masa corporal (IMC)>30 (RR=0.86, 95% IC=0.75-0.99).(14) Para el caso de los ICS, la asociación es más débil excepto cuando se mide en pacientes con *enfermedad renal crónica* la cual tiene una asociación fuerte con los ICS. Se desconoce si la relación positiva entre los diabéticos y los ICS se debe a la DM en sí misma, a la enfermedad renal crónica o a las comorbilidades cardiovasculares que las acompañan.(4)

En cuanto a la *dislipemia***,** la mayoría de estudios mostró que el *colesterol* total elevado y los niveles bajos de *colesterol transportado por lipoproteínas de alta densidad* (colesterol HDL) son FRV para el ictus isquémico. Los niveles altos de triglicéridos se han relacionado inconsistentemente con el ictus, la comparación entre estos estudios es difícil ya que algunos se realizaron en participantes en ayunas y en otros sin ayunas. Otra vez, en el caso de los ICS los resultados van en el mismo sentido que en el ictus clínico pero son menos consistentes.(15)

El beneficio de las estatinas en el ictus isquémico está más relacionado con su capacidad para reducir la ateroesclerosis que por la reducción de los niveles de colesterol. En el caso de los ICS se desconoce si pueden ser beneficiosas. La prevención primaria con estatinas sólo se recomienda en los sujetos con alto riesgo cardiovascular a 10 años (según las Guías de Prevención Primaria para el Ictus Americanas).(8)

En referencia a la *obesidad*, el aumento del *índice de masa corporal* (IMC=kg peso/m^2 altura) por encima de 25 y especialmente la *obesidad abdominal* son predictores independientes de ictus. (16) Otra vez en el caso de los ICS los estudios son insuficientes y conflictivos. En un estudio con un número grande de participantes se mostró que tener obesidad abdominal en el hombre o la mujer (perímetro abdominal>102 cm y >88 cm, respectivamente) o estar en el

tercio alto de obesidad comparado con el bajo se asociaban a ICS.(17) No obstante, con el IMC hay resultados en las dos direcciones: algunos estudios mostraron que el IMC>25 era protector o deletéreo para ICS comparado con los individuos que tenían el IMC≤25.(4)

El *síndrome metabólico* que se produciría al combinar al menos tres FR anteriores (HTA, glucemia alterada en ayunas, hipertrigliceridemia, HDL colesterol bajo y/o obesidad abdominal) también se asocia a ictus aunque esta asociación no parece ser mayor que la de la suma de sus componentes por separado. (8) Para los ICS, sucede algo similar, se desconoce si la asociación con el síndrome metabólico es independiente de los FRV (especialmente, HTA).(4)

En cuanto al *tabaquismo*, los análisis de los grandes estudios epidemiológicos en la comunidad (Estudio Framingham, Cardiovascular Health Study –CHS-, Honolulu Heart Study) han mostrado que el tabaquismo dobla el riesgo de ictus isquémico. El tabaquismo potenciaría el efecto sobre el ictus de la HTA o de los anticonceptivos orales estrogénicos. En EUA se estima que el 12-14% de la mortalidad por ictus se debe al tabaquismo.(8) Nuevamente, algunos estudios mostraron una mayor prevalencia de ICS en fumadores que en no fumadores pero la mayoría no mostraron ningún efecto independiente de otros FR.(4)

El *alcohol* tiene una relación en forma de "J" con el ictus isquémico. Es decir, el riesgo es menor para aquellos con un consumo leve-moderado y es mucho mayor para aquellos con un consumo excesivo (>300g/semana).(8) Para los ICS el riesgo existe en aquellos con un consumo excesivo y parece haber un efecto protector para aquellos con un consumo menor. (4)

La *fibrilación auricular* incluso en ausencia de valvulopatía es fuente de embolismo cardiaco y aumenta el riesgo de ictus en 4 o 5 veces.(8) También parece ser un FR para los ICS como se mostró en el Framingham Study donde fue el factor más fuertemente relacionado (OR=2.16; 95% IC 1.07,4.40) seguido por la HTA.(18)

La *enfermedad carotidea* estimada por la presencia de estenosis asintomática carotidea es un predictor de ictus. (8) Además de la estenosis carotidea, la presencia de placas de ateroma y algo menos el aumento en el grosor íntima media se han relacionado con la presencia de ICS en prácticamente todos los estudios.(4)

El tratamiento de la estenosis carotidea con *endarterectomía o angioplastia/stent* también son FR para los ICS. Los estudios son de pocos pacientes pero con ambas técnicas se producen lesiones isquémicas en el 22% aprox. de los individuos que son identificadas por secuencia de difusión de la RM cerebral tras el procedimiento.(19, 20) La mayoría de estas lesiones son asintomáticas y un 61% serán visibles en forma de ICS en la RM practicada meses después del procedimiento.

También la *enfermedad coronaria* y el *recambio de la válvula aórtica* son FR para ICS. (21)

En cuanto a los *biomarcadores plasmáticos*, el que tiene unos resultados más consistentes es la *homocisteína*. Esta se ha relacionado con el ictus, con otras enfermedades cardiovasculares, la demencia y la enfermedad de Alzheimer (EA). (22, 23) También en el estudio poblacional Framingham los niveles altos de homocisteína se asociaron a ICS y a la atrofia cerebral.(24)

Otros FR que han sido estudiados en menor frecuencia y se relacionaron positivamente con los ICS son el *síndrome de apnea obstructiva del sueño, la depresión, la hiperuricemia y el fibrinógeno*.

Tabla 1: Resumen de la fuerza de la asociación entre los factores de riesgo estudiados y los infartos cerebrales silentes. Modificado de Fanning y col.(4)

Fuerza de la asociación	Factor de riesgo
Fuerte	Edad
	Hipertensión arterial
	Síndrome metabólico
	Enfermedad carotidea
	Enfermedad renal crónica
Probable	Homocisteína
	Apnea obstructiva del sueño
	Enfermedad coronaria
	Insuficiencia cardiaca
No aclarado	Fibrilación auricular
	Dislipemia
	Diabetes Mellitus
	Obesidad
	Tabaquismo
	Alcohol
	Etnia
	Sexo

A.1.2.3. Las ecuaciones del riesgo cardiovascular

Las ecuaciones del riesgo cardiovascular sirven para estimar la probabilidad de tener un evento cardiovascular basándose en el efecto conjunto de los FRV que un individuo presente y la gravedad que estos alcancen. Se adaptó la ecuación derivada del estudio Framingham a

nuestra población con el Índice del Registre Gironí del Cor (REGICOR). (25) El REGICOR usa para su estimación las variables de edad, sexo, tabaquismo, DM, cifras de PA y cifras de colesterol.

En nuestra población no existen ecuaciones de riesgo especificas para ictus, las cuales si están disponibles para población de EUA (Framingham Stroke Risk Score).(26)

A.1.3. CLASIFICACIÓN DEL ICTUS ISQUÉMICO Y EL INFARTO CEREBRAL SILENTE (ICS)

El ictus es una enfermedad heterogénea con diferentes subtipos, fisiopatología, topografía, curso clínico y características en neuroimagen. Por lo tanto existen diferentes clasificaciones que considerando las características previas sistematizan su estudio.

A.1.3.1 Clasificación según la localización del ictus

La localización de los ictus isquémicos puede ser a nivel cortical, subcortical en la sustancia blanca y/o los ganglios basales, en el tronco y el cerebelo. Su localización está asociada a las diferentes manifestaciones clínicas.

A.1.3.2. Clasificación según el vaso y territorio vascular afectado

Según el tipo de vaso y el territorio vascular afecto, el ictus se puede clasificar en enfermedad de gran vaso o pequeño vaso y en territorio carotideo, vertebro-basilar o frontera. En la **Figura 1** se muestran los territorios vasculares de las arterias cerebrales.

-El *ictus de gran vaso arterial* es la que afecta a las arterias carótidas, vertebro-basilares y sus ramas principales.

-La *enfermedad de pequeño vaso* afecta a las arterias llamadas perforantes (lenticuloestriadas, talamogeniculadas, talamoperforantes y paramediadas pontinas). Las peculiaridades de las arterias perforantes son su pequeño diámetro, entre 100 y 400µm, su origen en arterias cerebrales principales y el hecho de no tener anastomosis terminales ni existir circulación

colateral para el territorio que irrigan que es la zona próxima a la línea media de los hemisferios cerebrales y del tronco encefálico.(27)

La obstrucción de dichas arterias perforantes ocasiona el infarto lacunar, cuyo diámetro máximo puede alcanzar los 20 mm (generalmente, menos de 15 mm), y el cual sucede en la quinta parte de los ictus isquémicos.(28) Los FRV clásicos para estos infartos son la HTA, la DM o ambos. El ICS acostumbra a ser un infarto lacunar localizado en territorios de la sustancia blanca o gris subcortical, no obstante en ocasiones puede producirse en áreas corticales.

-Los *ictus de territorio carotideo (o anterior)* son los más frecuentes de los ictus isquémicos. Incluyen los territorios arteriales de la arteria carótida interna y sus ramas: arteria cerebral anterior (ACA), arteria cerebral media (ACM), arteria coroidea anterior y ramas perforantes de la ACA y ACM.

-Los *ictus de territorio vertebro-basilar (posterior)* se producen en el territorio de las arterias vertebrales, arteria cerebelosa posteroinferior, arteria basilar y sus ramas: arteria cerebelosa anteroinferior, arteria cerebelosa superior, arteria cerebral posterior (ACP).

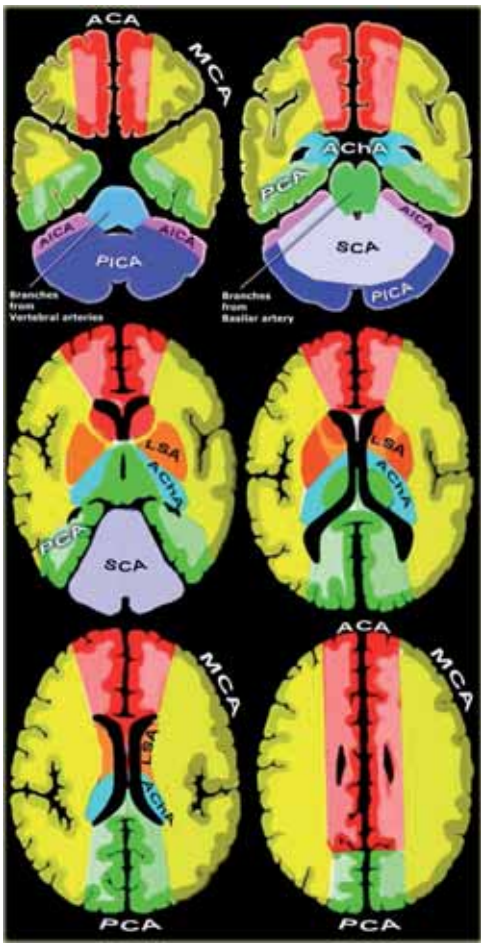


Figura 1: Territorios arteriales cerebrales. El territorio de las pequeñas arterias perforantes se muestra en naranja (LSA: arterias lenticuloestridas), rojo oscuro en caudado, en azul (AchA: arteria coroidea anterior) y verde (ramas de la arteria basilar). El resto de arterias indicadas son ACA (arteria cerebral anterior), MCA (arteria cerebral media), PCA (arteria cerebral posterior), PICA (arteria cerebelosa posteroinferior), AICA (arteria cerebelosa anteroinferior) SCA (arteria cerebelosa superior).

Tomada de http://www.radiologyassistant.nl/en/p484b8328cb6b2/brain-ischemia-vascular-territories.html

-El *ictus de territorio frontera (limítrofe)* es aquel que sucede entre la zona frontera de la ACA y ACM, entre la ACM y la ACP o entre el territorio superficial y profundo de una gran arteria cerebral. La **Figura 2** muestra el territorio de los ictus de territorio frontera.

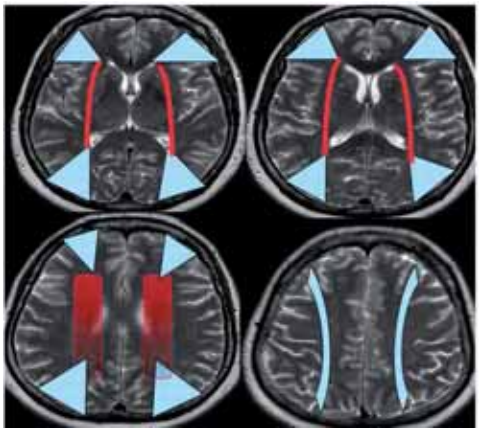


Figura 2: El fondo es una imagen de RM cerebral potenciada en T2. En azul se muestra el territorio frontera externo (cortical) y en rojo el interno (subcortical). Tomada de Mangla et al, 2011.(29)

Una de las *clasificaciones etiológicas* más usadas es la clasificación TOAST que clasifica el ictus en aterotrombótico, cardioembólico, lacunar, de causa rara o indeterminado.(30)

A.1.4. DIAGNÓSTICO DEL ICTUS: MANIFESTACIONES CLÍNICAS Y RADIOLÓGICAS

A.1.4.1. Características clínicas del ictus

Las características clínicas variarán según la zona afectada y se clasifican según la arteria y territorios afectados. No pretendemos explicar aquí los múltiples síndromes vasculares que existen, si bien en aras de un mejor entendimiento de los resultados de la tesis resumiremos las manifestaciones clínicas de los infartos corticales y los infartos lacunares.

Los *infartos corticales* acostumbran a producir déficits neurológicos de funciones superiores (trastorno del lenguaje o afasia, déficit motor de las extremidades o la cara, déficit sensitivo de extremidades o de la cara, negligencia, déficit visual tipo hemianopsia, discalculia, agrafia, alteración visuoespacial, etc.).

Las manifestaciones clínicas de los *infartos lacunares* son variadas, los síndromes lacunares están generalmente ocasionados por un infarto lacunar. Existen cinco síndromes lacunares

típicos: la hemiparesia motora pura (el más frecuente entre ellos, causa el 50% de los casos), el síndrome sensitivo puro, el síndrome sensitivo-motor, la disartria-mano torpe y la hemiparesia atáxica.

Ambos tipos de infartos (corticales y lacunares) pueden pasar de forma desapercibida o "silente", tal y como se comentó con anterioridad, por distintos motivos. Algunas veces los déficits fueron percibidos pero al ser sutiles de tipo visual, motor u otros no motivaron una consulta médica.

A.1.4.2. Características radiológicas del ictus

El diagnóstico del ictus es clínico y se confirma con las *pruebas de imagen cerebral* (Tomografía Computerizada –TC- o Resonancia Magnética –RM- cerebral). Estas son importantes para diferenciar la etiología isquémica o hemorrágica y hacer el diagnóstico diferencial con otras lesiones cerebrales que presentan síntomas similares.

El diagnóstico de **ICS** se puede establecer mediante TC y sobretodo RM cerebral, o en estudios post-mortem. Lo más habitual es encontrarlos como hallazgo casual en la RM cerebral al realizar la prueba por otro motivo o en estudios observacionales.(31)

La mayoría de estudios los definen como lesiones cavitadas, de tamaño igual o superior a los 3 mm en su diámetro máximo, con intensidad de señal similar al líquido cefalorraquídeo (LCR) en todas las secuencias de RM (hipointenso en T1, hiperintenso en T2 e hipointenso en Fluid Attenuated Inversion Recovery –FLAIR-). Además muchos estudios usan como criterio diagnóstico el tener un halo de gliosis alrededor de la lesión en la secuencia FLAIR.

En cuanto a su distribución, se vio que más de la mitad de los infartos silentes se localizan en los ganglios de la base (aunque p.ej. en el Rotterdam Scan Study, fueron el 80%), una tercera parte están en la substancia blanca subcortical y un 10-20% son corticales(32) (18). Aunque algunos estudios no incluyeron infartos mayores de 15 mm ni infartos corticales.(33)

La localización predominante en áreas no elocuentes del subcórtex es probablemente lo que hace que sean lesiones frecuentemente asintomáticas o no reconocidas como ictus.(34) En la **Figura 3** se pueden ver ejemplos de este tipo de infarto.

A.1.4.3. Diagnóstico diferencial radiológico de los infartos cerebrales silentes

Los criterios diagnósticos de ICS han ido cambiando ligeramente en los diferentes estudios. En la actualidad, el énfasis se pone en diferenciarlos de otras lesiones radiológicas sobretodo de los Espacios Perivasculares Dilatados (EPVD) y también de las Hiperintensidades de Sustancia Blanca (HSB).(35) La **Figura 3** muestra ejemplos de estas lesiones radiológicas.

A.1.4.3.1. ESPACIOS PERIVASCULARES DILATADOS

Los espacios perivasculares (o espacios de Virchow-Robin) son espacios anatómicos alrededor de las pequeñas arterias perforantes cerebrales donde drena el líquido intersticial. Pueden visualizarse en la RM convencional cuando están dilatados.(36) Se visualizan en secuencia ponderada en T1 y en T2 con similar intensidad de señal que el LCR (hipointensos en T1 e hiperintensos en T2), redondeadas en los ganglios de la base y lineales en la sustancia blanca subcortical en la RM axial. Durante tiempo se pensó que eran una manifestación de la atrofia. Y a nivel anatomopatológico se habían observado en gente mayor durante años y se pensaba que era un artefacto del procesado del tejido. La interpretación cambió a medida que las técnicas de imagen fueron avanzando y posibilitaron su visualización.(36)

El diagnóstico diferencial con los ICS se realiza en base a su tamaño (los EPVD son generalmente <3mm), forma bien definida, acumulación en áreas cerebrales concretas (los EPVD se acumulan en la parte baja de los ganglios de la base y por debajo de la comisura anterior) y generalmente no tienen halo de gliosis en FLAIR a su alrededor.

Se asocian a la existencia de otras lesiones radiológicas: infarto lacunar, HSB (37) y a los procesos inflamatorios de la esclerosis múltiple y probablemente del infarto lacunar.(38, 39)

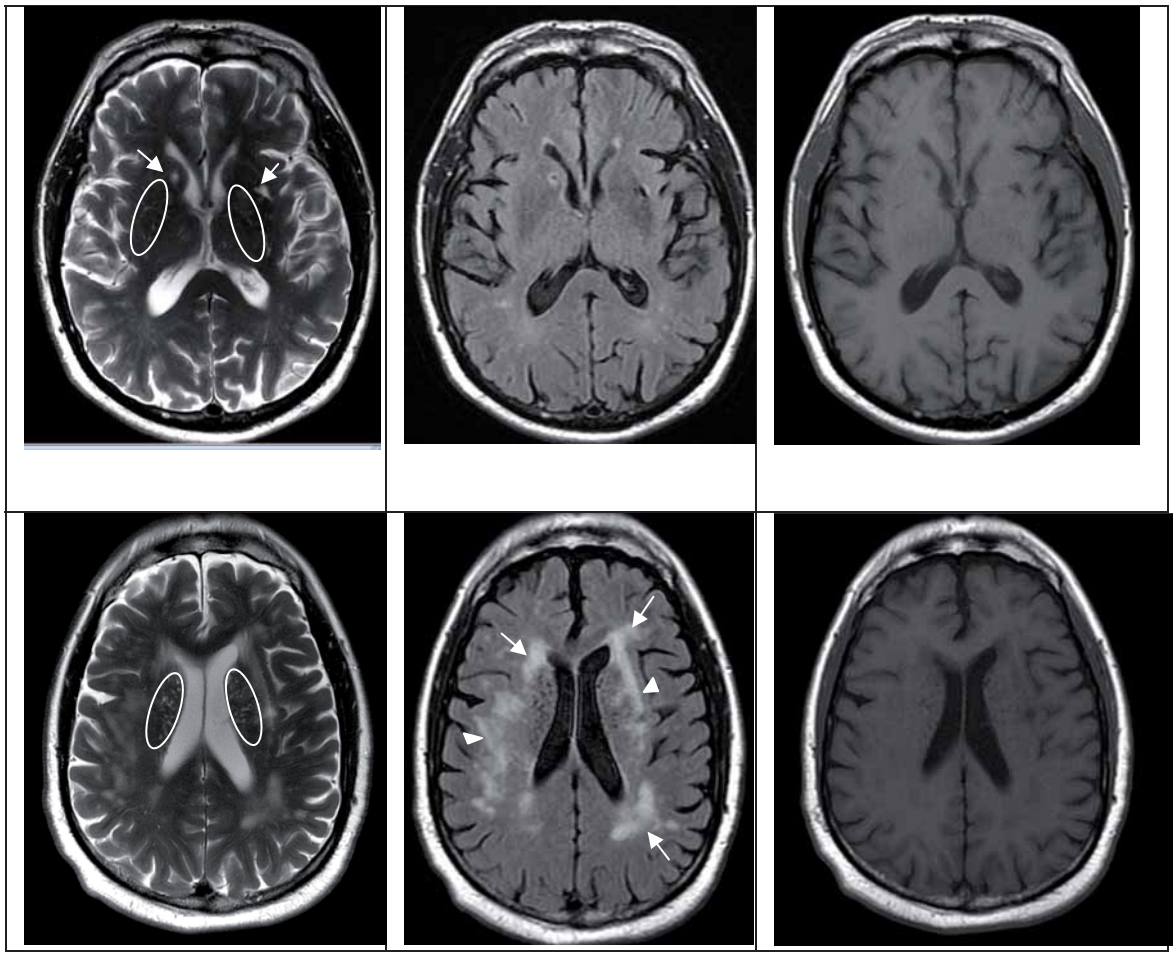
A.1.4.3.2. HIPERINTENSIDADES DE SUSTANCIA BLANCA

Se manifiestan como áreas de baja atenuación en el TC, generalmente simétricas y con tendencia a confluir. En la RM cerebral se presentan como lesiones hiperintensas en T2 y FLAIR e iso o hipointensas en la secuencia ponderada en T1. Se distribuyen típicamente por la sustancia blanca profunda y periventricular y por la sustancia gris de los ganglios de la base, también se pueden encontrar en tronco y sustancia blanca del cerebelo.(36)

Se diferencian de los ICS por su intensidad de señal, por su forma poco definida y por no tener halo de gliosis alrededor.

Se asocian con la presencia de otras lesiones radiológicas como el ictus lacunar,(40) lagunas en RM(41) y los EPVD.(37)

Figura 3: Ejemplos de lesiones cerebrovasculares silentes en resonancia magnética cerebral.



En la primera fila se muestran dos infartos lacunares (flechas) y EPVD en ganglios de la base (círculos); en la primera imagen de la izquierda la secuencia está potenciada en T2, la imagen central en FLAIR y la de la derecha en T1. En la segunda fila se muestran hiperintensidades de sustancia blanca en T2 (las flechas señalan la localización profunda y las puntas de flecha la localización periventricular) y EPVD en ganglios de la base (círculos). En la imagen izquierda la secuencia está potenciada en T2, en el centro está la misma imagen en FLAIR y a derecha en T1.

A.1.5. PRONÓSTICO DE LAS LESIONES CEREBROVASCULARES SILENTES

En cuanto al pronóstico se ha observado que los individuos con ICS y/o HSB tienen mayor probabilidad de padecer un ictus clínico, (42, 43) desarrollar deterioro cognitivo y padecer tanto demencia vascular (DVa) como enfermedad de Alzheimer (EA).(44) En el último apartado de la introducción hablaremos sobre el deterioro cognitivo asociado a estas lesiones.

Su prevalencia elevada y su mal pronóstico nos obligan a seguir avanzando en su estudio. En esta tesis nos hemos centrado en el estudio de algunas lesiones cerebrovasculares silentes en población hipertensa.

A.1.6. LA ENFERMEDAD DE PEQUEÑO VASO CEREBRAL

La enfermedad de pequeño vaso es considerada una enfermedad sistémica que afecta a varios órganos del cuerpo (cerebro, retina, riñón, etc.), en ocasiones el cerebro está preservado y en otras es la diana principal de la enfermedad.(28) En la presente tesis sólo vamos a abordar algunos aspectos clínicos y radiológicos de la enfermedad de pequeño vaso cerebral (EPVC).

La EPVC está entre las enfermedades neurológicas más frecuentes y tienen un papel crucial en el envejecimiento, el infarto cerebral y la demencia.(28)

Se caracteriza por el síndrome clínico, cognitivo, de neuroimagen y neuropatológico que se atribuye a la enfermedad de las pequeñas arterias, arteriolas, capilares y vénulas cerebrales que resulta en daño cerebral en la sustancia blanca y gris profundas.

La etiología más frecuente es la angiopatía (arterioloesclerosis) relacionada con el envejecimiento y los FRV, otras causas son la angiopatía amiloide cerebral esporádica o hereditaria (relacionada con la enfermedad de Alzheimer), causas inflamatorias e inmunomediadas, angiopatías hereditarias, colagenosis venosa y otras.(28)

Los mecanismos que causan la enfermedad son complejos y no se comprenden en su totalidad. La enfermedad ateroesclerótica se atribuye sobretodo a la hipertensión, a la microateromatosis (o depósito lipídico en la pared del vaso, de aquí la denominación de lipohialinosis), al vasoespasmo y más recientemente al fallo del endotelio.

A diferencia de los grandes vasos cerebrales, los vasos pequeños no pueden explorarse “in vivo”, por lo tanto se piensa que las lesiones del parénquima observadas en RM se originan de la lesión de estos vasos y son considerados los marcadores indirectos de esta enfermedad. Los signos de EPVC en la RM convencional incluyen los infartos subcorticales pequeños (sobretodo, el infarto lacunar del que se ha hablado extensamente con anterioridad), las HSB, los microsangrados, la atrofia y más recientemente los EPVD.(36)

A.2. COGNICIÓN EN EL ENVEJECIMENTO

A.2.1. LA FUNCIÓN COGNITIVA NORMAL

Las funciones mentales superiores o cognitivas son un conjunto de funciones bien integradas que nos definen como seres humanos y nos permiten aprender, procesar, guardar, y transmitir información, representar mentalmente el mundo, y comunicarnos a través de símbolos y del lenguaje. Nos capacitan para la creación, la enseñanza, la toma de decisiones y para tener una gran variedad y flexibilidad de comportamientos.

Las funciones cognitivas se mantienen intactas en la mayoría de las personas hasta los 60-70 años y luego empiezan un declive progresivo muy lento, difícil de medir, salvo que aparezcan trastornos metabólicos o enfermedades cerebrales específicas.(45, 46)

Los ancianos sin demencia pueden presentar alteraciones cognitivas leves básicamente de tres tipos:

Alteración de la memoria: El aspecto más afectado es la memoria episódica (recordar eventos específicos en tiempo y lugar), mientras la memoria remota (a largo plazo) está generalmente inalterada.

Alteración de la capacidad ejecutiva: Las funciones ejecutivas (razonamiento, planificación, anticipación de conductas, atención dirigida y mantenida, autosuficiencia y monitorización la propia conducta) son habilidades cognitivas complejas necesarias para realizar tareas complejas y adaptarse a los cambios en la tarea que pretendemos realizar. Su ejecución requiere de la integridad de varias regiones cerebrales: corteza prefrontal y frontal subcortical.(47)

Alteraciones en la rapidez del pensamiento, razonamiento y ejecución: Están relacionadas con la función ejecutiva. Un enlentecimiento generalizado a nivel motor, sensorial y cognitivo es

una de las características principales del envejecimiento. La rapidez con la que se piensa o realizan tareas puede estar relacionada con la demora en la propagación del impulso nervioso o con la integridad de las vías anatómicas.

Otras alteraciones cognitivas leves pueden aparecer en atención, aprendizaje, lenguaje, función visuoespacial y visuoconstructiva.

A.2.2. ESTUDIO DE LAS FUNCIONES COGNITIVAS. LA EXPLORACIÓN NEUROPSICOLÓGICA

La exploración neuropsicológica nos ayuda a sistematizar el estudio de las funciones cognitivas.

Previo a la aparición de las técnicas de imagen cerebral era una parte fundamental para establecer el diagnóstico de la enfermedad neurológica. En la actualidad se usa para el diagnóstico diferencial en patologías que muestran similares características clínicas y de neuroimagen como es el caso del deterioro cognitivo y las demencias, estudio de la topografía y extensión del proceso patológico y para sugerir medidas terapéuticas.

La exploración neuropsicológica se debe realizar con test cognitivos con base científica, con los que se puedan establecer un buen correlato cerebro-funcional y ser sensibles para el daño cerebral focal y difuso. Además deben estar bien traducidos al idioma del paciente y deben tener validez en la población a la que se aplican.

Es importante destacar aquí que deben existir unos datos normativos para una población con similares características al individuo que se pretende estudiar. Los datos normativos son los baremos de puntuación que obtuvieron los individuos con una función cognitiva normal de las mismas características que el sujeto de estudio (misma edad, mismo nivel educativo y/o mismo sexo). Dado que la obtención de datos normativos es un trabajo costoso en tiempo y dinero, los estudios normativos se han basado en pocas decenas o una centena de sujetos de

forma habitual. En los últimos años se han adaptado y validado numerosos test a la lengua castellana.(48)

A.3. DETERIORO COGNITIVO LIGERO (DCL) Y DEMENCIA

A.3.1. DEFINICIÓN Y EPIDEMIOLOGÍA DEL DCL Y LA DEMENCIA

La demencia es un síndrome clínico que se caracteriza por el declive o pérdida de múltiples funciones cognitivas, con frecuencia asociadas a alteraciones de la personalidad, de la afectividad o conductuales que llevan a la desadaptación social y a la pérdida de independencia del individuo.

El deterioro cognitivo ligero (DCL) es el estado transicional entre el envejecimiento cognitivo normal y la demencia inicial. Su prevalencia aumenta con la edad y se estima que es el doble que la de la demencia. Diferentes tipos de estudios mostraron que a partir de los 65 años el 10 al 20% de los individuos tienen DCL.(49)

La Demencia Vascular (DVa) ocupa el segundo puesto en el tipo de demencia más frecuente tras la demencia por Enfermedad de Alzheimer (EA) en los países occidentales desarrollados. En cambio en países orientales la DVa es la más frecuente. La prevalencia de DVa a partir de los 65 años se estimó 1.6% en Europa y de 6.4% para EA.(50) En EUA se estima que la prevalencia de DVa se dobla cada 5.3 años y que el DCL de causa vascular tiene una prevalencia similar a la de la DVa, estas cifras no se conocen con exactitud en Europa. Se estima que la demencia afectó a 36 millones de personas en 2010 (OMS).

En nuestro país las cifras son similares para los diferentes estudios, la EA es la primera causa de demencia (41.1-70%), la segunda es la DVa (14.3-41.1%) y el resto se deben a otros tipos de demencia primaria y secundaria.(51, 52) La prevalencia de DVa se situaría en torno al 1.2-1.8%.(52, 53)

Por otro lado la demencia fue por si sola la 6ª causa de muerte (4ª causa en la mujer) y una de las primeras causas de discapacidad en el adulto.(2) A demás, se calculó que en el 2010 había 608.011 afectados que tuvieron un gasto sanitario de 15.402 millones de euros, convirtiendo la

demencia en la enfermedad crónica del adulto con el mayor gasto sanitario por paciente y año (25.303 euros por enfermo). Por lo tanto retrasar o disminuir la aparición de esta enfermedad es un reto ineludible para los sistemas sanitarios.

A.3.2. DCL VASCULAR Y DEMENCIA VASCULAR

El *DCL vascular* sería el DCL que se produce antes de la DVa y se relaciona con la existencia de ictus y de lesiones cerebrovasculares subclínicas (básicamente con ICS, HSB). Se encuentra en la mitad de los pacientes con infarto lacunar, ya que este ictus es el que más predispone a DVa.(54, 55) Además, la aparición de nuevas lesiones vasculares se relaciona con el declive cognitivo y la demencia.

Los estudios epidemiológicos mostraron que aquellos participantes con patología vascular subcortical (infartos lacunares clínicos o silentes, HSB) tenían mayoritariamente déficits en funciones ejecutivas mientras la memoria estaba conservada. (55, 56) Los estudios clínicos han mostrado que los pacientes con DCL vascular tienen un deterioro cognitivo más amplio que puede incluir el déficit mnésico, especialmente en aquellos en que el ictus o ICS implica los lóbulos temporales o tálamos.(44, 57) Es cierto también que la mayoría de test neuropsicológicos que miden la memoria dependen del correcto funcionamiento de las funciones ejecutivas para llevarse a cabo. Por lo tanto, tener lesiones vasculares cerebrales y la exclusión de demencia son criterios más importantes que el dominio cognitivo afectado para el diagnóstico de DCL vascular.

Existen numerosas dificultades a la hora de interpretar la literatura científica en el campo de la DVa y el DCL vascular porque existen numerosos términos científicos, numerosas clasificaciones y muchos instrumentos para clasificar y medir esta heterogénea enfermedad. Las clasificaciones actuales son clasificaciones de consenso de expertos y tienen en común el síndrome cognitivo de demencia y la documentación de lesiones vasculares capaces de

producir dicha demencia. No obstante, el DCL vascular no se ha incluido de manera sistemática en las clasificaciones de DVa.

Los últimos criterios propuestos en 2011 por los expertos de la American Heart Association y la American Stroke Association salvan algunos de estos escollos. Clasifican el DCL de causa vascular en función de si hubo un ictus clínico que lo propició (DCL vascular probable) o no lo hubo pero existe patología cerebrovascular subclínica (DCL vascular posible).

A.3.2.1. Subtipos de demencia vascular

Los subtipos de demencia vascular se clasifican según sus FR, mecanismos patológicos, características clínicas o respuesta al tratamiento.

La *demencia post-infarto* es el prototipo de DVa. Normalmente los síntomas cognitivos que suceden en la fase aguda del ictus se recuperan, pero el 20% tendrán demencia tras los primeros meses post ictus. (58) El riesgo de demencia post-infarto será mayor para los de mayor edad, los que tengan pre-existencia de DCL, muestren HSB previas, atrofia global y temporal o hipoperfusión cortical.(59, 60) Puede ser el resultado de la acumulación de varios infartos de predominio cortical constituyendo la base para la demencia multi-infarto, puede estar causada por un infarto de localización estratégica (tálamo, giro angular, caudado, pálido, tronco basal o hipocampo) o puede deberse a un infarto isquémico o hemorrágico.

La *demencia mixta* se caracteriza por la presencia de características clínicas y neuropatológicas de DVa y de EA. En una población seleccionada de religiosas norteamericanas se mostró una relación de 1:20 para la demencia en aquellas con infarto lacunar y cambios tipo EA respecto las que no tenían infarto lacunar.(61) También en un estudio en la comunidad norteamericano se concluyó que la demencia más frecuente fue la demencia mixta, ya que el 57% de los participantes tenían patología de tipo EA en la histopatología y de estos más de la mitad

presentaban patología vascular cerebral.(62) Igualmente, los resultados en otras poblaciones fueron similares.

La *demencia vascular subcortical* está causada por ictus lacunares, ICS y HSB, es decir por lesiones de EPVC.(63, 64) El declive cognitivo se relaciona con tener un nuevo evento vascular, tener múltiples infartos y con la coexistencia de HSB, más aún si son periventriculares. (65, 66) Actualmente la EPVC es considerada la causa más frecuente de DVa y contribuye también como hemos comentado a la demencia mixta.(28)

El cuadro clínico habitual es un cuadro insidioso y lentamente progresivo en forma de DCL y demencia subcortical en pacientes con FRV (HTA, DM).(63, 67) Ver la **Figura 4** para el curso típico de la enfermedad.(67) Este cuadro podría ser el resultado de la interrupción de los circuitos paralelos que van de córtex prefrontal a ganglios de la base y de sus conexiones talamocorticales como consecuencia del ictus lacunar o la HSB. (63)

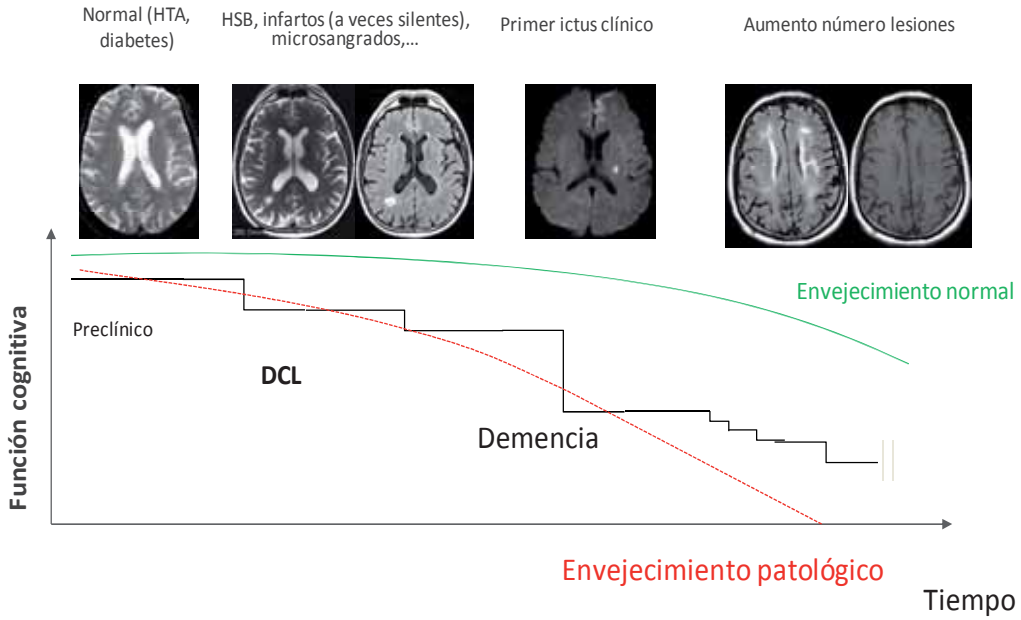


Figura 4: Curso evolutivo típico del deterioro cognitivo vascular subcortical.

Las manifestaciones clínicas de la DVa subcortical se caracterizan por bradipsiquia y bradicinesia, síndrome disejecutivo y déficits leves y no predominantes en la memoria de

evocación y aprendizaje. Además estos individuos suelen presentar síntomas psiquiátricos (depresión, irritabilidad, ansiedad, etc.) y conductuales (apatía, abulia, falta de iniciativa y de motivación),(68) déficits motores leves tipo alteración de la marcha, del equilibrio y de la frecuencia urinaria o incontinencia de curso temprano en la enfermedad.

A.3.3. DIAGNÓSTICO DEL DCL

La terminología con la que se identifican los sujetos que presentan DCL ha sufrido muchos cambios a lo largo de los años. Antes de los criterios diagnósticos que se utilizan en la actualidad, hubo diversos intentos de establecer unos criterios en base al proceso de envejecimiento cognitivo normal o patológico basándose en las quejas de memoria que presentaban los individuos. Krals y col. en 1962 fueron los primeros en hablar de las quejas de memoria benignas o malignas asociadas al envejecimiento. Después en EUA se propuso el término déficit de memoria asociado a la edad y en Canadá el término todavía en uso de deterioro cognitivo sin demencia.(69)

El término DCL fue acuñado más tarde por Reisberg para definir aquellos pacientes que se encontraban en estadio 3 de la Global Deterioration Scale (GDS). (70) Este estadio se refería a los individuos independientes pero que tenían déficits claros, p.ej. los compañeros de trabajo son conscientes de su declive en el rendimiento laboral o los familiares comentan un defecto evidente para evocar nombres de personas o cosas, en la exploración clínica es evidente un defecto de concentración o de memoria. Los síntomas causan ansiedad o los niegan.

Finalmente, en 1999 Petersen y col. definieron los criterios más usados para diagnosticar el DCL. Este se establece cuando existen quejas subjetivas de pérdida de memoria, preferiblemente corroboradas por un informador, con un rendimiento anormal (generalmente -1.5DE -Desviaciones Estándar- por debajo de lo esperable por su grupo normativo de edad y nivel educativo), con función cognitiva preservada por lo demás y sin tener empeoramiento en

las actividades de la vida diaria.(71) En 2004 un comité de expertos del International Working Group on Mild Cognitive Impairment formado por Winblad y el mismo Petersen hicieron una modificación de los criterios para dar cabida a diferentes tipos de deterioro. La diferencia básica entre los criterios previos y estos es la inclusión del deterioro cognitivo sin necesidad de que esté presente un déficit mnésico. Así, se definió como un estado cognitivo anormal que no cumple criterios de demencia y presenta un deterioro cognitivo según refieren el paciente o el familiar, respaldado por los test cognitivos o la evidencia de declive en test cognitivos objetivos y con preservación de las Actividades Básicas de la Vida Diaria (ABVD) aunque puede existir un déficit mínimo en las Actividades Instrumentales de la Vida Diaria (AIVD) complejas.(72) Estos criterios son ampliamente usados por grupos clínicos en la actualidad.

Diversos grupos de investigación han adaptado los criterios clínicos de Petersen y Winblad para su uso en estudios epidemiológicos. En la cohorte del CHS se consideró como test cognitivo fallido cuando el participante obtenía una puntuación de un test <-1.5 DE comparado con su grupo normativo ajustado por edad y escolaridad. Aquellos pacientes con dos tests mnésicos anormales fueron clasificados de *DCL de tipo amnésico* si presentaban un declive respecto evaluaciones previas. Y clasificaron *de DCL de tipo déficit cognitivo múltiple* aquellos participantes que tenían declive cognitivo en un dominio cognitivo no mnésico (dos test o más fallidos de un dominio que no sea memoria) o un test fallido en múltiples dominios no mnésicos (un test fallido en al menos dos dominios que no sea memoria) o fallos en AIVD, respecto el estado cognitivo previo. Los pacientes no tenían criterios de demencia, los déficits se mostraron en evaluaciones anuales e incluyeron participantes que mostraron defectos leves en las AIVD.

A demás, clasificaron el DCL según el grado de certeza diagnóstica y el tipo etiológico. El *DCL probable* lo formaba el grupo de pacientes que cumplía los criterios de DCL y a) los participantes y sus familias aquejaron los problemas cognitivos del participante y b) no había

enfermedades neurológicas, psiquiátricas o sistémicas concomitantes que explicaran los déficits cognitivos. El grupo de *DCL posible* estaba formado por los pacientes que cumplían los criterios de DCL y a) ni ellos ni sus familiares aquejaron quejas cognitivas o b) había otras enfermedades concomitantes que podrían explicar los déficits cognitivos o c) la evaluación fue incompleta (es decir, había menos de 5 evaluaciones neuropsicológicas con menos de 3 dominios evaluados siendo uno de ellos el dominio de memoria).(73) Estos criterios usados en el CHS han sido adaptados y utilizados posteriormente por un grupo clínico de nuestro país (Fundació ACE) para la evaluación de pacientes con DCL.(74)

Tabla 3: Criterios diagnóstico de DCL según diferentes autores y grupos.

Característica explorada	Criterios Winblad y Petersen	Criterios CHS	Criterios ACE
Quejas cognitivas	+	+/-	+/-
Test cognitivo alterado	+	+	+
AIVD levemente alteradas	+	+	+
Co-morbilidades	+/- (incluye enfermedad psiquiátrica, sistémica o neurológica concomitante)	+/- (incluye enfermedad psiquiátrica, sistémica o neurológica concomitante)	+/- (incluye ansiedad, depresión o ictus concomitante)
Declive cognitivo respecto evaluación cognitiva previa	+/-	+	+

+: tiene que estar presente. +/-: no es imprescindible que esté presente.

El estudio clínico del individuo con quejas cognitivas (p.ej. pérdida de la memoria, dificultad en sus quehaceres cotidianos o en sus relaciones con los otros, etc.) debe ser completo es decir, se deben tener en cuenta enfermedades neurológicas, psiquiátricas y otras (metabólicas, etc.) que pueden causar la sintomatología. Para la evaluación cognitiva en caso de deterioro cognitivo se deben escoger test neuropsicológicos que evalúen un amplio abanico de dominios cognitivos: memoria y aprendizaje, atención, fluencia verbal y lenguaje, función ejecutiva, función visuoespacial y visuoconstructiva.

A.3.4. CONVERSIÓN A DEMENCIA Y FISIOPATOLOGÍA DEL DCL

La conversión a demencia que puede suceder hasta en un tercio de los pacientes con DCL es la más temible de sus consecuencias. Se estimó que la conversión a demencia se sitúa en torno al 10-15% anual en clínicas especializadas y alrededor del 6-10% en los estudios epidemiológicos realizados en la comunidad.(49) El DCL también puede no evolucionar o revertir, lo último sucede en el 20-25% de los casos en estudios epidemiológicos a medida que mejora o se resuelve la causa que lo originó (p.ej. DCL asociado a trastornos del humor tipo depresión o DCL asociado a insuficiencia cardiaca).(75, 76)

El DCL amnésico generalmente convierte a EA, mientras el DCL amnésico o no amnésico multidominio puede evolucionar a DVa. (69) La gravedad del DCL es el factor clínico más destacado para el riesgo de conversión a demencia es decir, la gravedad del deterioro de la función cognitiva y también la presencia de alteración en las AIVD más complejas (control de las finanzas, realizar la compra, acudir a citas, conducir) predicen la conversión.(77)

La mayoría de predictores se han descrito para la evolución a la EA, la evolución a DVa se ha estudiado menos o se ha estudiado conjuntamente con el resto de demencias. Así los marcadores biológicos del LCR (niveles bajos de Aβ1-42, niveles elevados de tau y tau-fosforilada elevadas y la ratio Aβ1-42/tau baja), poseer un alelo o dos E4 en el gen ApoE o

tener una tomografía de emisión de positrones (PET) marcados con un radioligando de amiloide son los predictores más importantes para conversión a EA.(78)

La conversión a DVa se ha relacionado con el acúmulo de lesiones cerebrovasculares (ICS, ictus, HSB).(44) De hecho, tanto su número, localización como volumen de tejido afectado predicen el deterioro cognitivo.(65, 66) También la HSB periventricular se asoció a un posterior diagnóstico de EA.(79)

Desde el punto de vista histológico las lesiones cerebrovasculares se pueden entremezclar con las lesiones típicas de la EA (acúmulo de amiloide y acumulación de agregados intracelulares de proteína tau), lo cual sucede en el 25-50% de los casos.(80, 81) Podría existir una interacción y un efecto sinérgico entre las lesiones tipo EA y las lesiones cerebrovasculares ya que el depósito de amiloide en el vaso puede resultar en daño vascular (p.ej. provoca hemorragias) y la isquemia produce mayor acumulación de amiloide.(82) A nivel clínico se traduce en que el ictus aumenta el deterioro cognitivo en EA y se necesitan menos lesiones neurodegenerativas en los pacientes con deterioro cognitivo vascular para manifestar demencia.(80)

A.3.5. FACTORES DE RIESGO DE DCL

Los FRV no sólo se han visto implicados en el DCL vascular y la DVa sino que también están relacionados con la EA.(83) (84) Revisaremos aquí los FR que se han visto asociados con el DCL. Los estudios en DCL son comparativamente más escasos e incluyen muestras más pequeñas que los realizados en personas con demencia.

Los FR para el deterioro cognitivo son similares y van en la misma dirección que los FR explicados para el ictus, por lo tanto los resumiremos a continuación.

La fisiopatología del DCL en ocasiones refleja los mismos mecanismos que producen el ictus, p.ej. los ictus y los ICS producidos por la fibrilación auricular pueden causar secundariamente deterioro cognitivo. En el caso de otros FR la relación no se explica de una forma tan directa.

Igual que en el ictus, para el deterioro cognitivo vascular conocemos una serie de FR no modificables (edad, sexo, raza, factores genéticos) y otros modificables (el resto).

A.3.5.1. Factores no modificables

La *edad* hace que aumente la incidencia y prevalencia de DCL, sucede lo mismo para DVa y EA.(84)

Respecto al *sexo* los resultados no son consistentes, aunque hay algunos estudios que muestran una mayor predilección del DCL por el sexo masculino.(73, 85)

La *raza afroamericana* tiene más prevalencia de DCL según el estudio multiétnico CHS.(86) No obstante, esta cuestión no se ha valorado en la mayoría de estudios.

Entre los *factores genéticos* está bien descrita la conversión a demencia tipo EA de aquellos individuos con alelos E4 del gen de la ApoE.(78) Para la progresión a DVa no hay factores genéticos bien descritos.

A.3.5.2. Factores modificables

La baja *educación* se ha asociado a DCL en la mayoría de estudios pero no en todos.(85, 87)

La *hipertensión* es el FRV más estudiado.(88, 89) (90) Sobretodo la hipertensión sistólica en edades medias de la vida se ha relacionado con el DCL y la demencia posteriores.(91, 92) En cambio, en personas de edad avanzada es la hipotensión, especialmente la hipotensión sistólica, la que se relacionó con el deterioro cognitivo y la demencia.(84, 92)

Se creyó que el control de la PA y tratamiento de la HTA podría disminuir la incidencia de demencia. No obstante los ECA con anti-hipertensivos no han confirmado suficientemente la hipótesis de que lograr un mejor control de las cifras de PA mejore la función cognitiva.

Cuatro ECA con diferentes clases de hipotensores reportaron que no había un efecto sobre la función cognitiva o la demencia.(93-96) Otro presentó un efecto beneficioso con un inhibidor de los canales de calcio (nitrendipino vs. tratamiento estándar) sobre el riesgo de demencia (la mayoría EA) en 32 casos incidentes de demencia. Posteriormente, en la fase abierta del estudio, con casi 4 años de seguimiento y 64 casos incidentes, se confirmó el resultado y aquellos que habían recibido nitrendipino tenían menor riesgo de demencia (HR=0.38, IC 95% 0.23,0.64), incluyendo demencia mixta y DVa.(97)

Estos ECA han tenido diversas críticas metodológicas (seguimiento corto, escaso número de casos incidentes de demencia, diferente metodología de estudio de la función cognitiva, etc.) que hacen que los resultados se tengan que interpretar con cautela. También debido a estas limitaciones los diversos meta-análisis tienen alta heterogeneidad, los resultados no son robustos y han arrojado una reducción no significativa del 11 al 20% para demencia para los hipotensores. (84) Cuando se estratificó estos ECA en función de las clases de hipotensores, se mostró que la incidencia de demencia era menor en aquellos en que se consiguen menores cifras de presión arterial (diuréticos o un inhibidores de los canales de calcio dihidropiridínico).(98)

No obstante, la asociación entre HTA y déficits cognitivos específicos no es tan robusta como lo encontrado respecto a la enfermedad cerebrovascular. Es probable que la reserva cognitiva cerebral explique en parte la compensación funcional que presentan los hipertensos, pero la explicación es incompleta. Probablemente entre los hipertensos habrá un grupo de mayor riesgo de disfunción cerebral, podrían ser aquellos con más HSB, en los cuales la progresión de

las HSB se ha mostrado más acelerada, y en los que el tratamiento de la HTA ha sido más beneficioso como se mostró en el grupo de tratamiento del ECA PROGRESS.(99)

La *rigidez arterial* se ha relacionado con una peor función cognitiva, DCL y con la aparición de demencia en algunos estudios.(100) Resulta de la pérdida progresiva de elastina y el aumento de colágeno en la pared del vaso junto con otros cambios (que originan arterioesclerosis).(101) Está estrechamente relacionada con la presión arterial (PA) y se puede medir de manera indirecta en las arterias centrales (Aorta, carótidas) y arterias periféricas de las extremidades.

Se considera un predictor independiente de infarto cerebral (102) y también puede tener un papel en la EPVC.(103, 104) La rigidez arterial causa microangiopatía de los pequeños vasos cerebrales, la cual favorecería la hipoperfusión y la aparición de HSB, que podrán estar relacionadas con la pérdida de determinadas funciones cognitivas y finalmente con el deterioro cognitivo.(63, 105)

La *hiperglucemia, la resistencia a la insulina, el síndrome metabólico y la diabetes* se han asociado con una peor función cognitiva.(84) No obstante, la hipoglucemia recurrente también se ha asociado a deterioro cognitivo permanente. La diabetes se asoció con un mayor riesgo de DCL y también de DVa y EA.(85, 106)

La *hipercolesterolemia* en edades medias de la vida es un predictor de DCL (también de DVa y EA).(107) En cambio, en edades avanzadas los resultados son contradictorios, tanto la hipercolesterolemia como la hipocolesterolemia (que marca un mal estado nutricional) se asociaron a la demencia.

No obstante, el tratamiento con estatinas ha producido resultados contradictorios en cuanto a la preservación o deterioro de la función cognitiva en los estudios observacionales, el cual podría atribuirse al efecto generacional (el tratamiento con estatinas en gente actualmente

anciana fue menor que en gente de mediana edad). Los ECA tampoco mostraron diferencias significativas entre los grupos en tratamiento con estatinas y los grupos no tratados.(108, 109)

La *obesidad* también se ha relacionado con el DCL cuando se midió con el índice cintura-cadera.(85, 110) De manera similar a otros FRV, un elevado IMC mostró relación con el deterioro cognitivo en edades medias de la vida mientras en edades tardías fue el bajo IMC el que se relacionó con el deterioro cognitivo, la EA y la DVa.(111, 112)

El consumo excesivo de *alcohol* se ha relacionado con el DCL aunque el consumo moderado podría tener un efecto protector.(90) Un estudio en la comunidad mostró como la relación con el DCL tiene una forma de "U" (es decir, el riesgo fue el doble para los que eran abstemios o los de mayor consumo respecto los de consumo moderado).(113)

El *tabaquismo* se ha relacionado con el declive cognitivo de determinadas funciones cognitivas y la aparición de demencia, pero con el DCL los resultados son escasos y no consistentes.(84, 114)

Existe alguna evidencia de que la *dieta* de tipo Mediterráneo puede ser un factor protector para DCL y conversión a EA.(115)

La *actividad física* ha mostrado en diferentes estudios que es beneficiosa para evitar el declive cognitivo y la DVa. La frecuencia y el tipo de actividad física no están establecidos.(84)

La *depresión* está también asociada al DCL.(116, 117) En población general, la asociación entre síntomas depresivos y DVa es controvertida, en cambio en series clínicas se observó que los individuos con depresión de inicio en el adulto tienen más HSB.(118) Algunos síntomas de la depresión pueden revertir con tratamiento y entonces la cognición mejora.(119)

A.3.6. PREVENCIÓN DEL DETERIORO COGNITIVO VASCULAR

Las últimas guías sobre deterioro cognitivo vascular establecen las siguientes medidas preventivas:(84)

En edades medianas de la vida disminuir los niveles de presión arterial previenen la aparición de demencia en el futuro (clase IIa, nivel B).

La dieta mediterránea y el ejercicio físico podrían disminuir el deterioro cognitivo (clase IIb, nivel B).

La efectividad de tratar la hiperglicemia/diabetes y la dislipemia para evitar la demencia no están bien establecidas (clase IIb, nivel C)

B. OBJETIVOS

1) Diseñar un estudio observacional en hipertensos para investigar cuál es la prevalencia de lesiones vasculares cerebrales silentes y de Deterioro Cognitivo Ligero en nuestro medio.

2) Definir la prevalencia de lesiones cerebrovasculares silentes (infarto cerebral silente y espacios perivascular dilatados) en hipertensos españoles, sus factores de riesgo vascular, localización y su relación con la afectación de órgano diana de la hipertensión.

3) Estudiar la prevalencia de los infartos corticales pequeños, su localización y factores de riesgo y su relación con la función cognitiva en población general.

4) Diseñar y describir un protocolo de estudio para la evaluación cognitiva de una población española hipertensa.

5) Definir la prevalencia de Deterioro Cognitivo Ligero, sus factores de riesgo asociados y su relación con las lesiones cerebrovasculares silentes.

6) Estudiar la relación de la rigidez arterial con la función cognitiva y el Deterioro Cognitivo Ligero en hipertensos.

C. METODOLOGIA

En este apartado se describirá brevemente la metodología de las dos poblaciones de estudio que forman parte de esta Tesis Doctoral.

C.1. METODOLOGÍA DEL ESTUDIO ISSYS (Investigating Silent Strokes in hYpertensives, a magnetic resonance imaging Study)

C.1.1. OBJETIVOS GENERALES DEL ESTUDIO ISSYS

Los objetivos generales del estudio ISSYS son estudiar la prevalencia e incidencia de las lesiones cerebrovasculares silentes (especialmente el infarto cerebral silente) y del deterioro cognitivo en la población hipertensa de Barcelona.

Para lograr estos objetivos se realizó una estimación del tamaño de la muestra necesario para obtener un 10% de infartos cerebrales silentes con un intervalo de confianza del 95% y una precisión del 2% (n=865). Se decidió incluir un 20% más de pacientes para no perder potencia estadística a causa de la potencial pérdida de participantes, alcanzándose un tamaño muestral final de 1037 sujetos.

C.1.2. DISEÑO DEL ESTUDIO ISSYS

Esta Tesis describe los resultados obtenidos en el corte transversal de este estudio observacional realizado en individuos hipertensos entre 50 y 70 años de edad, sin antecedentes de ictus o demencia provenientes de los centros de atención primaria que dependen de nuestro Hospital terciario. El área sanitaria corresponde al área Norte de la ciudad de Barcelona (SAP Muntanya) donde se contabilizan 27000 pacientes con HTA en edades comprendidas entre 50 y 70 años. Para la selección de los participantes del estudio, se suministró a los médicos de familia de 14 Centros de Atención Primaria listados con sus pacientes elegidos tras muestreo aleatorio y estratificados por prevalencia de HTA según edad

y sexo. Dichos profesionales realizaron una selección mediante revisión de historia clínica de aquellos que cumplían los criterios de inclusión y exclusión del estudio.

La **Figura 5** muestra la situación geográfica de los Centros de Atención Primaria.

Figura 5: Mapa de la zona norte de Barcelona donde se indican los centros de Atención Primaria participantes en el estudio ISSYS.

Los pacientes seleccionados fueron invitados a participar en el estudio por vía telefónica. En la visita presencial se comprobó si los pacientes cumplían los criterios de inclusión y no de exclusión. La **Figura 6** muestra la selección de los pacientes del estudio ISSYS.

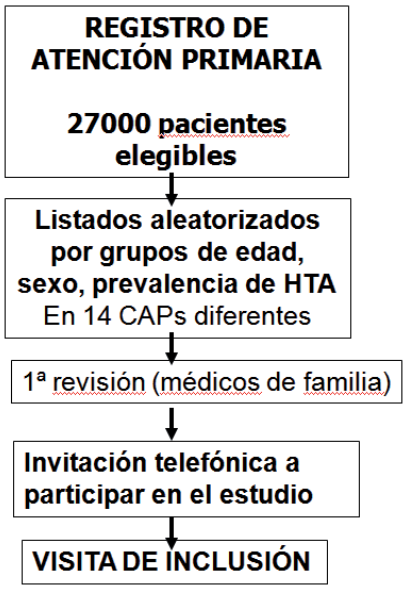


Figura 6: Diagrama de la selección de los participantes del estudio ISSYS.

Los *criterios de inclusión* fueron:

- ✓ Edad entre 50 y 70 años.
- ✓ Tener HTA esencial diagnosticada al menos desde hace un año.
- ✓ Firmar el consentimiento informado.

Los *criterios de exclusión* fueron:

- ✓ Tener un ictus o demencia previos.
- ✓ Tener contraindicación para realizarse una Resonancia Magnética cerebral.
- ✓ Existir sospecha de síndrome de bata blanca.
- ✓ Tener una neoplasia u otra enfermedad concomitante que limite la esperanza de vida a corto plazo.

C.1.3. VISITA BASAL DEL ESTUDIO ISSYS

La visita basal del estudio constó básicamente de una recogida de datos clínicos incluyendo antecedentes de enfermedades vasculares y otras, recogida de fármacos y cumplimiento

terapéutico, medición de presión arterial y variables antropométricas, un estudio vascular periférico de rigidez arterial, monitorización de la presión arterial ambulatoria, evaluación cognitiva y Resonancia Magnética cerebral (RM). Además se recogieron fluidos orgánicos (sangre, orina) para el estudio de biomarcadores.

En el apartado de resultados de esta tesis se presenta el protocolo general del estudio ISSYS, con la descripción detallada de todos los procedimientos.

C.1.4. EVALUACIÓN COGNITIVA EN EL ESTUDIO ISSYS

En la primera visita y como evaluación de cribado cognitivo se usó una adaptación al castellano del test Dementia Rating Scale-2 (DRS-2).

La DRS-2 es un test dividido en 5 subtest (que evalúan atención, memoria, iniciación/perseveración, construcción y conceptualización), cuya puntuación total va de 0 a 144 puntos. Los datos obtenidos en la DRS-2 se transformaron a puntuaciones escalares ajustadas por edad y escolaridad según un método de normalización propuesto por el grupo de investigación MOANS (Mayo Older American Normative Study). Los resultados de la normalización de los datos de la DRS-2 en castellano forman parte de los resultados de esta tesis doctoral.

Una puntuación ajustada por edad y escolaridad ≤ a 8 puntos escalares es sugestiva de la presencia de deterioro cognitivo.(120) En el estudio ISSYS, estos pacientes fueron invitados nuevamente a una visita cognitiva en la que se pretendía asignar el diagnóstico de DCL o envejecimiento cognitivo normal (ECN).

En esta segunda visita cognitiva, se realizó una evaluación por parte de una neuróloga la cual realizó una anamnesis dirigida a quejas cognitivas y de comportamiento, se administró un test de ABVD i AIVD, un test de depresión y se realizó una exploración física y neurológica estándar. Además una neuropsicóloga les administró una batería cognitiva que estudió los dominios de

memoria y atención, función ejecutiva, función visuoespacial, lenguaje y fluencia verbal y praxias. Se puede ver el nombre de los test y las funciones que evalúan en la **Tabla 4**.

En el apartado de resultados de esta tesis se describen de forma detallada el protocolo cognitivo del estudio.

C.1.5. CRITERIOS DIAGNÓSTICOS DE DCL

Como se comentó en el capítulo introductorio, los diferentes grupos de investigación han modificado los criterios clínicos de DCL para adaptarlos al contexto de los estudios epidemiológicos. En nuestro caso adaptamos los criterios de Petersen-Winblad y del CHS de forma similar a como lo hizo un grupo clínico de la Fundación ACE.(73, 74)

Así, clasificamos los pacientes en función de que tuvieran unos resultados normales o anormales en los test cognitivos elegidos (ver **Tabla 4** para los test cognitivos usados) y consideramos que un dominio estaba alterado cuando obtuvieron malos resultados en 2 o más test de ese dominio (generalmente, la puntuación obtenida en cada uno de los test era ≤ -1.5 DE de su grupo normativo).

Se clasificó como DCL a aquellos sujetos que tenían alterados uno o más dominios cognitivos y tenían quejas cognitivas del mismo/s dominio/s expresadas por ellos o el familiar y no tenían una enfermedad concomitante que pudiera explicar el cuadro clínico. También fueron clasificados de DCL aquellos que tenían alteración en uno o más dominios y a) no tenían quejas consistentes con el dominio/s afectos o b) existía una enfermedad psiquiátrica (depresión o ansiedad) concomitante. Estos dos grupos equivalen al DCL Probable (el primero) y al DCL posible (el segundo) de los criterios del CHS y la Fundación ACE. No obstante los análisis no se muestran por subgrupos al ser ambos de pequeño tamaño.

C.1.6. RM CEREBRAL EN EL ESTUDIO ISSYS

Se practicó una RM cerebral a todos los participantes del estudio ISSYS, excepto a aquellos que presentaron contraindicaciones para la técnica (mayoritariamente claustrofobia o tener piezas de metal desconocidas previamente). Finalmente 976 individuos tuvieron RM válidas.

La RM se realizó para todos los pacientes en el mismo resonador en el mismo centro externo. Las características de la RM se explican en los resultados del estudio.

Se definió los ICS como lesiones de tamaño ≥ 3mm, con las mismas características que el LCR en las diferentes secuencias y con un halo hiperintenso de gliosis alrededor de la lesión en la secuencia FLAIR.

Los EPVD fueron definidos como lesiones de < 3mm, bien delineadas, ovales o lineales dependiendo de la localización, en ganglios de la base (aunque las lesiones en la parte baja de los ganglios de la base fueron descartadas por su difícil diagnóstico diferencial con los ICS) y centro semioval y con las mismas características de señal en RM que el LCR, sin halo de gliosis. Se contaron el número de espacios por localización entre 0 y 40 y se consideró el número de espacios en el lado con más lesiones.(37) Después se clasificaron los EPVD en las dos localizaciones en EPVD extensos si había más de 10 lesiones y no extensos si había ≤ 10.(121)

Las HSB se clasificaron con la escala de Fazekas que ha sido utilizada en múltiples estudios. (122) Se definieron como lesiones hiperintensas en T2 localizadas en la sustancia blanca profunda o periventricular. También se clasificaron en las diferentes localizaciones como lesiones extensas cuando tenían grado ≥ 2 (a nivel profundo se refiere a tener lesiones confluentes y a nivel periventricular equivale a tener lesiones que se extienden hacia las áreas profundas) y no extensas cuando tenían grado 0 o 1.

C.1.7. ESTUDIO DE LA RIGIDEZ ARTERIAL EN EL ESTUDIO ISSYS

La rigidez arterial se estudió en la *clínica* con las mediciones de la Presión de Pulso (PP) y la velocidad de la onda de pulso carótido-femoral y de manera *ambulatoria* con la medición de la

PP durante 24 horas y en los periodos de día, noche y 24 horas. Se usaron aparatos oscilométricos para la adquisición de las medidas.

Para la medición de la PP clínica se usó el mismo aparato de medición de la PA (OMRON M6 confort) en todos los pacientes, las mediciones de PA se hicieron después de estar al menos 5 minutos en reposo. La PP se calculó como la diferencia entre la PAS y PAD medias de las 3 últimas determinaciones. Para la PP ambulatoria se usaron aparatos de medición de la PA ambulatoria (Spacelabs 90217-5Q) con registro de 24 horas. Se calculó la PP de 24 horas, nocturna y diurna realizando la resta de la PAS media-PAD media para cada periodo. Para medir la velocidad de la onda de pulso carótido-femoral se usó un aparato automático (VICORDER) en posición supina. Se situaron dos manguitos superficiales uno a nivel de la arteria carótida derecha (medía la onda de pulso carotideo) y otro a nivel de la arteria femoral derecha (medía la onda de pulso femoral) y se midió la distancia entre la escotadura yugular y el centro del manguito femoral (como se indica en la **Figura 7**). Se hincharon los manguitos por encima de 60 mm Hg y se obtuvieron al menos 10 latidos simultáneos. El aparato usa un algoritmo para calcular la velocidad de la onda de pulso en base a la distancia introducida y el tiempo de tránsito de la onda.

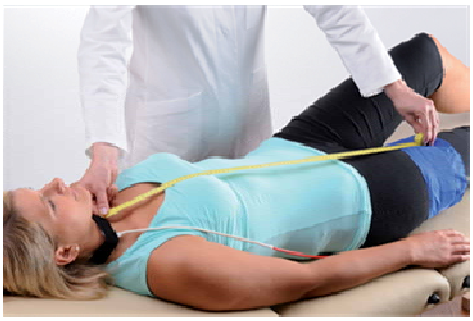


Figura 7: Posición de los manguitos carotideo y femoral y medición de la distancia entre ellos para la evaluación de la velocidad de la onda de pulso carótido-femoral.

Tomada de http://www.smt-medical.com/en/products/vicordercardio-and-peripher-vascular-testing.html

C.2. METODOLOGÍA DEL ESTUDIO ROTTERDAM

C.2.1. DISEÑO DEL ESTUDIO ROTTERDAM. OBJETIVOS GENERALES

Es un estudio poblacional prospectivo que se inició en una cohorte de 7.983 individuos (78% de los invitados) mayores de 55 años (sin límite de edad superior) y que vivían en el distrito Ommoord de la ciudad de Rotterdam (Países Bajos). Después de un estudio piloto en 1989, al siguiente año empezó el reclutamiento del estudio Rotterdam. El estudio se amplió con más participantes en dos ocasiones: en el año 2000 con 3.011 participantes de las mismas características que la cohorte original y en 2006 se amplió con 3.932 participantes de 45-54 años del mismo distrito. Finalmente, 14.926 individuos fueron incluidos en el estudio con una tasa de respuesta global del 72% (de 20.744 invitados, 14.926 aceptaron).(123) La **Figura 8** muestra las diferentes cohortes y sus visitas en orden cronológico.

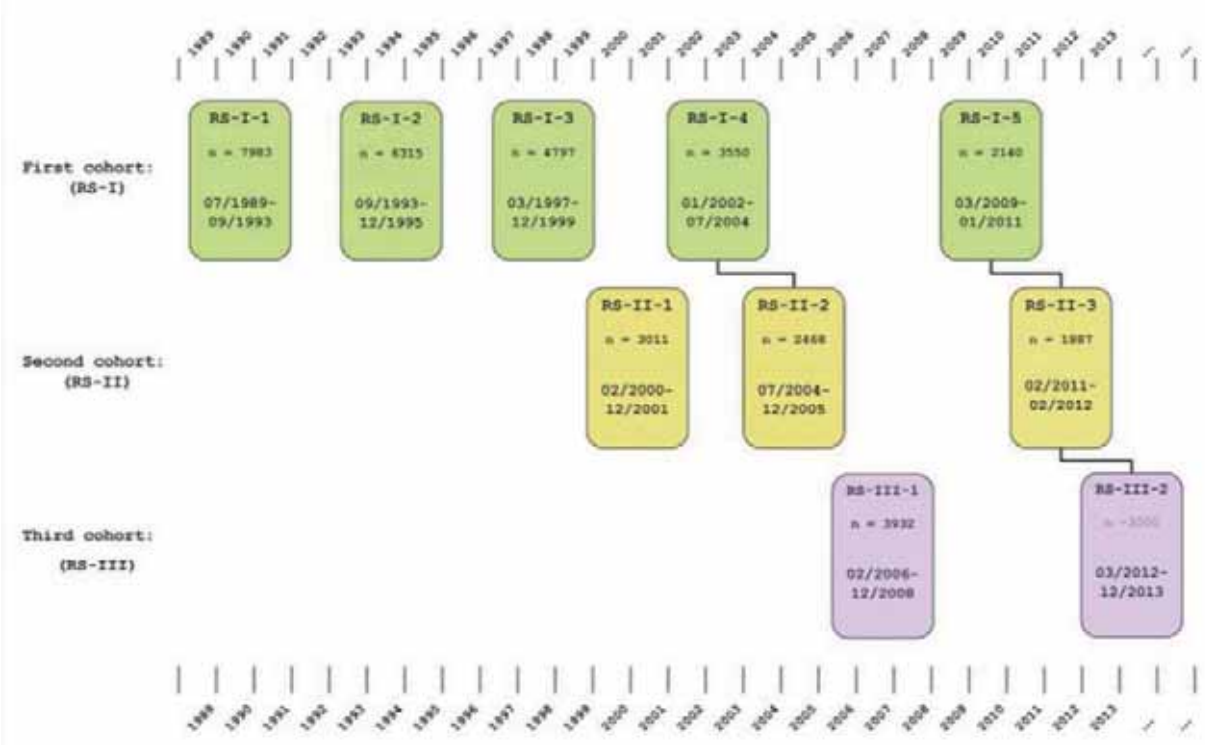


Figura 8: Diagrama de las cohortes y visitas realizadas en el estudio Rotterdam. Tomada de Hofman et al., 2014.(123)

Los objetivos principales del estudio son estudiar las principales enfermedades y estados clínicos asociados al envejecimiento siguiendo técnicas actuales. El énfasis sobre todo se puso en estudiar con técnicas de imagen el envejecimiento de corazón, vasos sanguíneos, esqueleto y después el encéfalo y recoger fluidos corporales para estudiar biomarcadores moleculares y genéticos. Los participantes acuden cada 3-4 años al centro especialmente diseñado para el estudio para realizar las visitas.

Los objetivos de la parte de neurología del estudio son averiguar la frecuencia, etiología y el reconocimiento temprano de las enfermedades más frecuentes en el envejecimiento (demencia tipo EA y enfermedad de Parkinson, ictus isquémico y hemorrágico) y recientemente estudiar la polineuropatía y la migraña. Además tienen un interés especial en el estudio de las causas y las consecuencias de la enfermedad neurológica preclínica. Los estudios no son invasivos y consisten en test neuropsicológicos, RM cerebral, estudio del equilibrio y electromiograma.

C.2.2. ESTUDIO DE LA FUNCIÓN COGNITIVA Y DE RM CEREBRAL EN EL ESTUDIO ROTTERDAM

La función cognitiva global se estudió en todas las visitas con el Mini Mental State Examination (MMSE).(124)

Desde la tercera visita de la cohorte original (año 1997) se incluyeron diferentes test para estudiar con mayor detalle la función ejecutiva y memoria: Test de Stroop, Tarea de sustitución de letras y dígitos (en inglés, Letter Digit Substitution Task –LDST-), un test de fluencia verbal (Word Fluency Test -WFT-) y un Test de aprendizaje de listado de 15 palabras (Word Learning Test –WLT-). A partir de la cuarta visita de la cohorte original (año 2002) se amplió la batería neuropsicológica con la inclusión del estudio de la función motora con el test de Purdue (Purdue Pegboard Test) y a partir de la quinta visita (año 2009) se añadió el Design Orientation Test para estudiar la orientación visuoespacial.(123) En la **Tabla 4** se comparan las

funciones cognitivas exploradas y los test neuropsicológicos usados en los estudios Rotterdam y ISSYS.

Aquellos individuos con MMSE<26 o con Geriatric Mental Schedule>0 se les realiza un estudio de deterioro cognitivo más completo que incluye el Cambridge Examination of Mental Disorders y la entrevista con el informador. Un grupo de consenso realiza finalmente el diagnóstico de demencia.

La RM cerebral empezó a realizarse en dos grupos elegidos al azar en 1991 (en 111 individuos para el estudio de HSB) y en 1995 (en 563 individuos no dementes). Desde la segunda visita de la primera expansión de la cohorte en 2005 todos los participantes son evaluados por RM en cada visita.

El resonador tiene 1.5 Teslas y no se han hecho ampliaciones de hardware/software durante el tiempo del estudio. Se obtienen secuencias potenciadas en T1, T2, densidad protónica (DP), FLAIR, T2* (o ECO GRAD), difusión (DWI), etc. y más recientemente tensor de difusión (DTI) sin espacio entre los cortes.(123)

Se definió el infarto cortical como lesiones de la sustancia gris supratentorial, hipointensas en T1, hiperintensas DP y con un halo de gliosis alrededor en FLAIR. Se consideraron en base a su tamaño medio como lesiones grandes si tenían un diámetro de pérdida de tejido > 15 mm y pequeñas si ≤ 15 mm.

Tabla 4: Funciones cognitivas estudiadas y test empleados en el estudio ISSYS y en el estudio Rotterdam.

Función Cognitiva	**ISSYS**	**Estudio Rotterdam**
Global	DRS-2	MMSE *Cambridge Examination of Mental Disorders
Función ejecutiva (atención, lenguaje, inhibición de la respuesta, velocidad de procesamiento)	*Test de Fluencia Verbal *Test de colores y palabras de Stroop *Test de fluencia categorial fonética (COWAT) *Test del trazo (Trial making Test)	Test de Fluencia Verbal Test de colores y palabras de Stroop Tarea de sustitución de letras y dígitos
Función motora Praxias	*Gesto simbólico del test Barcelona *Imitación de posturas y secuencias del test Barcelona	Test de Purdue Pegboard
Memoria	*Test de aprendizaje audio-verbal de Rey *Reproducción visual I y II de la Weschler Memory Scale	Test de aprendizaje de listado de 15 palabras
Visuoespacial y perceptiva	Test de copia y dibujo del reloj Test del diseño de cubos del WAIS III	Design Orientation Test

* Test administrado en aquellos individuos en los que se sospecha deterioro cognitivo.

C.3. ANÁLISIS ESTADÍSTICOS

En la estadística descriptiva se analizó la normalidad de las variables continuas con el test de Kolmogorov-Smirnov y se expresaron las variables categóricas en números y porcentajes y las continuas en media y DE o mediana y rango intercuartílico dependiendo de su distribución. En los análisis univariantes, las diferencias intergrupos para datos categóricos se analizaron con $\chi 2$ o test exacto y para variables continuas con test *t*, *ANOVA*, Mann-Whitney *U* o Kruskal-Wallis. La correlación entre datos continuos se analizó con el test de Pearson o de Spearman dependiendo de su distribución.

En los análisis multivariantes se usaron regresiones lineales cuando la variable respuesta era continua y regresiones logísticas cuando la variable era dicotómica. Se usaron regresiones multinomiales cuando la variable respuesta fue categórica ordinal y análisis de covarianza cuando la variable repuesta fue continua y los predictores categóricos y continuos. Como covariables se usaron aquellas variables que habían mostrado significación estadística con la variable respuesta y/o variables extraídas de la literatura que habían mostrado relación con la variable respuesta.

Los valores de $p<0.05$ se consideraron estadísticamente significativos. Los análisis se realizaron usando el paquete estadístico SPSS versiones 15, 17 y 19.

D. RESULTADOS. COPIA DE LAS PUBLICACIONES

D.1 Investigating silent strokes in hypertensives: a magnetic resonance imaging study (ISSYS): rationale and protocol design. BMC Neurol. 2013 Oct 2;13:130.

BMC Neurology

STUDY PROTOCOL Open Access

Investigating silent strokes in hypertensives: a magnetic resonance imaging study (ISSYS): rationale and protocol design

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Abstract

Background: Silent brain infarcts are detected by neuroimaging in up to 20% of asymptomatic patients based on population studies. They are five times more frequent than stroke in general population, and increase significantly both with advancing age and hypertension. Moreover, they are independently associated with the risk of future stroke and cognitive decline.

Despite these numbers and the clinical consequences of silent brain infarcts, their prevalence in Mediterranean populations is not well known and their role as predictors of future cerebrovascular and cardiovascular events in hypertensive remains to be determined.

ISSYS (Investigating Silent Strokes in Hypertensives: a magnetic resonance imaging study) is an observational cross-sectional and longitudinal study aimed to: 1- determine the prevalence of silent cerebrovascular infarcts in a large cohort of 1000 hypertensives and to study their associated factors and 2-to study their relationship with the risk of future stroke and cognitive decline.

Methods/Design: Cohort study in a randomly selected sample of 1000 participants, hypertensive aged 50 to 70 years old, with no history of previous stroke or dementia.

On baseline all participants will undergo a brain MRI to determine the presence of brain infarcts and other cerebrovascular lesions (brain microbleeds, white matter changes and enlarged perivascular spaces) and will be also tested to determine other than brain organ damage (heart-left ventricular hypertrophy, kidney-urine albumin to creatinine ratio, vessels-pulse wave velocity, ankle brachial index), in order to establish the contribution of other subclinical conditions to the risk of further vascular events. Several sub-studies assessing the role of 24 hour ambulatory BP monitoring and plasma or genetic biomarkers will be performed.

Follow-up will last for at least 3 years, to assess the rate of further stroke/transient ischemic attack, other cardiovascular events and cognitive decline, and their predictors.

Discussion: Improving the knowledge on the frequency and determinants of these lesions in our setting might help in the future to optimize treatments or establish new preventive strategies to minimize clinical and socioeconomic consequences of stroke and cognitive decline.

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Background

Hypertension is the most important modifiable vascular risk factor for stroke and it is commonly widespread in the aging population.

For a long time, treatment for hypertension has been focused on blood pressure (BP) levels as the main measure to determine the need and type of treatment. This approach has changed over the past years, emphasizing that diagnosis and treatment should be based on the quantification of global cardiovascular risk. According to the European guidelines on hypertension [1], common variables used to stratify risk are based on the presence of vascular risk factors (family history of premature cardiovascular disease, smoking habits, glucose and lipid parameters) plus further identification of clinical or subclinical target organ damage. Hypertension-related disease in several organs might indicate progression and markedly increase the risk beyond that caused by the BP levels or risk factors presence.

Since evidences advise for different goals of treatment in high risk individuals as compared with lower risk hypertensives [1], whenever possible, it is recommended to measure target organ damage in different tissues (i.e. heart, blood vessels, kidney and brain) because multiorgan damage is associated with worse prognosis [2]. Many different markers have been already described, such as electrocardiographic/echocardiographic markers, intima media thickness, pulse wave velocity as a marker of arterial stiffness or markers of endothelial dysfunction, among others, that can be useful identifying target organ damage. The main limitations are of course, costs and availability of diagnostic procedures and particularly for subclinical conditions, there is still limited knowledge on their predictive capacity for risk evaluation.

Regarding brain as hypertension target organ, subclinical or "silent" vascular brain lesions (i.e. infarcts, microbleeds, white matter changes) are often detected by neuroimaging in asymptomatic patients. Specifically, silent brain infarcts are five times more frequent than stroke in general population, and increase significantly both with advancing age and hypertension [3]. The term "silent" might not be entirely appropriate since these lesions could be often associated with unnoticed or subtle symptoms in patients that never asked for an evaluation, making impossible a diagnosis of stroke. The prognosis associated with these "silent" infarcts is not favourable at all, and their presence independently predicts further stroke and cognitive decline [4,5]. For all these reasons, silent brain infarcts have been recently included in the AHA Updated definition of stroke, thus emphasizing their clinical relevance [6]. This will have important consequences in public health, as it is expected to largely increase stroke prevalence. Moreover, their detection might have the potential to improve the selection of patients at higher risk for future stroke and cardiovascular events, who might benefit from more aggressive preventive treatments.

Hypertension has been related not only to the presence of silent vascular brain lesions but to the appearance of new lesions on follow-up, which can occur in up to 40%, considering progression of white matter changes [7]. Interestingly, this effect on progression is much more relevant at younger or midlife patients than later on [7,8]. Therefore, preventive strategies should pay much more attention to younger subjects, who are likely to have long term exposure to an increased risk in the following years [1].

Studies focusing on hypertensive participants have been performed, and reported a prevalence of silent brain infarcts that ranges from 20 to 86% of subjects aged 40 to 88 years old. Of note, most of these studies have included mainly Japanese populations, whereas data on Mediterranean Caucasian populations is still limited [7].

With this background, the ISSYS is designed as a cross-sectional and longitudinal study aimed to: (1) investigate the prevalence of silent cerebrovascular lesions, as signatures of brain organ damage, in a cohort of middle and advanced aged (50–70 years old) caucasian Mediterranian hypertensives and (2) to study their relationship with the risk of future stroke and cognitive decline.

Methods/Design

ISSYS (Investigating Silent Strokes in Hypertensives: a magnetic resonance imaging study) is an observational cross-sectional and longitudinal study aimed to determine the prevalence of silent cerebrovascular lesions in a large cohort of hypertensives and to study their associated factors.

On baseline all participants will be also tested to determine other than brain (vascular, kidney, heart) organ damage, in order to establish the contribution of other subclinical conditions to global vascular risk.

Follow-up is planned to last for at least 3 years, to assess the rate of further Stroke/TIA and cardiovascular events as well as cognitive impairment, and their predictors.

Subject selection

The basic design of ISSYS is a cohort study among 87000 persons aged 50 to 70 years old and living in the district of the north metropolitan area of Barcelona (SAP Muntanya). This site was chosen for several reasons. First, in the Primary Healthcare system there is a computer-based registry for all patients in this area who mainly attend these services rather than other private options. Second, the study is coordinated between the Primary HealthCare services in this area and the researchers from Research Institute and Vall d'Hebron

Hospital, which is the public health tertiary reference centre for this area.

The study is carried out in patients diagnosed of essential hypertension who are routinely attended by general practitioners. According to the registry, around 27000 participants could be eligible for the study, since they are hypertensives and stroke-free and have been randomized after stratification by age, gender and prevalence of hypertension covering all the area.

After randomization, patients have been invited by phone to participate in the study and scheduled for a baseline evaluation at their own Primary Care centre.

Estimated sample size will be 1000 participants, who will be enrolled during 18 months and then participants will be followed-up, for at least three years.

The study protocol has been approved by the Ethics Committee of Vall d'Hebron Hospital and IDIAP Jordi Gol (University Research Institute in Primary Care).

Baseline visit and procedures

Inclusion and exclusion criteria

At inclusion visit, fulfilment of inclusion and exclusion criteria is re-assessed by investigators. Briefly, inclusion criteria consists on: 1)Patients with essential hypertension diagnosed at least one year earlier; 2) Age comprised between 50 and 70 years; 3) Patients who give their consent to participate in the study.

Patients are excluded when: 1) they have history of previous stroke or dementia; 2) Brain MRI is contraindicated; 3) there is a suspicion of white coat hypertension syndrome or 4) patients affected by a terminal illness preventing future follow-up examinations, based on the investigator criteria.

A particular effort is made to rule out the presence of a previous stroke, and for that purpose investigators are trained and an adaptation of the Stroke Symptom Questionnaire by Berger K and collaborators is used [9].

Likewise, when a suspicion of dementia appears, following DSM-IV-R criteria [10] the patient is not included in the study and a proper evaluation in the presence of a caregiver is therefore recommended.

Clinical data collection

All procedures for baseline and follow-up visits are summarized in Figure 1.

After inclusion, the participant is asked about demographical and personal medical history. Briefly, demographical information includes age, gender, ethnicity, current or former occupation, and the maximum educational level (or completed years of schooling) achieved by the patient.

Regarding medical history, the participant is asked about the duration of hypertension, the presence of other vascular risk factors such as diabetes mellitus, hyperlipidemia, alcohol intake (grams per week), smoking habit (current, former, never) and family history of premature vascular disease and dementia in first grade relatives.

Also a directed questioning is performed to assess for the existence of an established cardiovascular, kidney or systemic disease, together with the history of retinal abnormalities or the presence of a sleep apnea syndrome.

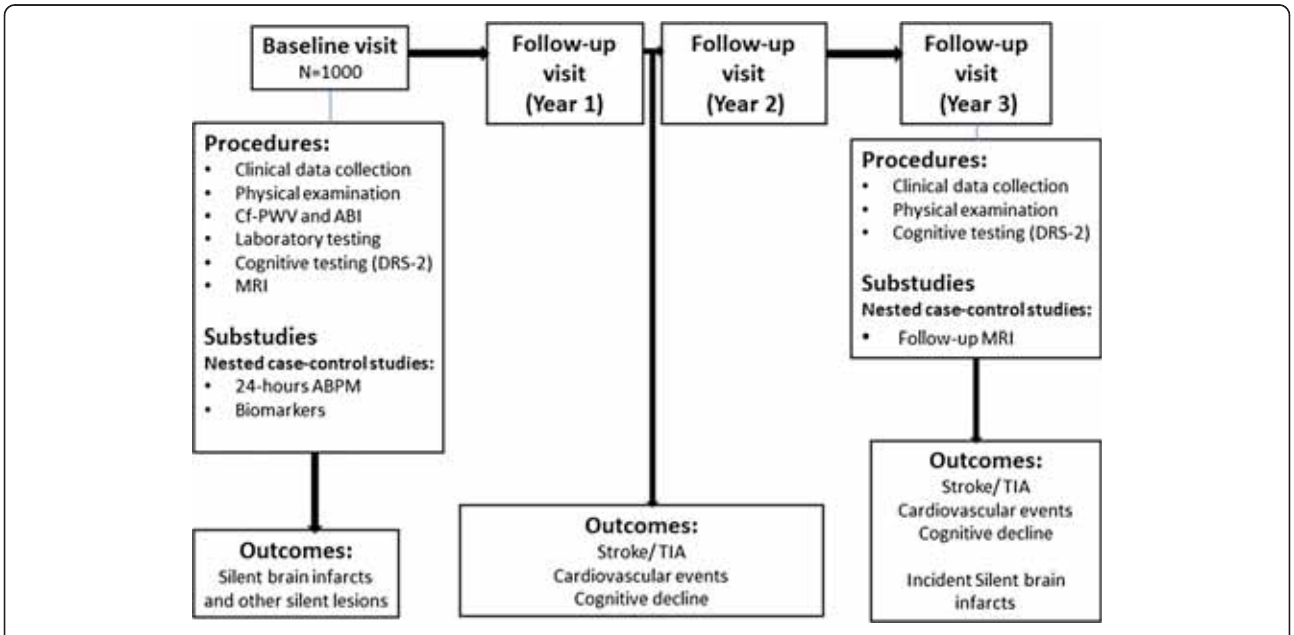

Figure 1 ISSYS procedures and outcomes for baseline and follow-up visits.

Global vascular risk is calculated applying the SCORE risk charts and Framingham-calibrated REGICOR function when appropriate [11,12].

Data concerning ambulatory and home blood pressure, home medication and treatment adherence is collected. To evaluate treatment adherence, the validated questionnaire published by Morisky and collaborators [13] is used. Briefly, this scale was developed to assess treatment compliance in hypertension and currently is used in many other chronic conditions. It consists in 4 questions, with yes/no answers which should be asked along the clinical interview, and reflect the patient's attitude towards treatment. It is useful to find out whether or not the patient is a good complier and the causes for non-adherence.

Finally, the clinical interview ends with two self-administered questionnaires assessing life-style habits (physical activity and diet). Physical activity is evaluated by means of the International Physical Activity Questionnaire (IPAQ) [14] and dietetic habits are evaluated with a short questionnaire on frequency of dietary intake [15].

Physical examination and vascular testing

Regarding physical examination, some measures are taken and recorded such as height, weight, waist circumference and BP (mean of the last two out of three measurements after five minutes rest).

Plus, a standard 12-lead ECG is performed to assess for signs of left ventricular hypertrophy (single measurement of R wave in aVL [16]) and heart rhythm disorders.

Afterwards, vascular testing is performed with the Vicorder™ device (Skidmore Medical Ltd, Bristol, UK). The Vicorder™ is small, portable, non-invasive and non-operator dependent device suited for use in community based studies [17]. This system provides two BP measurement channels and two Photoplethysmography (PPG) channels for the measurement of blood flow.

Briefly, two measurements are taken for each patient: carotid-femoral pulse wave velocity (cf-PWV) and the ankle-brachial index (ABI).

Cf-PWV is measured as the best approximation of aortic pulse wave velocity (aPWV), a marker of arterial stiffness. For the measurement, the patient should be resting in a supine position, with the head and shoulders raised by about 30 degrees allowing venous return from the brain and avoiding signal contamination by the Jugular vein. A neck-pad should be placed at the lower centre part of the Right Common Carotid Artery as tightened as possible without discomforting the patient. A distal BP cuff should be located on the ipsilateral upper thigh, as high to the groin as possible. The neck-pad and thigh cuff are inflated by the Vicorder to 60 mmHg and then deflated to obtain a pressure tracing. Cf-PWV is calculated by the Vicorder by comparing carotid and femoral pressure tracings after a stable pattern is obtained. Then, cf-PWV is defined as the ratio of the distance between the carotid and the thigh position and the time it takes for the pulse wave to travel from the proximal to the distal locations. For anatomical reasons, the distance between suprasternal notch and the centre of femoral cuff is chosen as the best estimation of the distance between the two arterial sites.

ABI is measured according to the current guidelines of the American Heart Association for each side as the ratio of the highest systolic BP of each ankle and the highest systolic BP of both upper limbs [18]. The lowest of the right and left ABI values will be used.

In this case, systolic BP is determined by PPG, and as it has been previously described [19]. PPG is a fast and accurate technique and can be considered a good alternative to Doppler ABI measurement. Both sides can be examined simultaneously. Briefly, a cuff is placed around the limb of interest and a PPG signal is obtained distal to the cuff. Then, the cuff is inflated to a pre-defined target pressure and afterwards the cuff will automatically bleed pressure and the PPG signal reappears when the systolic BP is reached.

Cognitive assessment

On baseline, all patients will be evaluated by means of the Dementia Rating Scale-2 developed by Mattis, which is a screening tool for dementia and mild cognitive impairment. Our complete cognitive assessment protocol on baseline and follow-up has been published in detail previously [20].

Laboratory testing

A blood sample will be drawn after overnight fast where the basic hematology (hemoglobine, leukocyte and platelet count) and biochemistry profile (glucose, total cholesterol, creatinine, sodium, potassium and liver function) are determined. Also, plasma and serum will be obtained on baseline visit after 15 minutes centrifugation (3500 rpm) and frozen at −80°C for future biomarker determination. DNA and RNA will be also obtained and stored for further studies.

Finally, a urine sample will be collected and sent to central laboratory for albumin to creatinine ratio (UACR) determination.

Neuroimaging protocol

A brain MRI with a pre-stablish data acquisition protocol (Table 1) will be performed within the next month after study entry. All examinations will be performed with the same 1.5 Tesla MR (Signa HDx 1.5, General Electrics, Waukeska, WI). MR will include axial and sagittal T1 weighted images. Midline sagittal images will be used to identify the anterior-posterior commissure

Table 1 MRI parameters in the ISSYS

Sequence	Mode	Time	TR/TE	TI	Number of slices	Slice thickness/gap (mm)	FOV	Matrix
Localizer	3D							
SE SAG T1-w	2D	3:06	400/10		20	5/1.5	256	256x224
SE AX T1-w	2D	2:58	520/10		24	5/1.0	256	256x224
Propeller AX T2-w	2D	2:40	5500/125		20	5/1.5	256	448
AX FLAIR	2D	3:20	10000/120	2200	20	5/1.5	256	320x192
AX GRE	2D	1:55	675/18		20	5/1.5	256	288x224

SE Spin Echo, *SAG* Sagital, *AX* Axial, *Propeller* Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction, *FLAIR* Fluid Liquid Attenuated Inversion Recovery, *GRE* Gradient Echo, *TR* Repetition Time, *TE* Echo Time, *FOV* field of view, Matrix (Frequency x Phase).

line, along which all oblique axial images are aligned. Also, Axial Propeller T2-weighted images, axial fluid-attenuated inversion recovery (FLAIR) and axial GRE images will be obtained. Images will be displayed on workstations monitors to be evaluated by trained readers blinded to patients' characteristics. All images will be primarily assessed by two neuroradiologists and in a second term by the same readers plus an experienced stroke neurologist. Intra and inter-reader concordance will be provided for all lesions of interest and disagreements in assessment will be solved by consensus.

Silent brain infarcts will be defined as previously [21] as lesions of ≥ 3 mm in diameter in their widest dimension, with cerebrospinal fluid signal characteristics in all pulse sequences, and with a hyperintense rim surrounding the lesion in FLAIR images. A particular effort will be made to differentiate these cavitated lacunes from large dilated perivascular spaces for lesions >3 mm, based on location criteria. Lesions located in areas with high prevalence of enlarged perivascular spaces, such as the lower third of basal ganglia will not be considered as infarcts. Anatomical localization for infarcts will be recorded as cortical, subcortical, basal ganglia, brainstem and cerebellum and number of lesions will be counted in case of multiple lesions.

An additional analysis will be performed for lacunar infarcts, defined as those of minimum 3 mm diameter and maximum 20 mm, located at the basal ganglia, internal capsules, thalamus, deep cerebral white matter and brainstem. An infarct located in the cortex, even if it reaches the subcortex will be recorded as cortical.

White matter hyperintensities will be rated according to the Age-related white matter changes (ARWMC) scale developed by Wahlund and col [22] that assesses presence and severity of white matter changes in the frontal, parietooccipital, temporal, basal ganglia and infratentorial areas separately in each hemisphere, ranging from 0 to 30 points.

Enlarged perivascular spaces (EPVs) or Virchow-Robin spaces will be defined as small (<3 mm), sharply delineated structures of cerebrospinal fluid (CSF) intensity following the course of perforating vessels and will be rated in T2-weighted images at the centrum semiovale, basal ganglia and midbrain following the scale reported by Doubal and collaborators [23]. Briefly, for basal ganglia and centrum semiovale, the rating will be as follows: 0: Absent; 1: Mild (from 1 to 10 EPVs); 2: Moderate (from 11 to 20 EPVs); 3: Frequent (from 21 to 40 EPVs); 4: Severe (more than 40 EPVs). For midbrain a rating of 0 will be considered when no EPVs is visible, and a rating of 1 when they are visible. For rating purposes, both hemispheres will be considered separately and the highest score of them will be chosen.

The presence of brain microbleeds, together with their number and location will be recorded following the Brain Observer Microbleed Scale (BOMBS) scale developed by Cordonnier and collaborators [24].

Representative MRI images for the lesions of interest are shown at Figure 2.

Follow-up visits

The participants will be contacted yearly by phone, one and two years after the inclusion visit. They will be asked about BP control, appearance of new vascular risk factors, and the presence of stroke/TIA or new vascular events. In case of any event has occurred, this will be verified by checking clinical records from their family doctors and hospital records. Participants will also be asked about medical treatment adherence using the same questionnaire performed at baseline and treatment adverse events.

Finally, three years after inclusion a new visit is planned by the investigator's team at the primary care center where the patient belongs, when data relative to new medical history and physical examination (blood pressure, height and weight and waist circumference measurement) will be collected, together with a new cognitive assessment with the Dementia Rating Scale-2.

Preventive treatments during follow-up

After baseline visit is completed and MRI is performed, primary care physicians will receive a summary with the most relevant results for each participant. Family doctors

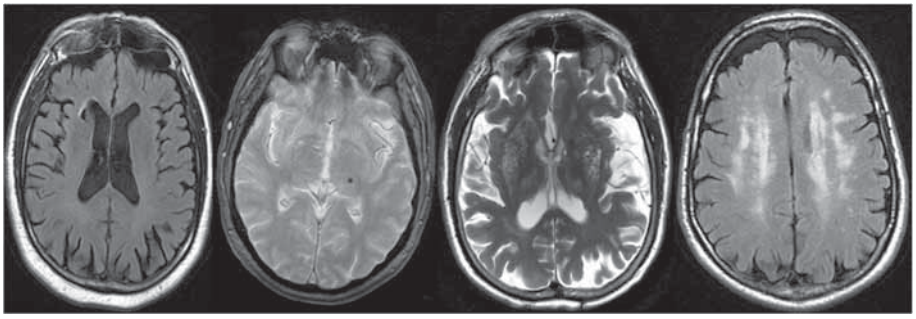

Figure 2 Representative examples of subclinical/silent cerebrovascular lesions. From left to right: Brain infarct affecting caudate nuclei (FLAIR MRI), brain microbleed in left thalamus (GRE MRI), enlarged perivascular spaces involving basal ganglia (T2 MRI) and extensive white matter changes (FLAIR MRI).

will take care of vascular risk factor control, following their routine practice. As for silent brain infarcts, since at present there is no clear evidence of whether a secondary stroke prevention should be applied to these patients and until new information comes from randomized clinical trials, recommendations will be to optimize BP control in all cases as much as possible and considering start antiplatelet treatment and/or cholesterol-lowering drugs in cases with the estimated global vascular risk is high (≥10 score in the Framingham-calibrated REGICOR function) [1].

Study outcome

The primary outcomes of this study are the determination of the prevalence of silent brain infarctions and other silent lesions (as described in the neuroimaging protocol) and the presence and time to first-ever stroke (fatal or non-fatal ischemic or hemorrhagic stroke) or TIA. Stroke will be defined clinically as a focal neurological deficit thought of vascular origin, lasting more than 24 hours and confirmed by clinical evaluation and the use of a brain CT scan or MRI. TIA will be defined according to the classical definition, as an acute focal neurologic deficit due to cerebral ischemia that resolves completely within 24 hours, regardless of neuroimaging findings.

Other cardiovascular events will be analysed as secondary events: coronary events (myocardial infarction, angina requiring hospitalization, coronary angioplasty or surgery); cardiac failure requiring admission to hospital; vascular complications (lower limbs, aorta or carotid arteries) requiring revascularization and vascular death.

Finally, cognitive decline will be evaluated as secondary end-point during follow-up.

Substudies (case–control studies nested in the ISSYS cohort)

Twenty-four hour ambulatory blood pressure monitoring (ABPM)

A nested case–control study within the ISSYS cohort will be performed with 24-hour ambulatory BP monitoring. Cases will be considered as participants in whom silent brain infarctions are detected versus controls (participants with no brain infarctions). Cases will be matched with controls by age, gender, other vascular risk factors and antihypertensive treatment in a ratio of 1 to 2/ 1 to 3.

Oscillometric ABPM measurements will be obtained using a Spacelabs 90217-5Q device (Spacelabs Healthcare, Issaquah, Washington, USA), validated according to the protocol of the British Hypertension Society [25]. The BP measurements will be made every 20 minutes during daytime and every 30 minutes during sleeptime in a day of standard activity and with a cuff suited to the size of the patient's arm. All recordings with at least 70% of valid readings or at least 45 measurements will be considered for the analysis.

Daytime ambulatory hypertension will be defined as a mean daytime BP ≥ 135/85 mmHg and sleeptime ambulatory hypertension as a mean BP ≥ 120/70 mmHg, according to the ESH Guidelines(1).

Circadian BP patterns will be assessed, considering a nondipping status as a night to day ratio of mean systolic blood pressure (SBP) of 0.9 or more. Also the sleep-through morning surge defined as the morning BP (2-hour average of four 30-minute BP readings just after wake-up) minus the lowest nocturnal BP (1-hour average of the 3 BP readings centered on the lowest nighttime reading) will be calculated [26].

Biomarkers determination

Also, substudies on protein and genetic biomarkers will be performed following the same strategy of a case–control study nested in this cohort.

Follow-up neuroimaging studies

A follow-up MRI is planned after the third year of follow-up for a nested cohort of cases and controls according to the presence of silent infarcts at baseline. This will allow us to describe the incidence of new lesions.

Data entry and monitoring

Data will be collected by investigators and supporting staff and transferred to an electronic case report form (eCRF) on a weekly basis. No personal data enabling the identification of the participants will be included in the eCRF. Previous training is warranted for all investigators before access to the live database. Data are secured from external violation by limiting access to the computer system by individual user name and password protection.

In order to minimize missing or wrong data, external monitoring for the main outcome variables is planned, including clinical and radiological variables for at least 10% of randomly selected participants.

Statistical methods

Sample size calculation representative for our population concerning prevalence of silent infarcts has been estimated using data of population-based studies published before, which reported specific data on silent brain infarcts prevalence in participants aged 50 to 70 years old [27-30]. According to them, the expected prevalence should be about 10%. Therefore, after applying the Ene 2.0 software, with a confidence interval of 95% and an accuracy of 2%, sample size should be of at least 865 individuals, which was increased to 1000 individuals by taking into account possible losses.

Statistical analysis will be performed with the SPSS 15.0 statistical package (Chicago, Ill., USA). Statistical significance for intergroup differences will be assessed by the χ^2 or Fisher's exact test for categorical variables and by the T-test, ANOVA, Mann–Whitney U and Kruskal-Wallis test for continuous variables. The correlations between continuous variables will be determined with Spearman's or Pearson's coefficients, as appropriate. A p value <0.05 will be considered significant. Logistic regression models will be performed to identify potential predictors of silent brain infarcts and other silent lesions. Finally, Cox proportional hazards multivariate analysis will be used to identify clinical predictors of stroke/TIA or further CVE, adjusted by variables showing p values <0.1 on univariate testing. Results will be shown as OR or HR, as appropriate, with their corresponding 95% confidence intervals.

Discussion

Silent brain infarcts have been recently included into the new definition of stroke, given that their high prevalence and clinical consequences, such as further strokes and cognitive decline do not support to treat them as innocent findings anymore.

Although it is known that silent infarcts are associated with age and vascular risk factors, particularly hypertension, there is limited information on the prevalence of this condition in our setting. Studies restricted to hipertensives participants have been performed mainly in Asian populations and they are mostly cross-sectional, with no prospective follow-up to address either the incidence of new lesions on imaging or the presence of future strokes or cognitive decline.

ISSYS is designed to investigate both the prevalence of silent brain infarcts and the incidence of strokes, cognitive decline and appearance of new brain infarcts after three years of follow-up in a cohort of 1000 Mediterranian hypertensives.

Moreover, we will study the risk factors associated with their presence and the relationship between them and other hypertensive target organ damage, such as those occurring in heart, kidney or vessels, in order to know their single and combined contribution to the global vascular risk in each patient.

Hopefully, the better knowledge on the frequency and determinants of these lesions will help in the future to optimize treatments or establish new preventive strategies to minimize clinical and socioeconomic consequences of stroke and dementia.

Consent

Written informed consent was obtained from the patient for the publication of this report and any acompanying images.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

I R-L has drafted the first version of this manuscript and contributed to design, will carry out baseline visits and will participate in analysis and interpretation. CJ will carry out baseline visits and coordination with Primary Healthcare. XM and FO contributed to protocol design, randomization and selection of participants and coordination with Primary Healthcare. JT has participated in the design and provided expertise in ambulatory BP monitoring substudies. A L-R and JL F contributed to neuroimaging protocol design and will carry out MRI imaging readings. CN and I F-C have participated in the subjects' enrolment and will perform phone follow-up visits and cognitive testing. XC has contributed to design of vascular studies and will participate in baseline visits. MD has contributed to acquisition and interpretation of electrocardiographic studies and will participate in baseline visits. J A-S and OM have contributed to design and coordination with other hospital departments. JM is the director of the Neurovascular Research Lab and has contributed to conception, design, revised critically this article for intellectual content and will provide support for the study development. PD has conceived and designed the study and is the principal investigator. All authors have read and approved the final manuscript.

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D.2 Prevalence and associated factors of silent brain infarcts in a Mediterranean cohort of hypertensives. Hypertension. 2014 Sep;64(3):658-63.

Prevalence and Associated Factors of Silent Brain Infarcts in a Mediterranean Cohort of Hypertensives

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Abstract—Silent brain infarcts (SBIs) are detected by neuroimaging in approximately 20% of elderly patients in population-based studies. Limited evidence is available for hypertensives at low cardiovascular risk countries. Investigating Silent Strokes in Hypertensives: a Magnetic Resonance Imaging Study (ISSYS) is aimed to assess the prevalence and risk factors of SBIs in a hypertensive Mediterranean population. This is a cohort study in randomly selected hypertensives, aged 50 to 70 years old, and free of clinical stroke and dementia. On baseline, all participants underwent a brain magnetic resonance imaging to assess prevalence and location of silent infarcts, and data on vascular risk factors, comorbidities, and the presence of subclinical cardiorenal damage (left ventricular hypertrophy and microalbuminuria) were collected. Multivariate analyses were performed to determine SBIs associated factors. A total of 976 patients (49.4% men, mean age 64 years) were enrolled, and 163 SBIs were detected in 99 participants (prevalence 10.1%; 95% CI, 8.4%–12.2%), most of them (64.4%) located in the basal ganglia and subcortical white matter. After adjustment, besides age and sex, microalbuminuria and increasing total cardiovascular risk (assessed by the Framingham-calibrated for Spanish population risk function) were independently associated with SBIs. Male sex increased the odds of having SBIs in 2.5 as compared with females. Our results highlight the importance of considering both global risk assessment and sex differences in hypertension and may be useful to design future preventive interventions of stroke and dementia. **(*Hypertension*. 2014;64:658-663.)** • **Online Data Supplement**

Key Words: hypertension ■ stroke

Although a large amount of data are available on the prevalence of silent brain infarcts (SBIs) in the general population and of their role as independent predictors for future stroke and dementia, still further studies are needed to determine their frequency in various populations, particularly those at high risk. This information may be potentially useful to design further studies for prevention of stroke and dementia.[1] Besides age, hypertension is the risk factor most consistently associated with SBIs. Remarkably, in most of these studies, the diagnosis of hypertension was based on self report from participants or on single measurements of blood pressure (BP). Also, some studies have been conducted specifically in selected groups of essential hypertensives and described a wide SBIs prevalence ranging from 20% to 86%. Several factors may be related to this large variation in prevalence. Among all studies, nearly half of them included few participants, and from those with larger sample size (Table 1),[2–17] it should be noted that patients with hypertension were mainly selected among those who attended specialized units (cardiology, internal medicine, kidney departments, etc) at hospitals and were probably more representative of newly diagnosed or more severe or resistant forms of hypertension than average.

Moreover, the vast majority of studies have been conducted in Asian cohorts, which indeed differ from western countries about their distribution of vascular risk factors and stroke incidence.[18] A few studies have been conducted in European countries, such as those from 1 group in The Netherlands which described prevalences of SBIs ranging from 22% to 29%.[4,5,19] Because some of them included ambulatory BP monitoring, only patients in whom treatment could be removed before monitoring were enrolled.

Even less information is available for lower cardiovascular and stroke risk populations, such as those living at Mediterranean areas.[20] To our knowledge, 1 group from Italy[16] reported a prevalence of asymptomatic brain damage in 54.9% hypertensive individuals. However, they included not only lacunes and territorial

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Table 1. Other Published Studies Describing Silent Brain Infarcts in Hypertensive Cohorts

Authors	Country	Sample Size	Patient Selection	Sex, % Male	Age	Office BP	SBI %	Previous Antihypertensive Treatment
Kwon et al[2]	Korea	550	Voluntary health check	68.2	59.3 (25–83)	Control, 136/91 SBI, 141/90	11.1	Previous treatment in 79% of the controls and 85% SBI patients
Kato et al[3]	Japan	100	Selected from outpatient office (cardiovascular and renal medicine)	66	62 (42–81)	NA	24	Treatment for ≥1 mo prior inclusion
Henskens et al[4,5]	The Netherlands	192	Referral to internal medicine department	49	51.6 (20–83)	170/104	29 (23–36)	Nontreated patients
Kario et al[6–15]	Japan	519	Patients coming from 2 hospitals, 3 clinics, and 1 outpatient clinic	40	72 (≥50)	164/90	50	58% of those with sustained HTN (removed for ABPM)
Selvetella et al[16]	Italy	195	Patients who visited the department of angio-cardio-neurology	44.1	SBD, 67±1 No SBD, 54±1	Control, 140/86 SBI, 147/85	54.9	90% were treated with anti-hypertensive drugs
Ma et al[17]	China	188	Retrospective analyses from hospital records	42.5	64 (45–75)	NA	59	All treated (monotherapy)

Only studies with a minimum sample size of 100 participants are shown. Studies are sorted by increasing silent brain infarcts (SBIs) prevalence. Office BP is expressed in mm Hg. Age is expressed as mean±SD or mean (range) as it was provided by the authors. ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; HTN, hypertension; NA, not available; and SBD, silent brain damage.

lesions but also other punctate lesions (>5 mm) that might not be infarcts in all cases. Also in Spain, Sierra et al[21] performed a study in middle-aged hypertensives, in which they found that white matter lesions (also manifestations of subclinical brain damage) were a common finding (40.9%). However, lesions appearing as lacunar infarcts were not assessed in their study.

The differentiation of SBIs from other similar lesions, such as enlarged perivascular spaces, has been done poorly in the past,[22] and more efforts are needed to overcome the lack of consistency and advance in this field.[23]

With all that in mind, we aimed to determine the prevalence of SBIs in a large cohort of randomly selected hypertensives in a Mediterranean population and to study their associated risk factors.

Methods

Subjects Selection

Investigating Silent Strokes in Hypertensives: a Magnetic Resonance Imaging Study (ISSYS) is an observational, cross-sectional, and longitudinal study aimed to determine the prevalence of SBIs and their relationship with future stroke and dementia in a large cohort of Mediterranean hypertensives.[24]

Briefly, this study has been carried out in patients aged 50 to 70 years and diagnosed of essential hypertension who are routinely attended by general practitioners in our health area.

Participants were randomly selected after stratification by age and sex among 27 000 potentially eligible subjects living in the district of the north metropolitan area of Barcelona. They were invited by phone to participate and a visit was then scheduled where fulfillment of inclusion and exclusion criteria was assessed by trained investigators. Inclusion criteria consisted of (1) patients with essential hypertension diagnosed ≥1 year earlier; (2) age comprised between 50 and 70 years, and (3) patients who gave their informed consent to participate. Patients were excluded when (1) they had history of previous clinical stroke or dementia, (2) brain magnetic resonance imaging (MRI) was contraindicated, (3) there was a suspicion of white coat hypertension syndrome, or (4) patients were affected by a terminal illness preventing any future follow-up examination, based on the investigator criteria.

To rule out the presence of a previous stroke, medical records were reviewed and the patient was interviewed following an adaptation of the Stroke Symptom Questionnaire.[25] Also, when dementia was suspected, following *Diagnostic and Statistical Manual of Mental Disorders, fourth edition*, revised (*DSM-IV-R*) criteria, the patient was not included in the study and a proper evaluation in the presence of a caregiver was recommended.[26]

Enrollment visits were conducted between November 2010 and May 2012. Among 1037 participants who were initially enrolled in this study, 94.1% (n=976) completed all baseline procedures, including a brain MRI scan. The remaining participants were excluded as a result of claustrophobia (n=17), presence of a cranial metallic artifact (n=8), consent withdrawal (n=33), and lost to follow-up before MRI was performed (n=3). Excluded patients were more often men, overweighted, and diabetic than those who were finally included.

Clinical Data Collection and Physical Examination

The study protocol was approved by the Ethics Committee of Vall d'Hebron Hospital and IDIAP Jordi Gol (University Research Institute in Primary Care).

Assessment of all covariates was done by interviewing participants and reviewing medical records. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of antihypertensive medication. We obtained data on demographical characteristics and personal medical history, including duration of hypertension and presence of other vascular risk factors, such as smoking habit, alcohol abuse, dyslipidemia, and diabetes mellitus. The presence of a previous cardiovascular, kidney, or systemic disease was also assessed. For those participants without previous vascular disease, global vascular risk was estimated applying the Framingham-calibrated Registre Gironí del Cor (REGICOR) function, and participants were divided into the following categories depending on their 10-year estimated risk of having a coronary event: low risk (<5%), moderate risk (5%–9.9%), high risk (10%–14.9%), and very high risk (≥15%).[20]

Data concerning office and home BP, BP control (optimal/ poor), and antihypertensive treatment were collected, and treatment compliance was assessed with the Moriski questionnaire.[27]

Also weight, height, and waist circumference were measured, and abdominal obesity was recorded.[28] Office BP was measured with an oscillometric device (Omron M6 Comfort), and the mean of the last 2 of 3 determinations after 5-minute rest was recorded.

A detailed description of all covariates is presented in the online-only Data Supplement (Expanded Materials and Methods).

Several other well-known hypertensive target organ damage (TOD) markers, such as the presence of left ventricular hypertrophy or renal dysfunction (microalbuminuria and decreased estimated glomerular filtration rate [GFR]), were analyzed. Specifically, a standard 12-lead ECG was performed to assess for signs of left ventricular hypertrophy (single measurement of R wave in aVL [augmented vector left])[29] and heart rhythm disorders. Regarding kidney function, a single-spot urine sample was collected and sent to central laboratory for albumin-to-creatinine ratio determination. Microalbuminuria was determined as >21 mg/g in men and >30 in women.[28] Moreover, GFR was estimated with the Modified Diet in Renal Disease-Isotope Dilution Mass Spectrometry formula.[30] Impaired renal function was considered whenever values were below 60 mL/min per 1.73 m^2.

Neuroimaging Protocol

A brain MRI was performed within the next month after study entry. Data acquisition details have been published elsewhere.[24] SBIs were defined as in previous studies as lesions of ≥3 mm of diameter in their widest dimension, with cerebrospinal-like fluid signal characteristics in all pulse sequences, and the presence of an hyperintense rim surrounding the lesion in fluid attenuation inversion recovery sequence was also required.[22] All MRIs were assessed by 2 neuroradiologists and an experienced stroke neurologist, and disagreements were solved by consensus. Intrarater agreement was calculated for each reader in a training set before undertaking the present reading, ranging from 0.60 to 0.75. The main source of disagreements came from the differentiation of SBIs from enlarged perivascular spaces; therefore, lesions located in areas with high prevalence of enlarged perivascular spaces, such as the lower part of basal ganglia, were not considered as infarcts.

Statistical Methods

Sample size calculation representative for our population concerning prevalence of SBIs was estimated using data from population-based studies published before, which reported specific data on SBIs prevalence in participants aged 50 to 70 years old.[24] According to them, the expected prevalence should be ≈10%. Therefore, after applying the Ene 3.0 free software (GlaxoSmithKline S.A., Spain; http://sct.uab.cat/estadistica/es), with a confidence interval of 95% and an accuracy of 2%, sample size should be of ≥865 individuals, which was increased to 1000 individuals by taking into account possible losses.

Statistical analysis was performed with the SPSS 17.0 statistical package (Chicago, IL). Intergroup differences were assessed by the χ^2 or Fisher exact test for categorical variables and by the *t* test, ANOVA, Mann–Whitney *U* test, and Kruskal–Wallis test for continuous variables. The correlation between continuous variables was determined with Spearman or Pearson coefficients, as appropriate. A *P* value <0.05 was considered as significant. To evaluate independently associated factors of SBIs in our sample, we constructed forward stepwise logistic regression models with all variables associated with SBIs showing a *P* value <0.1 in the univariate analysis (model 1). Odds ratios and 95% confidence intervals were further adjusted by adding smoking habit and antihypertensive treatment to the model. In a second term (model 2), REGICOR score was used as a measure of total cardiovascular risk as covariate. Interaction terms of age and BP (model 1) and REGICOR score and microalbuminuria (model 2) were also tested.

Results

Baseline Demographical and Clinical Characteristics

Nine hundred seventy-six patients were included in this study. Demographical characteristics and cardiovascular risk profile are shown in Table 2. Median age was 64 years, and 49.4% of the sample were men. Besides hypertension, most of the participants had dyslipidemia (71.7%) and 23.5% were diabetic. Overall, 120 (12.3%) had already a history of an established cardiovascular disease. From those free of vascular disease at baseline, total cardiovascular risk was estimated by means of the REGICOR risk charts; the majority of the participants belonged to the moderate or high risk categories (median=6 [4–9]).

Regarding BP, mean systolic and diastolic BP were 141.5 and 77.5 mm Hg, respectively. All patients had been recommended to follow lifestyle recommendations to control their BP, and also the vast majority (95.4%) were taking antihypertensive drugs at the time of the study entry (40.2% monotherapy, 37.2% were on 2 drugs, 18% on ≥3 drugs). Only 54% of participants self-reported correct treatment compliance.

Table 2. Univariate Analysis: Description of Demographic and Clinical Baseline Factors in the Total Sample and in Those With or Without SBIs

Characteristics	All Patients	Absence of SBI (n=877)	Presence of SBI (n=99)	*P*
Age, y*	64 (60–67)	64 (59.5–67)	65 (61.7–69)	<0.01
Sex, male*	49.4%	46.9%	71.7%	<0.01
Tobacco use	15.2%	15.3%	14.1%	0.76
Alcohol abuse	6.4%	6.7%	4.8%	0.78
Diabetes mellitus	23.5%	22.7%	30.3%	0.09
Dyslipidemia	71.7%	70.8%	79.6%	0.07
Abdominal obesity	72.7%	72.7%	72.4%	0.95
Body mass index, kg/m^2	29.9 (27.1–33.2)	30.0 (27.1–33.2)	29.9 (26.9–33)	0.86
Mean office SBP, mm Hg	141.5 (132–153)	141.5 (132–153)	144 (130–155.6)	0.69
Mean office DBP, mm Hg*	77.5 (71–84)	77.5 (70.5–84)	81.5 (72.8–89.7)	0.03
Duration of hypertension, y	8.6 (5.3–12.4)	9.1 (5.7–12.8)	8.8 (4.5–12.8)	0.52
REGICOR score*	6 (4–9)	6 (4–8)	7 (5–10.75)	<0.01
Previous cardiovascular disease*	12.3%	11.2%	22.2%	<0.01
No. of antihypertensives	2 (1–2)	2 (1–2)	2 (1–2.75)	0.18
Treatment compliance	54.4%	54.8%	50.5%	0.43

Data are expressed in median (interquartile range), mean±SD, and percentage as appropriate. DBP indicates diastolic blood pressure; REGICOR, Registre Gironí del Cor; SBI, silent brain infarct; and SBP, systolic blood pressure.

*Significant results.

SBIs and Their Associated Factors

A total of 99 participants had SBIs, leading to a prevalence of 10.1% of the sample (95% confidence interval, 8.4%–12.2%). Most of the patients had a single lesion (69%), whereas 31% presented multiple lesions (ranging 2–11), accounting for a total number of 163 infarcts. The majority of lesions were located in the basal ganglia (35.6%) or subcortical white matter (28.8%), followed by the cerebellum (16%), brain stem (11%), and cortex (8.6%).

As expected, increasing age was related to the presence of SBIs but also sex differences were found. Prevalence of SBIs was gradually increased for both sexes with age, but they were more often in men than in women at any age category. However, men and women differed in the frequency of many baseline characteristics as shown in Table S1 (online-only Data Supplement).

Other baseline differences in SBI presence about vascular risk factors, total cardiovascular risk, or BP levels are shown in Table 2.

Finally, because subclinical organ damage may affect prognosis in hypertensives, we evaluated the kidney function by means of urine albumin-to-creatinine ratio and estimated GFR. After exclusion of 10 participants who showed serum creatinine levels (>132.6 μmol/L in men and 114.9 μmol/L in women) or proteinuria (urine albumin-to-creatinine ratio ≥300 mg/g at least once) suggestive of overt nephropathy, 13.7% presented microalbuminuria, 7.8% had low estimated GFR, and in 1.1% of participants both alterations were present. Also, left ventricular hypertrophy was detected as signature of hypertensive heart damage in 9.1% of the cohort.

Looking into how these markers of TOD were interrelated, we found that microalbuminuria was associated with the presence of SBIs (27.2% in those with microalbuminuria versus 12.2% in those without it, $P<0.001$), whereas finding a decreased GFR or left ventricular hypertrophy presence was not ($P=0.25$ and $P=0.22$, respectively).

In Table 3, we present results from the multivariate analyses. Increasing age, male sex, and microalbuminuria (model 1) were all independently associated with SBIs. Moreover, because current guidelines support that diagnosis and management of hypertension should be related to quantification of global (or total) cardiovascular risk, we included in the analysis the Framingham-calibrated REGICOR score (model 2) and found that it was also predictor of SBIs, in addition to microalbuminuria. A graded response was found between REGICOR risk categories and SBI, with the strongest associations corresponding to those at high or very high-risk categories.

It should be noted that despite the fact that microalbuminuria was independently associated with SBIs in both models, in our sample, still 66% of the participants with SBIs had no renal or heart involvement.

Table 3. Multivariate Analysis: Independent Associated Factors With the Presence of Silent Brain Infarcts

Characteristics	OR (95% CI)	*P*
Model 1		
Age, per 5 y	1.54 (1.22–1.94)	<0.01
Sex, male	2.53 (1.55–4.15)	<0.01
Microalbuminuria	2.28 (1.33–3.918)	<0.01
Model 2		
Total cardiovascular risk (REGICOR)		0.05
Low (<5%)	1 (reference)	
Moderate (5–9.9%)	1.29 (0.66–2.51)	0.46
High (10–14.9%)	2.17 (1.00–4.69)	0.05
Very high (≥15%)	3.17 (1.22–8.22)	0.02
Microalbuminuria	2.34 (1.29–4.26)	<0.01

Values represent odds ratios (OR) and their corresponding 95% confidence intervals (CI). Model 1 includes covariates age, sex, dyslipidemia, mean office diastolic blood pressure (per 1 mm Hg increase), diabetes mellitus, previous cardiovascular disease, microalbuminuria, smoking habit, antihypertensive treatment (number of drugs received), and the interaction term of age and blood pressure. Model 2 includes categorized Registre Gironí del Cor (REGICOR) score (low-risk category as reference), microalbuminuria, antihypertensive treatment, and the interaction term between REGICOR and microalbuminuria.

Discussion

Here, we described the prevalence of SBIs in a large Mediterranean cohort of middle- and old-aged hypertensives. SBIs were found in 10.1% of participants, a prevalence that is similar to other population-based studies but lower than that reported in hypertensive cohorts. Although this might be surprising, several differences should be noted between ours and previous studies in hypertensives, apart from ethnicity, as mentioned before. First, our population was younger and the majority of our participants was long-term (median 8.6 years since diagnosis) and treated hypertensives with office BP levels that were lower as compared with previous studies selecting hypertensives (Table 1).[2–17] Most importantly, the selection of participants was performed randomly from a primary care setting. The cohort was routinely treated and monitored by general practitioners, avoiding the bias that might be caused by selection in more specialized contexts, such as hospital units. Moreover, our sample size was estimated taking into account previous studies on this matter in general populations, and to date, it is almost twice larger than that of previous studies in a purely hypertensive cohort.

We found that SBIs were strongly associated with age, as it has been shown consistently before, and much more frequent in hypertensive men than women. This is also remarkable, taking into account that stroke is the leading cause of death for women in our country. Other population-based studies, such as the Rotterdam Scan Study[31] and the Cardiovascular Health Study,[32] found opposite results, with more SBIs in women than in men, although their participants were older than ours. In opposition, our results agree with those from the Northern Manhattan Study, a multiethnic community-based cohort.[33] It is well known that women have lower BP levels across the lifespan than their age-matched counterparts. However, hypertension becomes increasingly prevalent in postmenopausal women.[34] We randomized participants taking into both sex and age, but still several differences were found in the distribution of vascular risk factors, with women displaying less global vascular risk and comorbidities than men in our cohort. These differences might explain the lower prevalence of SBIs in women. It is also possible that because we did not perform ambulatory BP monitoring to select participants, some of them might have indeed a white coat effect. This condition is associated with an intermediate risk of cardiovascular events between those with sustained hypertension and normotensive individuals, and it is described to be particularly frequent in women.[35] However, we

excluded participants with suspected white coat hypertension, and the vast majority of them had been treated for a long time before inclusion, thus making this possibility less likely.

Our results, therefore, emphasize the need to uncover sex differences to better understand pathological processes associated with aging and stroke and to personalize preventive health care.

We also found an independent association between microalbuminuria and SBIs. This is important because these results extend previous knowledge on the role of microalbuminuria as predictive marker of cardiovascular events and stroke risk.[36] Less is known on how microalbuminuria is interrelated to other subclinical TOD, such as that present in the brain. Specifically, this was reported in hypertensives by Henskens et al[5] in a cohort of 192 young untreated hypertensives, in whom different TOD markers were evaluated, including microalbuminuria. Interestingly, although the proportion of subjects with damage in heart, kidney, brain, or any combination of them was higher in that study than in our population, half of the patients with brain damage (including SBIs but also other lesions such as white matter hyperintensities or microbleeds) did not present cardiorenal damage and were classified as having no-target organ involvement. Likewise, in our study, in almost 66% of those with SBIs, these lesions did not coexist with heart or kidney involvement, which are the organs routinely screened to assess risk in hypertension. Although both Henskens et al[5] and our results suggest that screening for SBI might improve risk stratification in hypertensives, longitudinal studies with stroke (and possibly other vascular events) as outcomes are needed to determine their predictive value.

Microalbuminuria is generally interpreted as an early sign of kidney disease or as a marker of endothelial dysfunction.[37] As kidney and brain display common hemodynamic properties such as low vascular resistance, as compared with other vascular beds, they might be unprotected against increased pulsatile stress occurring with aging and hypertension.[38] This could lead to endothelial damage and progress toward both the appearance of microalbuminuria and brain infarcts, even in the absence of an impaired kidney function. However, to properly address the occurrence of these events over time, prospective studies are needed.

Finally, we found that total cardiovascular risk is not only associated with the odds of symptomatic future vascular events but also related to the presence of subclinical brain disease. These results are in agreement with those reported in the Framingham Offspring cohort study,[39] but as original Framingham function scores overestimate risk in low-risk countries such as Spain,[20] we used a validated and easy-to-use tool (REGICOR) that is already extensively used by general practitioners in our area. In our study, total cardiovascular risk predicted the presence of SBIs better than any risk factor taken separately, highlighting the importance of treating patients preferably according to their estimated global cardiovascular risk, rather than based on the presence of any individual risk factor.

Strengths and Limitations

This study has some strengths and some limitations. As strengths, this is a large study, representative for a population of middle-aged hypertensives living in a low cardiovascular risk country in the Mediterranean area.

Moreover, inclusion procedures required careful review of medical records and interview with the participants to remove nonessential hypertension and rule out participants with previous stroke or dementia. We also have some limitations. Lack of ambulatory BP monitoring for selecting participants might have led to increased frequency of white coat hypertension effect. Urine albumin-to-creatinine ratio was measured in this study with a single-spot urine sample. In clinical practice, it is recommended to confirm this observation with multiple testing, to avoid false-positive results attributable to variability of the measurement. Also hypertensive heart damage could be determined with higher accuracy with the use of echocardiography or other imaging techniques.

Perspectives

This study characterizes the prevalence and risk factors of SBIs in a large hypertensive cohort, from a low cardiovascular risk country in the Mediterranean area. Other markers of TOD, such as microalbuminuria, or total cardiovascular risk are independently associated with silent brain vascular disease and might be useful to screen those at high risk of future stroke and dementia, while taking into account sex differences in the design of preventive strategies.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Silent brain infarcts are present in ≈10% of hypertensives in a low-cardiovascular-risk Mediterranean population.
- Total cardiovascular risk and microalbuminuria could be useful to determine those with subclinical brain vascular disease and, therefore, with higher risk of future stroke and dementia.

What Is Relevant?

- Our results emphasize the need of assessing total cardiovascular risk in hypertensives, to determine the burden of clinical and subclinical disease.
- Sex differences need to be further explored in stroke prevention.

Summary

Silent brain infarcts prevalence reached 10% of hypertensives between 50 and 70 years old in a low cardiovascular risk Mediterranean population, with striking sex differences. Microalbuminuria and increased total cardiovascular risk are independently associated with silent brain infarcts presence in long-term treated essential hypertensives.

ONLINE SUPPLEMENT

FULL TITLE:PREVALENCE AND ASSOCIATED FACTORS OF SILENT BRAIN INFARCTS IN A MEDITERRANEAN COHORT OF HYPERTENSIVES

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Short Title: Silent brain infarcts in Mediterranean hypertensives

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Expanded Materials and Methods:

Covariates definition:

-Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP≥90 mmHg and/or use of antihypertensive medication.

-Duration of hypertension was assessed as the time from first diagnosis to inclusion visit, and it was expressed in years.

-Diabetes mellitus was defined as fasting glucose levels over 7 mmol/L and/or the use of oral antidiabetic drugs or insulin.

-Dyslipidemia was defined as total cholesterol over 5.2 mmol/L, triglycerides over 2.3 mmol/L and/or the use of lipid lowering treatments.

- Alcohol abuse was defined as ≥280 grams per week in males and ≥170 grams per week in females.

-Smoking habit was categorized into current, former or never.

-Previous cardiovascular disease includes coronary artery disease (angina, myocardial infarction) and peripheral artery disease (intermitent claudication, by-pass surgery, aortic aneurism).

-Previous kidney disease: presence of diabetic or hypertensive nephropathy and/or renal failure.

-Systemic disease: including any other disease affecting a number of organs and tissues.

-REGICOR function: it is a Framingham-calibrated function for 10-year cardiovascular risk calculation. It includes age, gender, tobacco intake, diabetes, systolic and diastolic BP, total and HDL-cholesterol. An online calculator can be found at:
http://www.imim.cat/ofertadeserveis/software-public/regicor/?1

-BP control: Optimal BP control was defined as BP<140/90 (or <130/80 in diabetic and those at high or very high risk, such as those with clinical conditions, including myocardial infarction, renal failure or proteinuria).

- Treatment compliance was assessed with the Moriski questionnaire. This scale consists in 4 questions, with yes/no answers which should be asked along the clinical interview, and reflect the patient's attitude towards treatment. It is useful to find out whether or not the patient is a good complier (all questions answered as no) and the causes for non-adherence.

- Abdominal obesity was defined as a waist circumference >88 centimeters in females and >102 cms in males, according to the European Society of Hypertension.

Table S1. Description of main baseline characteristics regarding gender.

Variables	Women (n=494)	Men (n=482)	p value
Age, years	64 (59-67)	63 (58-67)	0.14
Tobacco use	9.3%	21.2%	<0.001
Alcohol abuse	6.1%	6.6%	0.82
Diabetes	20.2%	26.8%	0.016
Dyslipidemia	71.3%	72.1%	0.79
Abdominal obesity	83.8	61.1	<0.001
Body mass index (Kg/m2)	30.3 (26.9-34.4)	29.7 (27.2-32.1)	0.036
Mean office SBP	143 (133-154)	140.5 (130-151)	0.035
Mean office DBP	76 (69.1-81.5)	80 (73-86)	<0.001
Duration of hypertension, years	9.4 (5.9-12.9)	7.9 (5-12.1)	0.002
Resistant hypertension	4.1%	5.1%	0.47
REGICOR score	5 (4-7)	7 (5-11)	<0.001
Previous cardiovascular disease	6.5%	18.3%	<0.001
Number of antihypertensives	2 (1-2)	2 (1-2)	0.29
Treatment compliance	57.2%	51.4%	0.079

Data are expressed in median (interquartile range), mean +/- standard deviation and percentage as appropriate. SBP: Systolic blood pressure is expressed in mmHg, DBP: diastolic blood pressure, is expressed in mmHg. *p<0.05.

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Cognitive assessment protocol design in the ISSYS (Investigating Silent Strokes in hYpertensives: A magnetic resonance imaging Study)☆

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ABSTRACT

Hypertension and silent cerebrovascular lesions (SCL) detected by brain magnetic resonance imaging (MRI) are associated with an increased risk of cognitive decline. In a prospective observational study in 1000 hypertensive patients, aged 50–70 years, with no prior history of stroke or dementia, we will study the presence of mild cognitive impairment (MCI) and the relationship between SCL and cognition. All participants will be assessed by means of the Dementia Rating Scale—2 (DRS-2) and will undergo a brain MRI. In order to better characterize MCI and future dementia risk in our cohort, those patients that are suspected to be cognitively impaired according to the DRS-2 results will have a further neurological evaluation and complete neuropsychological testing. Follow-up for the entire cohort is planned to last for at least 3 years.

1. Introduction

Growing evidence suggests that vascular risk factors, such as hypertension, diabetes and hypercholesterolemia, among others, contribute to cognitive decline and increase the risk of mild cognitive impairment (MCI) and incident dementia [1].

MCI is estimated to affect about 5.5% of the population aged 55 years or older and to increase over time with advancing ages, reaching about 30% in patients over 85 years old [2]. The MCI prevalence doubles that of dementia prevalence. Moreover, patients with MCI are at high risk of developing dementia. The annual conversion rate to dementia, Alzheimer's disease (AD) and vascular dementia (VaD) is estimated in 9.6%, 8.1% and 1.9% respectively, in specialized clinical settings and in 4.9%, 6.8% and 1.6% in community based studies [3]. Several characteristics such as memory tasks impairment or hippocampal atrophy are associated with the risk of conversion to AD, whereas patients with dysfunction in executive tasks or presenting vascular subcortical lesions are more prone to develop a VaD [4,5].

Other neuroimaging and cerebrospinal fluid (CSF) biomarkers have been related with the risk of AD conversion and probably, a combination of CSF biomarkers (such as high phosphorylated and total tau or low β-amyloid 42 [6,7]), APOE genotype [8], brain MRI and brain nuclear techniques might be the most useful strategies for predicting conversion to AD [9–12].

Among all vascular risk factors, hypertension is the most prevalent in general populations and is associated with MCI, AD and VaD [13]. Several studies have shown that sleep blood pressure variations, such as the lack of a physiological dipping pattern and also the diagnosis of midlife hypertension might be related with poor cognitive performance [14,15]. Therefore, blood pressure control might help reducing the risk of dementia and MCI [13].

Also, there is a link between hypertension and the presence or appearance of new SCL, such as brain infarcts and white matter changes, which independently increase the risk of having MCI and dementia [16–18]. Thus, subjects with vascular MCI have more white matter changes and lacunar infarcts than subjects with neurodegenerative MCI [19] and the location and number of silent infarcts

☆ Conflict of interest: none.

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is also important, since having more than one infarct affects memory performance, processing speed and executive function, and probably is involved in cognitive impairment development [20].

The prevalence of MCI and risk of incident dementia in a Mediterranean hypertensive population is largely unknown. Our aim is to assess the prevalence of MCI in a midlife hypertensive Spanish population and to determine the risk of incident dementia after 3 years of follow-up. The relationship between SCL and cognition is also investigated. Here we present a summary of the cognitive protocol used for those purposes.

2. Materials and Methods

2.1. Study population

Our study population will comprise 1000 non-demented individuals, aged 50 to 70 years old, and diagnosed of essential hypertension at least one year before inclusion in the study. All participants are involved in an epidemiological ongoing study aimed to investigate the prevalence and risk factors for silent cerebrovascular lesions and stroke; the ISSYS (Investigating Silent Strokes in hYpertensives: A magnetic resonance imaging Study). This study was approved by the Local Ethics Committee of Vall d'Hebron Hospital and IDIAP Jordi Gol and all participants gave their informed written consent.

2.2. Cognitive assessment

On baseline, all patients will be evaluated by means of the Dementia Rating Scale—2 (DRS-2) developed by Mattis, which is a screening tool for dementia and MCI [21]. This scale includes the evaluation of five cognitive domains: attention, memory, initiation/perseveration, construction and conceptualization. Illiterate participants will be assessed by means of The Eurotest, a dementia screening test developed in Spain [22].

A Spanish version of the DRS-2 will be used for our population [23] and since scarce normative data for non-demented Mediterranean populations exists [24], total crude scores will be adjusted by age and years of formal education received, following the methodology proposed by Peña-Casanova et al. [25].

After data normalization, further neurological and neuropsychological assessment will be carried out in a further visit in all subjects with cognitive complaints and poor performance in the screening test (defined as total adjusted score ≤ 8).

In this visit, a cognitive, behavioral and functional anamnesis will be carried out, as well as a complete neurological examination and a short general examination. The Spanish IDDD Scale for functional assessment will be applied [26] and the presence of depressive symptoms will be evaluated with the Spanish version of the Zung Scale for Depression [27]. Neuropsychological testing will be carried out by a professional with appropriate training in the administration and interpretation of psychological tests. Our detailed protocol for neuropsychological testing cognitive assessment is shown in Table 1.

Following this evaluation, MCI will be diagnosed according to the definition of the "Guidelines for Clinical Practice in Dementia" of the Spanish Society of Neurology of 2009 [28]. Briefly, MCI is considered in subjects who present an alteration of one or more cognitive domains: attention and executive function, language, memory or visuospatial functions, this alteration should be acquired, reported by the patient or caregiver, months to years of duration and showing a cognitive performance below 1.5 or 1 standard deviations of the adjusted mean, depending on the pre-morbid patient's status. Moreover, this alteration should not interfere with daily activities or do it minimally and the patients should not have delirium or altered level of consciousness at the time of diagnosis.

MCI patients will be further classified into predefined subtypes: amnesic MCI (single or multiple domains) and non-amnesic MCI (single or multiple domains) [29].

Table 1
Cognitive protocol assessment.

Cognitive test	Function evaluated
Rey Auditory Verbal Learning Test [35]	Immediate and delayed verbal memory
Visual reproduction I and II of WMS-III [36]	Immediate and delayed visual memory
TMT A and B [37]	Visual attention and task switching
Block design of WAIS-III [35]	Spatial component of perception
Fluency tests of COWAT [38]	Language and executive function
Stroop test [39]	Selective attention, cognitive flexibility and processing speed
Clock drawing [35]	Visuospatial and constructional abilities
Symbolic gesture of Barcelona's test [40]	Gestural praxis
Sequences and imitation of postures of Barcelona's test [40]	Ideomotor praxis

2.3. MRI protocol

After the inclusion visit all participants will be scheduled for a brain MRI which will be conducted within the next 30 days after inclusion. All exams will be performed in the same 1.5 T GE Sigma Infinity scanner using an identical protocol. Several vascular lesions will be considered for analysis. Briefly, brain infarcts will be defined as lesions ≥ 3 mm with signal characteristics of CSF in all pulse sequences. In order to differentiate infarcts from dilated perivascular spaces, a hyperintense rim will be required in FLAIR sequences [30,31]. Microbleeds will be evaluated and assessed in GRE sequence according to the BOMBS scale developed by Cordonnier et al. [32] and finally, white matter changes will be evaluated according to a visual rating scale, as previously reported [33].

2.4. Follow up-visits

Once a year, for the first and second year after inclusion, the patients will be contacted by phone for follow-up. Patients and/or caregivers will be asked for blood pressure control, appearance of new vascular risk factors, vascular diseases and appearance or worsening of cognitive decline. Also, the telephonic version of the MMSE [34], which has been adapted and validated in Spanish population before, will be administered within the same visit. After 3 years of follow-up a new visit will be carried out for the whole cohort. This last visit is planned in the ISSYS and includes a new assessment with DRS-2 to study cognitive changes in the whole cohort.

3. Discussion

Given the vast socioeconomic burden of neurovascular and neurodegenerative diseases, early diagnosis and the identification of risk factors for dementia should provide useful tools to minimize the impact of this disease in the future. Our study will provide useful clinical, neuropsychological and neuroimaging characterization of cognitive state in hypertensives and their changes over time. Besides, we hope to better characterize MCI in a high risk Spanish population.

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D.4 High Daytime and Nighttime ambulatory pulse pressure predict poor cognitive function and mild cognitive impairment in hypertensive individuals. Journal of Cerebral Blood Flow & Metabolism (2015, en prensa)

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ORIGINAL ARTICLE

High daytime and nighttime ambulatory pulse pressure predict poor cognitive function and mild cognitive impairment in hypertensive individuals

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High blood pressure accelerates normal aging stiffness process. Arterial stiffness (AS) has been previously associated with impaired cognitive function and dementia. Our aims are to study how cognitive function and status (mild cognitive impairment, MCI and normal cognitive aging, NCA) relate to AS in a community-based population of hypertensive participants assessed with office and 24-hour ambulatory blood pressure measurements. Six hundred ninety-nine participants were studied, 71 had MCI and the rest had NCA. Office pulse pressure (PP), carotid–femoral pulse wave velocity, and 24-hour ambulatory PP monitoring were collected. Also, participants underwent a brain magnetic resonance to study cerebral small–vessel disease (cSVD) lesions. Multivariate analysis–related cognitive function and cognitive status to AS measurements after adjusting for demographic, vascular risk factors, and cSVD. Carotid–femoral pulse wave velocity and PP at different periods were inversely correlated with several cognitive domains, but only awake PP measurements were associated with attention after correcting for confounders (beta = − 0.22, 95% confidence interval (CI) − 0.41, − 0.03). All ambulatory PP measurements were related to MCI, which was independently associated with nocturnal PP (odds ratio (OR) = 2.552, 95% CI 1.137, 5.728) and also related to the presence of deep white matter hyperintensities (OR= 1.903, 1.096, 3.306). Therefore, higher day and night ambulatory PP measurements are associated with poor cognitive outcomes.

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Keywords: ambulatory blood pressure monitoring; arterial stiffness; cerebral small–vessel disease; cognitive function; mild cognitive impairment

INTRODUCTION

Aging and hypertension, among other vascular risk factors (VRFs), determine the risk of cardiovascular diseases and contribute to structural and functional changes in the arterial wall, which becomes less elastic and stiffer.[1]

Arterial stiffness (AS) is a surrogate marker of major cardiovascular events in the general population[2] and in clinical settings (like stroke in hypertensive patients).[3] Besides AS was associated with some features of cerebral small-vessel disease (cSVD) such as white matter changes and lacunar infarcts.[4,5]

Moreover, AS was independently associated with cognitive function, in demented and nondemented individuals, and with cognitive decline and dementia in most[6] but not all studies.[7,8] A relationship has also been suggested between AS and mild cognitive impairment (MCI).[9] Studying MCI predictors is a priority because it is the main risk factor for conversion to dementia.[10] However, some important limitations of these studies on AS in cognitive function, dementia, and especially MCI have to be acknowledged: most had small sample sizes, some used only screening tests for cognitive assessment, and most did not adjust AS by the presence of VRFs or cSVD.[11]

Among the different indirect ways to assess AS, carotid–femoral pulse wave velocity (cf-PWV) is considered the reference standard. However, there are a number of external factors (i.e., white-coat hypertension phenomena, tobacco, alcohol, polyphenol consumption, etc.) that might affect these estimations, decreasing its predictive accuracy, particularly in routine clinical care.[12] Other indirect ways to estimate AS as calculating the pulse pressure (PP) can be achieved by techniques such as 24-hour ambulatory blood pressure monitoring (ABPM), which may provide relative advantages over a single evaluation at the clinic.

Our objectives are to describe how cognitive function and cognitive status (MCI and normal cognitive aging (NCA)) relate to AS in a community-based population of hypertensive patients. Specifically, we aimed to compare whether AS measured with different methodologies (cf-PWV versus office PP assessment; 24-

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hours daytime or nighttime PP assessment) relate differentially to these cognitive outcomes, and to study whether the effect of AS on cognitive function/status varies in the presence of cSVD.

MATERIALS AND METHODS

Study Population

Our study population is nested within the ISSYS project (Investigating Silent Strokes in hypersensitive individuals, a magnetic resonance imaging Study). This is an observational, prospective study in 1,037 hypertensive individuals in Spain. Inclusion criteria of the study were essential hypertension diagnosed at least 1 year before inclusion, age 50 to 70 years old, and no history of clinical stroke or dementia. Individuals who had contraindications for magnetic resonance imaging (MRI; i.e., carried a pacemaker or were claustrophobic) or those who had a terminal illness were excluded. ISSYS general aims are to investigate the prevalence of silent cerebrovascular lesions and cognitive impairment. The participants were selected at random from 14 primary care centers in the North area of Barcelona city. Our study protocol was published elsewhere.[13]

The study followed the Declaration of Helsinki and was approved by the Vall d'Hebron's Research Hospital Ethics Committee, and all patients gave their informed written consent before inclusion.

Cognitive Assessment

At baseline all participants were evaluated by means of a dementia screening test (Dementia Rating Scale second version, DRS-2).[14] Total DRS-2 score goes from 0 to 144 points and is divided in several subscales (memory, attention, initiation/perseveration, conceptualization, and construction).

Seven hundred ninety-eight participants of the ISSYS had valid data on DRS-2, they were literate and did not have any condition that could interfere with their cognitive performance (e.g., severe sensory deficit, previous central nervous system disorder, uncontrolled metabolic diseases, or alcohol consumption) or dementia. All of them belonged to the same ethnic group (white Mediterranean).

In a further step, all participants who obtained age- and education-adjusted scores below 8 points (considered as a cutoff to suspect cognitive impairment) were reevaluated to assess cognitive status.[14] In this second evaluation an extended cognitive, behavioral, and functional anamnesis and a standard physical and neurologic examination was performed. Besides, cognitive performance was determined using a battery of cognitive tests evaluating memory, attention, processing speed, executive function, motor, and visuospatial functions. Our cognitive protocol was published previously elsewhere.[15] The diagnosis of MCI was established following previously published criteria by the neurologist and neuropsychologist who attended the patients, who were masked to other clinical data.[16] In brief, MCI was considered when the subject or caregiver manifest an acquired cognitive impairment that lasted months to years and this alteration was shown on cognitive testing (performance mainly below 1.5 s.d. of the adjusted mean). The impairment did not (or minimally) interfere with daily instrumental activities. Those with delirium or altered consciousness at the time of diagnosis were excluded. Participants with a previous depression were considered for the present analysis if it was under treatment and controlled. Sixteen participants refused to be further evaluated.

All those with normal results in the screening tool (total DRS-2$\geq$ 8) or who did not fulfill criteria for cognitive impairment or MCI were considered as having NCA.

Brain Magnetic Resonance Imaging

All participants underwent a brain MRI with the same 1.5 Tesla MR.[13] Magnetic resonance imaging examinations were rated by two neuroradiologists and a stroke neurologist who were also masked to clinical data. Presence and number of lacunar brain infarcts were assessed. Lacunar infarcts were considered when there was a lesion of tissue loss of 3- to 20-mm diameter in their widest dimension, with cerebrospinal fluid–like signal characteristics in all pulse sequences, and with the presence of a hyperintense rim surrounding it in fluid-attenuated inversion recovery sequences. Localization of lacunar infarcts was the basal ganglia, thalamus, internal or external capsules, or brainstem. Cortical infarcts were not considered for the analysis.

Presence and grade of white matter hyperintensities (WMHs) in fluid-attenuated inversion recovery or T2-weighted images were rated with a semiquantitative scale.[17] White matter hyperintensities in periventricular and deep localizations were considered separately. For periventricular WMHs, the score was as follows: grade 0 = no WMHs, 1 = caps or pencil-thin lining, 2 = smooth 'halo', and 3 = irregular WMHs extending to the deep white matter. For deep WMHs, the score was 0 = no lesions, 1 = punctuate foci, 2 = beginning confluence of foci, and 3 = large confluent areas. Intrarater and interrater agreement for all the markers was good to excellent ($k = 0.6$ to 0.81).

Participants with either lacunar infarct(s) or WMHs ≥ 2 on Fazekas deep score or with both lesions were considered as having cSVD, otherwise were considered as not having cSVD.

Those participants who had incomplete, invalid, or no data from MRI (n = 52) were excluded for this analysis.

Office Arterial Stiffness Measurements

Office PP was calculated as the difference between mean systolic BP (SBP) and mean diastolic BP. Office BP was measured with a validated oscillometric OMRON (M6 CONFORT, Hoofddorp, The Netherlands) device after 5-minute rest.[18] Systolic BP and diastolic BP were calculated as the mean of the last two out of three measurements.

Carotid–femoral pulse wave velocity was assessed in supine position after 10-minute rest using the oscillometric automatic VICORDER (SMT Medical, Würzburg, Germany) device.[19] To obtain the measurement, two inflatable cuffs were placed, one smaller over the right carotid region to measure carotid pulse wave and one larger around the right upper thigh to measure the femoral pulse wave. Both cuffs were inflated to 60 mm Hg and at least 10 consecutive carotid and femoral beats were recorded simultaneously. The distance between external notch and the center of the femoral cuff was measured with a tape over the body surface and used as the path distance. The transit time between the two cuffs was computed and cf-PWV calculated as the ratio between distance and transit time in meters per second (m/s) with an in-built cross-correlation algorithm. Participants with rhythm disorders were excluded to avoid interference with AS measurements (n = 65).

Twenty-Four-Hours Ambulatory Blood Pressure Monitoring

Twenty-four-hours–ABPM recordings were performed at working days with the automated Spacelabs 90217-5Q (Spacelabs Healthcare, Issaquah, WA, USA) device, validated according to the protocol of the British Hypertension Society.[20] Participants were asked to fill a questionnaire regarding sleeping and awaking periods and to follow their usual activities, although avoiding intense physical exercise and excessive movement on their nondominant arm during measurements. Readings were performed every 20 minutes during daytime (0600 to 2259 hours) and every 30 minutes during nighttime (2300 to 0559 hours).

Twenty-four-hours–ABPM data were not considered in those with $<$ 70% valid measurements, $<$ 2 measurements per hour during daytime, and $<$ 1 during the sleeping period or in those participants who refused to be tested.

Flowchart of the study taking into account cognitive diagnosis, brain MRI, and valid AS measurements is presented in Figure 1.

Definition of Covariates

Education was calculated as the maximum years of formal education accomplished from childhood to early adulthood. Baseline total cholesterol was measured on an automated clinical chemistry analyzer (Olympus AU2700, Diamond Diagnostics, Holliston, MA, USA). Diabetes mellitus was defined by clinical records, history of diabetes, or being under oral glucose–lowering drugs or insulin. Smoking habit was defined as active or inactive. Blood pressure–lowering drug (BPLD) compliance was evaluated by means of Morisky-Green scale.[13] The use of several common BPLDs was considered for this study: dihydropyridine calcium–channel blockers, thiazides, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and also statin and antiplatelet use.

Statistical Analysis

For cognitive function analysis, DRS-2 total and subscale scores were transformed into Z scores (individual mean – sample mean/s.d.) to obtain distributions centered in 0 (s.d. = 1). Initiation/perseveration and conceptualization subscales were averaged to obtain an executive function score.

In univariate analysis, we related demographics, VRFs, AS measurements, and cSVD with both cognitive function (total, attention, executive function,

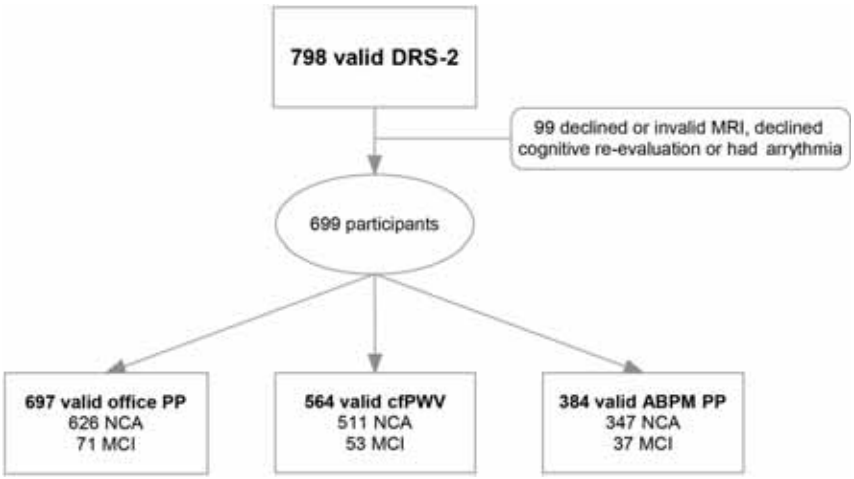

Figure 1. Study flowchart. ABPM, ambulatory blood pressure monitoring; cf-PWV, carotid–femoral pulse wave velocity; DRS-2, Dementia Rating Scale second version; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NCA, normal cognitive aging; PP, pulse pressure.

and memory scores) and cognitive status (MCI and NCA). Categorical variables were compared using Pearson's χ^2, whereas T-test or Mann–Whitney U-tests were used for continuous variables depending on their distribution. Correlations with cognitive function scores were assessed by means of Spearman's test.

To determine whether AS measurements in the office or obtained during the ABPM recordings were independently associated with cognitive function and cognitive status, multivariate models were performed.

Each model tested the effect of a different office (PP or cf-PWV) or ABPM-related (24 hours, day or night PP) AS measurement with cognitive outcome and was adjusted by age, sex, education, diabetes, total cholesterol, smoking, heart rate, BPLDs, statins, antiplatelet treatment (when appropriate), SBP of the period being analyzed (model 1), and additionally by number of lacunar infarcts and deep WMHs (model 2). The selection of these covariates as confounders was based either in the results of our analysis or in the previous literature concerning cognitive function and cognitive status. Heart rate was included since it influences AS measurements. Interactions between PP and cSVD lesions were tested but none was significant.

In the case of cognitive function linear regression models were used and results are given as beta and 95% confidence interval (CI). For cognitive status, logistic regression models were performed and results were given as odds ratio (OR), CI of 95%. Statistical significance was set at P-values < 0.05. All analyses were performed using SPSS version 17.0. (SPSS Inc., Chicago, IL, USA)

RESULTS

Baseline Characteristics

The mean age of the sample was 62.8 years and 50.1% were women. Almost all participants (95%) received BPLDs and were long-standing hypersensitive individuals (median time since diagnosis was 8 years). Few participants had moderate to severe periventricular (4.6%) and deep (8.6%) WMHs and 7.5% had lacunar infarcts.

Regarding AS measurements, cf-PWV was 10.6 (±2.2) m/s. Office, 24-hour, daytime, and nighttime PP values are shown in Table 1. Office PP was higher than any of the other ABPM-related PP measurements.

Factors Related to Cognitive Function

Demographical characteristics such as age (correlation coefficient r ranging from −0.11 to −0.29) and education (r ranging from 0.23 to 0.49) were correlated to global, attention, memory, or executive functions as expected. As it is shown in Supplementary Table 1, cognitive function was also different in men and women and smokers and nonsmokers. Concerning BPLDs, we found that those who were on angiotensin-converting enzyme inhibitors had lower attention score than those who were not ($P < 0.05$).

Regarding measures of AS, cf-PWV was inversely correlated with executive function ($P = 0.02$) and total ($P = 0.06$) scores. As for PP, all measurements (office and all ABPM-related measurements) were negatively correlated to all cognitive subscales (all $P < 0.05$), except memory, with the strongest correlations for total DRS-2.

Regarding cSVD lesions, whereas the number of lacunar infarcts was not related to cognitive function, higher WMH grade, especially in deep localization, was inversely related to total and some cognitive subscales (all $P \leq 0.01$).

Next, we evaluated whether all these AS-related measurements were independently associated with cognitive function after adjustment by age, sex, education, BPLDs, antiplatelet and statin treatments (when appropriate), SBP of the period analyzed and other VRFs (model 1), and after further correction for cSVD lesions (model 2) in several linear regression models (one for each cognitive subscale and for each office or ABPM-related PP measurement). After adjustment, most associations were lost and only daytime PP remained as independent predictor for attention (beta = −0.22, 95% CI −0.40, −0.04, model 1) together with education (for the rest of analyses, data not shown). Further adjustment for cSVD yielded similar results for daytime PP (beta = −0.22, 95% CI −0.41, −0.03, model 2) and education (beta = 0.07, 95% CI 0.05, 0.10; for rest of the analyses, data not shown).

Factors Associated with Cognitive Status (Mild Cognitive Impairment and Normal Cognitive Aging)

Regarding cognitive status, our univariate analysis showed that MCI participants had less education years than NCA (8[5,8] versus 8,[7,12] $P < 0.05$), who were more on thiazide treatment (62.7% versus 45.4%, $P < 0.05$) and antiplatelet drugs (29.2% versus 16.2%, $P < 0.01$). Higher SBP of ABPM was found for any period in MCI participants than in NCA.

Besides, PP was higher in MCI participants than NCA in ABPM at 24 hours (55.2 (10.6) versus 49.3 (10.4), $P = 0.01$), day (56.0 (10.3) versus 50.8 (10.8), $P < 0.05$), and night (52.7 (12.4) versus 47.1 (11.1), $P < 0.05$). We explored whether the relation between PP and MCI was linear or there were any J- or U-shape relationship and the last were not found. Therefore, PP was considered as a continuous variable afterwards.

In contrast to ABPM, none of the office measurements, neither PP nor cf-PWV were significantly different between groups. Results comparing cognitive status are shown in Table 2.

Table 1. Descriptive characteristics of the study sample

Characteristics	All (N = 699)
Office characteristics	
Age, years	62.8 (5.3)
Sex, female	350 (50.1%)
Education, years	8 (7, 12)
Office SBP, mm Hg	142.7 (15.8)
Office DBP, mm Hg	77.5 (71.0, 83.5)
Office PP, mm Hg	65.2 (13.4)
BP-lowering drugs	664 (95.0%)
Poor compliance of BP-lowering drugs	309 (44.2%)
Hypertension duration, years	8 (5,12)
Heart rate, bpm	69.1 (11.1)
Diabetes mellitus	160 (22.9%)
Total cholesterol, mg/dL	218.0 (188.0, 245.0)
Current smoker	104 (14.9%)
Cf-PWV, m/s	10.6 (2.2)
Treatments	
Dihydropyridine calcium–channel blocker	104 (15.5%)
Thiazide	316 (47.1%)
β-Blocker	151 (22.5%)
Angiotensin-converting enzyme inhibitor	189 (28.2%)
Angiotensin receptor blocker	319 (47.5%)
Statin	277 (41.3%)
Antiplatelet	122 (18.2%)
Ambulatory blood pressure monitoring	
24-hour SBP, mm Hg	126.4 (12.3)
24-hour DBP, mm Hg	76.6 (71.3, 81.0)
24-hour PP, mm Hg	49.9 (10.5)
Day SBP, mm Hg	132.2 (12.3)
Day DBP, mm Hg	81.1 (75.7, 86.2)
Day PP, mm Hg	69.4 (8.0)
Night SBP, mm Hg	117.1 (14.6)
Night DBP, mm Hg	69.2 (63.4, 74.6)
Night PP, mm Hg	47.6 (11.3)
Cerebral small–vessel disease	
Lacunar infarcts, any	51 (7.5%)
Number of lacunar infarcts	
None	648 (92.5%)
Single	38 (5.6%)
Multiple	13 (1.9%)
Periventricular WMH (Fazekas scale)	
Grade < 2	667 (95.4%)
Grade ⩾ 2	32 (4.6%)
Deep WMH score (Fazekas scale)	
Grade < 2	639 (91.4%)
Grade ⩾ 2	60 (8.6%)

Abbreviations: BP, blood pressure; bpm, beats per minute; cf-PWV, carotid–femoral pulse wave velocity; DBP, diastolic BP; PP, pulse pressure; SBP, systolic BP; WMH, white matter hyperintensity. For continuous variables mean (s.d.) or median (interquartile range) and for categorical variables count (%) are given.

Multivariate analyses considering cognitive status as the outcome measure were performed. For time periods, only nocturnal PP remained independently associated with MCI, (OR per s.d. increase in nocturnal PP = 2.254, 95% CI 1.029, 4.939) together with education after adjustment by covariates of model 1 (age, sex, education, thiazide and antiplatelet use, SBP of the corresponding period, and the other VRFs). Additional correction for the presence of cSVD lesions yielded similar results in night PP per s.d. increase (OR = 2.552, 95% CI 1.137, 5.728). In this last model also years of education (OR = 0.860, 95% CI 0.759, 0.976) and deep WMHs (OR = 1.903, 95% CI 1.096, 3.306) were associated with MCI. Systolic BP was not independently associated with MCI in any period. Results for other time periods are shown in Table 3.

Moreover, ABPM-related PP measurements were also increased in subjects with cSVD (all P < 0.05, data not shown).

We explored the relation of cognitive status jointly with the presence of cSVD lesions and AS. Figure 2 represents levels of daytime and nighttime PP according to cognitive diagnosis and presence or absence of cSVD.

DISCUSSION

This observational study in middle- and old-aged hypertensive participants showed that daytime and nighttime PP (as measures of AS) obtained with 24-hour ABPM were associated with attention function and with MCI, respectively. These findings were independent of demographic factors, BP levels, treatments, and other VRFs and, were not attenuated considering the presence of cSVD.

The relation between large-artery stiffness with cognitive function, cognitive impairment, or dementia was reported by several[6] (but not all)[7,8] clinical and community-based studies. Several of those studies used cf-PWV, to assess AS. When PP was used to assess AS a relation with cognitive outcomes were seen.[21,22] Poor global cognition or poor performance in selected cognitive functions, such as executive function and memory, were reported in those with higher PP in the general population.[21,23] Also a relation between cognitive impairment, especially vascular dementia including Alzheimer's disease, and cognitive decline was observed in those with higher cf-PWV and PP.[11,24]

In our case, inverse correlations were observed between cf-PWV and global and executive functions, although they were lost after correcting for VRFs and cSVD. Some remarkable differences exist between ours and previous studies. Most of the previous studies on cf-PWV and cognitive outcomes performed only univariate analysis or adjusted their analysis only by age, sex, and educational level as main confounders.[6] Some others corrected also for VRFs[7,22] and one further adjusted by cSVD.[21] In the latter, including the presence of cSVD in the analyses led to the loss of the associations between cf-PWV and cognitive function, as we found. In addition, our study characteristics may underlie these differences, as our participants were younger than in previous cohorts and most of them were treated with BPLDs.

In contrast to office cf-PWV and also office PP, here we provide evidences that serial PP determinations obtained by means of 24-hour ABPM are independently associated with cognitive status and function. Ambulatory blood pressure monitoring provides a more accurate and reproducible BP measurement than office BP assessment and it is a well-recognized tool to predict cardiovascular risk in hypertensive patients.[25] Besides, office measurements are greater influenced by environmental circumstances like white-coat effect that alters values of both cf-PWV and PP measurements.[12,25] The main advantage of ABPM as compared with cf-PWV assessment is its widespread use in the primary care setting, which is the first place where those with cognitive complaints are evaluated.

Previous studies investigated the role of ABPM-related PP measurements in relation to cognition and cognitive status. One of these studies diagnosed MCI participants after sequentially applying two screening tests in hypertensive patients at a cardiology clinic and found an association between MCI and higher 24-hour, day, and night PP measurements in the univariate analysis.[9] Another one, also showed that in a memory clinic, ambulatory PP measurements were inversely associated with attention function after adjusting for age and education and showed a relation between higher PP and vascular dementia, but no association was found between MCI and 24-hours PP

Table 2. Univariate analysis of cognitive status with VRFs, arterial stiffness measurements, and cerebral small–vessel disease

Characteristics	Normal cognitive aging (N = 628)	Mild cognitive impairment (N = 71)	P-value
Office characteristics			
Age, years	62.7 (5.3)	63.2 (5.5)	0.35
Sex, female	309 (49.2%)	40 (56.3%)	0.25
Education, years	8 (7, 12)	8 (5, 8)	*o* 0.05
Office SBP, mm Hg	142.3 (15.6)	143.5 (17.6)	0.73
Office DBP, mm Hg	77.5 (71.0, 84.0)	76.5 (67.0, 82.5)	0.10
Office PP, mm Hg	64.9 (13.2)	67.7 (14.4)	0.11
Poor compliance of BPLDs	276 (43.9)	33 (46.5)	0.68
Heart rate, bpm	69.4 (11.1)	66.1 (10.9)	0.27
Diabetes mellitus	140 (22.3%)	20 (28.2%)	0.26
Total cholesterol, mg/dL	218.0 (188.0, 245.0)	224.5 (185.0, 246.7)	0.39
Current smoker	92 (14.6%)	12 (16.9%)	0.61
Cf-PWV, m/s	10.7 (2.2)	10.5 (2.5)	0.64
Treatments			
Dihydropyridine calcium–channel blocker	90 (14.9%)	14 (20.9%)	0.19
Thiazide	274 (45.4%)	42 (62.7%)	*o* 0.05
β-Blocker	137 (22.7%)	14 (20.9%)	0.74
Angiotensin-converting enzyme inhibitor	291 (48.2%)	28 (41.8%)	0.32
Angiotensin receptor blocker	165 (27.3%)	24 (35.8%)	0.14
Statin	271 (41.3%)	34 (47.2%)	0.33
Antiplatelet	106 (16.2%)	21 (29.2%)	*o* 0.01
Ambulatory blood pressure monitoring			
24-hour SBP, mm Hg	125.9 (12.1)	130.6 (13.1)	0.02
24-hour DBP, mm Hg	76.5 (71.5, 81.1)	77.7 (70.3, 80.3)	0.37
24-hour PP, mm Hg	49.3 (10.4)	55.2 (10.6)	*o* 0.01
Day SBP, mm Hg	131.8 (12.2)	135.6 (13.0)	0.06
Day DBP, mm Hg	81.1 (75.9, 86.2)	79.4 (72.8, 86.4)	0.18
Day PP, mm Hg	50.8 (10.8)	56.0 (10.3)	*o* 0.05
Night SBP, mm Hg	116.6 (14.3)	121.9 (16.6)	0.04
Night DBP, mm Hg	69.2 (63.6, 74.6)	69.9 (62.7, 75.0)	0.49
Night PP, mm Hg	47.1 (11.1)	52.7 (12.4)	*o* 0.05
Cerebral small–vessel disease			
Number of lacunar infarcts			0.04
None	585 (93.2%)	63 (88.7%)	
Single	34 (5.6%)	4 (5.9%)	
Multiple	9 (1.4%)	4 (5.9%)	
Periventricular WMH (Fazekas scale)			0.12
Grade *o* 2	578 (92.0%)	61 (85.9%)	
Grade ⩾ 2	50 (80%)	10 (14.1%)	
Deep WMH score (Fazekas scale)			0.01
Grade *o* 2	604 (96.2%)	63 (88.7%)	
Grade ⩾ 2	24 (3.8%)	8 (11.3%)	

Abbreviations: BPLD, blood pressure–lowering drug; bpm, beats per minute; cf-PWV, carotid–femoral pulse wave velocity; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; VRF, vascular risk factor; WMH, white matter hyperintensity. For continuous variables mean (s.d.) or median (interquartile range) and for categorical variables count (%) are given. Significant values are shown in italics.

Table 3. Associations between cognitive status and arterial stiffness

	Model 1 OR for MCI (95% CI)	Model 2 OR for MCI (95% CI)
Office PP per s.d.	1.429 (0.825, 2.478)	1.485 (0.857, 2.575)
24-hour PP per s.d.	1.642 (0.834, 3.231)	1.969 (0.966, 4.102)
Day PP per s.d.	1.564 (0.785, 3.116)	1.842 (0.895, 3.791)
Night PP per s.d.	2.254 (1.029, 4.939)	2.552 (1.137, 5.728)
Cf-PWV per s.d.	1.143 (0.816, 1.602)	1.102 (0.775, 1.567)

Abbreviations: Cf-PWV, carotid–femoral pulse wave velocity; CI, confidence interval; MCI, mild cognitive impairment; OR, odds ratio; PP, pulse pressure. Model 1: Adjusted by age, sex, education, diabetes mellitus, total cholesterol, smoking, heart rate, thiazides, antiplatelets, and systolic blood pressure of the analyzed period. Model 2: Additionally adjusted by the number of lacunar infarcts and deep white matter hyperintensities. Significant values are shown in italics.

measurements.[26] Our results are therefore in agreement with those studies but some important differences should be noted among them. They had small sample size not only in MCI but also in control groups, one only used cognitive screening tools to diagnose cognitive impairment, the other one did not separate the results for the different ABPM periods and none of them corrected their analysis for VRFs and MRI lesions.

Regarding the relevance of the timing of PP assessment, it is well known that PP is defined by structural (stroke volume, velocity of ventricular ejection, and arterial compliance) and functional components and indeed these components might differ between day and night, after a circadian rhythm. During daytime, neurohumoral systems like the renin–angiotensin–aldosterone system are activated and sympathetic activity (that causes vasoconstriction) predominates. In contrast, while we sleep parasympathetic activity increases while a decrease in sympathetic and renin–angiotensin–aldosterone system activity is observed. Thus, the sleeping

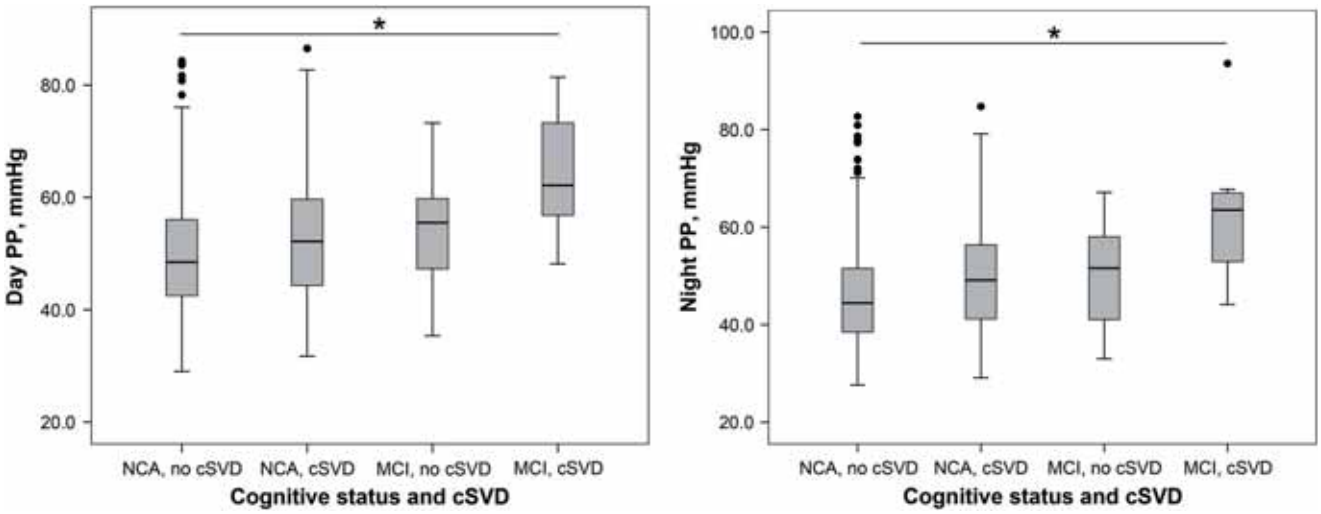

Figure 2. Relation between cognitive status and cSVD with day and night PP. No cSVD: participants without lacunar infarct and grade < 2 in deep WMHs. cSVD: participants who had either a lacunar infarct, deep WMH grade ⩾ 2 or both. cSVD, cerebral small–vessel disease; MCI, mild cognitive impairment; NCA, normal cognitive aging; PP, pulse pressure; WMHs, white matter hyperintensities. *P-value< 0.05; •, Outlayer case.

period is less dependent on the effect of neurohumoral factors like renin–angiotensin–aldosterone system and other environmental stimulus and might be more suitable to predict outcomes. Our results show a cross-sectional association of nocturnal PP with MCI patients, which is independent of nocturnal BP values. This might be surprising given the increasing evidence suggesting a role for nocturnal hypertension predicting cardiovascular risk.[27] But, in the case of cognitive function and status, only a few case–control studies have linked higher night SBP with lower cognitive performance with Mini-Mental State Examination or mainly with neurodegenerative dementia (Alzheimer's disease).[28,29]

Recently, 24-hours brachial PWV–recording devices have appeared and showed good and reproducible measurements.[30] Future studies should investigate whether 24-hours, daytime, or nighttime PWV provide useful predictive information on cognitive function and dementia, as we have shown for PP.

Other important findings in our study are that in middle-aged and older-treated hypersensitive individuals, PP was also related to the presence of cSVD and both were related to MCI. A previous observational study showed that ambulatory SBP at nighttime was associated with the presence and progression of WMHs and SBP at daytime was only related to WMH progression.[31] Indeed, a crosstalk has been described between large and small brain arteries that might partly explain our findings. In normal conditions, cerebrovascular autoregulation maintains cerebral blood flow constant despite the changes in BP in large vessels such as carotid and vertebral arteries thereby protecting the brain from changes in perfusion pressure. However, an increase in PP has a greater effect on brain cells than in peripheral organs, since they lack the protection of upstream-vasoconstricted vessels. So, small brain arteries depend on their own resilience to adapt to high-pressure fluctuations and the failure in this adaptation leads to microvasculature damage (hypertrophic remodeling of the vessel wall, lumen narrowing, and vessel rarefaction), which may not only serve to protect the microcirculation from pulsatile barotrauma in the presence of high PP, but also in return will cause an increased resistance to blood flow.[32] Microvascular disease may produce hypoperfusion that could lead to cognitive impairment.[33] Also, microvascular disease may result in cerebral infarctions and takes part in the genesis of WMHs as seen in previous studies.[34] Then, both the number of silent brain infarcts and WMHs were related to cognitive impairment and dementia, in part because of disconnection of cortico-subcortical loops.[35] Our results also showed that daytime PP was associated with attention function, which is considered to be localized in frontal regions that have cortico-subcortical connections.[36]

Our findings might have therapeutic implications. Lifestyle interventions like aerobic physical exercise have been shown to reduce AS[37] and also, a protective role for cognitive decline has been suggested.[38] Clinical trials with antihypertensive medication also shown to be effective to reduce AS.[39] However, inconsistent results were shown when analyzing if antihypertensive treatment was able to reduce the progression of cognitive decline and the clinical onset of dementia.[40] Although limitations of these trials have been noted (i.e., cognitive results were analyzed as secondary outcomes and with small sample sizes, short follow-up time, etc.), it remains to be determined if reducing AS has any added effect on reducing dementia and cognitive decline beyond what should be expected by BP reduction. In our case, differences were seen with different BPLDs both for cognitive status and cognitive function (although they were not independent of VRFs and AS), further research is therefore needed to clarify the differential effect of BPLDs in cognitive impairment.

The strengths of this study are the relatively large sample size of community-dwelling hypersensitive individuals without dementia and stroke. Besides, AS measurements were performed by different approaches with oscillometric devices, at different places (office and ambulatory) and as single and multiple (24 hours) assessments. Similarly, we used a standard MRI protocol for the whole cohort and adjusted our results also for VRFs and cSVD. We used a quite extensive cognitive screening test for the selection and diagnosis of the participants that provide more information than for instance Mini-Mental State Examination or other shorter tests. However, using a comprehensive cognitive battery for all the participants, and not in those who failed the DRS-2, just would have diminished the rate of misdiagnosis associated with screening tests. Also using volumetric assessment of white and gray matter would permit a more accurate quantification of cSVD.

AUTHOR CONTRIBUTIONS

IR-L helped in study conception and design, acquisition of data, analysis and interpretation of data, drafted the manuscript, and approved the final version of the manuscript. CN helped in acquisition of data, interpretation of data, drafted the manuscript, and approved the final version of the manuscript. JF helped in acquisition of data, drafted the manuscript, and approved the final version of

the manuscript. JLT, XM, and AV-B helped in interpretation of data, revised it critically for intellectual content, and approved the final version of the manuscript. EV helped in study design, interpretation of data, revised it critically for intellectual content, and approved the final version of the manuscript. CIJ helped in acquisition of data, revised it critically for intellectual content, and approved the final version of the manuscript. JM helped in study conception and design, interpretation of data, revised it critically for intellectual content, and approved the final version of the manuscript. PD is the corresponding author and helped in study conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it for intellectual content, and approved the final version of the manuscript.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Journal of Cerebral Blood Flow & Metabolism website (http://www.nature.com/jcbfm)

Supplemental Table 1. Univariate analysis of cognitive function with VRF, arterial stiffness and cerebral small vessel disease.

Characteristic	Z Total	Z Attention	Z Executive function	Z Memory
Age, years	**r=-0.29, p<0.01**	**r=-0.21, p<0.01**	**r=-0.27, p<0.01**	**r=-0.11, p<0.05**
Sex, male vs female	**0.08(0.97) vs -0.09(1.02)**	**0.11(0.82) vs -0.12(1.16)**	**0.10(1.22) vs -0.11(1.16)**	-0.01 (0.99) vs 0.01(0.98)
	p=0.01	**P<0.05**	**P<0.05**	p=0.60
Education, years	**r=0.49, p<0.01**	**r=0.34, p<0.01**	**r=0.45, p<0.01**	**r=0.23, p<0.01**
Diabetes mellitus, yes vs. no	-0.11(1.09) vs 0.03(0.97)	-0.08(1.26) vs 0.02(0.92)	-0.05(1.17) vs 0.01(1.19)	-0.13 (1.16) vs 0.04(0.94)
	p=0.15	p=0.43	p=0.47	p=0.12
Total cholesterol, mg/dl	r=0.03, p=0.42	r=-0.03, p=0.37	r=0.04, p=0.32	r=-0.01, p=0.84
Current smoker, yes vs no	**0.17(0.91) vs -0.04(1.01)**	**0.18(0.83) vs -0.04(1.03)**	0.18(1.12) vs -0.04(1.20)	0.10(0.97) vs -0.02(1.00)
	p=0.05	**p=0.02**	p=0.07	p=0.22
cfPWV, m/s	r=-0.07, p=0.06	r=0.01, p=0.91	**r=-0.09, p=0.02**	r=-0.02, p=0.61
Long acting Calcium channel blocker use, yes vs. no	-0.15(1.1) vs. 0.03(0.98)	-0.10(1.0) vs. 0.01(1.03)	-0.14(1.30) vs. 0.03(1.17)	-0.06(1.11) vs. 0.02(0.98)
	p=0.12	p=0.31	p=0.19	p=0.48
Thiazide use, yes vs. no	-0.06(1.01) vs. 0.05(0.99)	-0.08(0.99) vs. 0.06(1.05)	-0.03(1.21) vs. 0.04(1.16)	-0.03(0.99) vs. 0.04(1.01)
	p=0.12	vs. p=0.07	p=0.43	p=0.35
Beta blocker use, yes vs. no	0.03(0.97) vs. -0.10(1.01)	-0.01(0.83) vs.-0.01(1.08)	0.07(1.22) vs. -0.14(1.17)	-0.04(0.99) vs. 0.02(1.00)
	p=0.61	p=0.98	p=0.43	p=0.53
Angiotensin converting enzyme inhibitor use, yes vs. no	-0.04(0.95) vs. -0.04(1.05)	**0.11(0.78) vs. -0.12(1.20)**	0.00(1.23) vs. 0.00(1.015)	0.05(0.91) vs. -0.04(1.07)
	p=0.28	**p=0.003**	p=0.21	p=0.99
Angiotensin receptor	-0.10(1.08) vs. 0.04(0.97)	-0.07(1.07) vs. 0.02(0.01)	-0.07(1.18) vs. 0.03(1.18)	-0.09(1.08) vs. 0.04(0.96)

blocker use, yes vs. no	p=0.13	p=0.29	p=0.32	p=0.13
Office PP, mmHg	**r=-0.15, p<0.01**	**r=-0.09, p=0.01**	**r=-0.15, p<0.01**	r=-0.01, p=0.80
24 PP, mmHg	**r=-0.24, p<0.01**	**r=-0.14, p<0.05**	**r=-0.21, p<0.01**	r=-0.08, p=0.10
Day PP per SD increase, mmHg	**r=-0.23, p<0.01**	**r=-0.13, p<0.05**	**r=-0.20, p<0.01**	r=-0.08, p=0.11
Night PP, mmHg	**r=-0.22, p<0.01**	**r=-0.14, p<0.05**	**r=-0.18, p<0.01**	r=-0.08, p=0.12
Any lacunar infarct	p=0.53	p=0.57	p=0.35	p=0.79
Number of lacunar infarcts	r<-0.01, p=0.86	r=0.02, p=0.54	r=0.01, p=0.69	r<-0.05, p=0.95
Subcortical WMH	**r=-0.16, p<0.01**	**r=-0.09, p=0.01**	**r=-0.13, p<0.01**	**r=-0.10, p<0.05**
Periventricular WMH	**r=-0.09, p=0.01**	r=-0.03, p=0.35	**r=-0.10, p<0.05**	r=-0.02, p=0.54
Total WMH	**r=-0.15, p<0.01**	**r=-0.08, p=0.02**	**r=-0.13, p<0.01**	r=-0.07, p=0.04

Associations between continuous variables are expressed as correlation coefficient r and p-value, mean (SD) and p-value or count (%) and p-value when one variable is not continuous. PP: pulse pressure. Cf-PWV: carotid-femoral pulse wave velocity. WMH: white matter hyperintensities.

Significant values are shown in bold.

D.5 Small cortical infarcts: prevalence, determinants and cognitive correlates in the general population. International Journal of Stroke, 2015 (manuscrito aceptado para publicación)

Small Cortical Infarcts: Prevalence, Determinants And Cognitive Correlates In The General Population

Small cortical infarcts in the general population

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Background **Cortical brain infarcts are defined as infarcts involving cortical grey matter, but may differ considerably in size. It is unknown whether small cortical infarcts have a similar clinical phenotype as larger counterparts. We investigated prevalence, determinants and cognitive correlates of small cortical infarcts in the general population and compared these to large cortical infarcts and lacunar infarcts.**

Methods **4905 individuals from a population-based study (age 63.95±10.99). Infarcts were rated on MRI and participants were classified according to mean infarct diameter into small (≤15mm in largest diameter) or large (>15mm) cortical infarcts, lacunar infarcts or a combination of subtypes. Spatial distribution maps were created for manually labeled small and large infarcts. Participants underwent cognitive testing. Analyses were performed using multinomial regression and analysis of covariance.**
Results **381 (7.8%) persons had any infarct on MRI, among whom 54 with small (1.1%) and 77 (1.6%) with large cortical infarcts. Small cortical infarcts were mainly localized in external watershed areas, whereas large cortical infarcts were localized primarily in large arterial territories. Age (OR=1.06; 95% CI= 1.02,1.09), male sex (1.98;1.01,3.92) and smoking (2.55;1.06,6.14) were determinants of small cortical infarcts. Participants with these infarcts had worse scores in delayed memory, processing speed and attention tests than persons without infarcts, even after adjustment for cardiovascular risk factors.**

Conclusions **In the elderly, small cortical infarcts appear as frequent as large infarcts but in different localization. Our results suggest that small cortical infarcts share cardiovascular risk factors and cognitive correlates with large cortical, but also with lacunar infarcts.**

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Introduction

In old age, cerebrovascular disease with ischemic stroke as the most common manifestation is highly frequent. Apart from their clinical presentation, brain infarcts are also common findings on brain MRI studies in the general elderly population.[1] These MRI-defined infarcts have been related to risk of dementia and lower cognitive function,[2, 3] even when the infarcts were clinically asymptomatic.[1]

The localization and number of infarcts have clinical implications. Cortical infarcts, especially if multiple, have been related to poor global and memory performance and inconsistently to worse processing speed.[4-6] Conversely, lacunar infarcts in the subcortical regions have been frequently associated to executive dysfunction, decline of psychomotor speed and also memory deficits when affecting thalamic nuclei.[1, 7]

Recently, attention has been focused towards cortical microinfarcts, very small size infarcts only seen on microscopic pathologic studies or in vivo high field MRI.[8-10] Based on features on pathologic examination and on their presentation in selected patient populations, these microinfarcts are currently considered a marker of cerebral small vessel disease. Although few clinical-pathological and community-based studies have suggested that these lesions are related to dementia and low cognitive performance,[11-14] potential clinical implications of these tiny lesions during life remain largely unknown. Though not microscopic in size, small sized cortical infarcts are also frequently seen on imaging studies in populations of asymptomatic persons or in community dwelling cohorts. However, to date we do not know if differences exist between small (but still visible) and larger cortical infarcts on conventional MRI. For example, it is unknown whether small cortical infarcts are pathophysiologically similar but just smaller in size compared to their larger counterparts or whether they should be considered as a separate subtype between microinfarcts and large cortical infarcts. It is in particular interesting to study whether these small cortical infarcts share determinants with their larger counterparts, whether they demonstrate a similar spatial distribution, and how these small cortical lesions affect cognitive function.

Aim of the present study was to investigate the prevalence and distribution of small cortical infarcts in a general aging population, study their determinants and how these infarcts relate to cognitive function. We compared this to large cortical infarcts, lacunes and combined infarct types.

Methods

Participants The study is based on participants from the Rotterdam Study, a population-based study in The Netherlands that aims to investigate determinants of several chronic diseases among elderly people[15]. The original cohort consists of general population older than 55 years (n=7983) followed since 1990 and had been expanded with participants older than 45 twice, in 2000 (n=3011) and in 2006 (n=3932). Participants are invited every two or three years for the follow-up visits. Since 2005 participants with no contraindications for brain MRI were invited to undergo brain MRI in each round of visits.

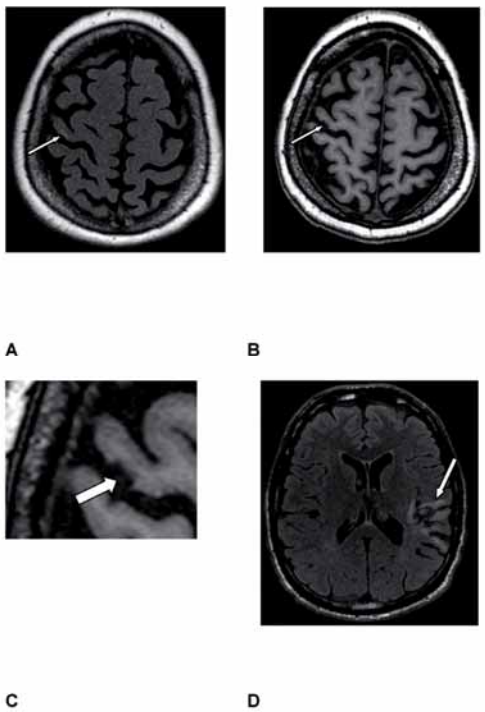
For this analysis we used data from the last completed visit of the three cohorts (from 2005 to 2011). All participants underwent a brain MRI, were not demented and had data at least in one of the cognitive tests (N=4905).

The Rotterdam Study has been approved by the medical ethics committee according to the Wet Bevolkingsonderzoek

ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants gave written informed consent.

MRI-defined infarcts The MRI protocol was described elsewhere.[16] In short, we performed an identical brain MRI protocol with the same 1.5-T scanner. Brain infarcts were rated on T1 weighted (T1), proton density weighted (PD) and axial fluid-attenuated (FLAIR) sequences. For this study, only supratentorial infarcts were considered. We defined cortical infarcts as supratentorial lesions involving cortical gray matter, hypointense in axial T1 and hyperintense in PD and FLAIR sequences with a hyperintense rim surrounding them. A cut-off of 15 mm size between small and large cortical infarcts was based on mean cortical infarct diameter across the population as well as previous literature[17] .So, in practice cortical infarcts were considered small when the widest diameter of tissue loss was ≤ 15 mm and large when >15mm. Examples of these infarcts are displayed in Figure 1. Lacunar infarcts were defined as lesions from ≥ 3 to <15 mm in the supratentorial region, without cortical grey matter involvement, and with cerebrospinal-like signal characteristics in all pulse sequences and with the presence of a hyperintense rim surrounding them on FLAIR. .[16] Participants were categorized according to infarct type (no infarct, small cortical infarcts, large cortical infarcts, lacunar infarcts or combination of infarcts). Combination of infarct types was considered when a participant had both lacunar infarct(s) and any cortical infarct(s). Persons with both small and large cortical infarcts were categorized in the large cortical infarct category. In a sensitivity analysis, we checked whether grouping of these persons into the combination of infarct types changed the results (see also Statistical Analysis).

Figure 1: Examples of small and large cortical infarcts. In the upper panels, a small cortical infarct (arrows) is shown in FLAIR (A) and T1 (B) weighted sequences. A magnification of the small cortical infarct image showing tissue loss (arrow) is displayed in C. A large cortical infarct (arrow) in the left temporal cortex is seen (D).



Rating of presence of all infarcts was done by trained physicians. [16] Distinction between small and large cortical infarcts was performed afterwards by a single trained physician who was blinded to clinical information. First, the reading and measuring of cortical infarcts was performed with a digital picture archiving and communication system. Doubtful cases were decided by consensus of a senior neuroradiologist and a senior trained researcher. Second, labeling of small and large cortical infarcts was performed by marking the center of the lesion using in-house developed software. For analysis across the study population all T1 weighted MR scans and marked locations were registered to MNI template space (http://www.mni.mcgill.ca/).Using the marked locations spatial probability maps were constructed with kernel density estimation for small and large cortical infarcts separately. A Gaussian kernel was used to obtain the probability density function which showed the spatial distribution of the cortical infarcts.

Cognitive assessment Cognitive performance was assessed in the same round of visits of the MRI examination. The cognitive battery included the 15-word verbal learning test (WLT, based on Rey's recall test), the Letter-digit substitution test (LDST), the Stroop test, the Purdue Pegboard test and a verbal fluency test (semantic category).

We standardized the raw data with its Z score (individual test score minus mean test score of the entire sample divided by the standard deviation).

As described previously,[18] we calculated a general cognitive factor (G-factor) performing a principal component analysis incorporating Color-word interference subtask of the Stroop test, LDST, verbal fluency test, delayed recall score of the 15-WLT and Purdue Pegboard Test of both hands. This analysis was performed on complete case data of 4135 persons. The G-factor was identified as the first unrotated component of the factor analysis and explained 50.9% of all variance in the cognitive tests.

Assessment of covariates Cardiovascular risk factors were assessed during study visits either by interview or by physical examination or laboratory tests.[19] Cardiovascular risk factors in our analysis included systolic and diastolic blood pressure, total and high-density (HDL) cholesterol, diabetes mellitus, smoking (never, previous smoker and current smoker) and being under blood pressure lowering drugs.

Education level was divided into 7 categories: 0= primary , 1=lower vocational , 2=lower secondary , 3=intermediate vocational , 4=general secondary , 5=higher vocational and 6=university.

ApoE genotyping was performed on coded genomic DNA samples in 4587 cases (93.5%). Distribution of ApoE genotype and allele frequencies was in Hardy-Weinberg equilibrium.

Statistical analysis For descriptive purposes, categorical variables were expressed in numbers and percentages. For continuous variables mean and standard deviation or median and interquartile range were used depending on their normality.

We investigated the relation of several cardiovascular risk factors, blood pressure lowering drugs, education and ApoE to the different infarct groups (no infarcts, small cortical, large cortical, lacunar and combined infarct types) using multinomial logistic regression. Results are given in OR and 95% confidence interval.

We used analysis of covariance to assess the relation of each cognitive test (Z score and G-factor) with the different infarct groups. In the first model the analysis was adjusted by age, sex and education. In the second model we additionally adjusted for several cardiovascular risk factors, blood pressure lowering drugs and ApoE4 alleles.

We repeated the analysis after classification of participants with both small and large cortical infarcts into the combination of infarcts category. Also, we repeated the analysis after excluding those individuals who had a prevalent stroke. Results are given in mean group differences and 95% confidence interval. No infarct group was the reference category.

All the analyses were done using SPSS 19. P-values <0.05 were considered significant.

Results

Prevalence of any supratentorial brain infarct was 7.8% (n=381) in the entire population. Cortical infarcts had a mean diameter of 14.4±15.32. Of persons with infarcts, 54 (14.2%) had small, 77 (20.2%) had either large cortical infarct(s) or large and small cortical infarcts, 224 lacunar (58.8%) and only 26 (6.8%) had combined infarct types.

Table 1 shows the characteristics of the study population. Mean age was 63.9 years and 55% were women.

Table 1. Population characteristics.

Characteristic	N=4905
Age at scan (years)	63.9(±11.0)
Sex, male	2208(45.0%)
Systolic blood pressure (mmHg)	139.1(±21.4)
Diastolic blood pressure (mmHg)	82.5(±10.9)
Lowering blood pressure drugs	1329(36.1%)
Diabetes mellitus	478(9.8%)
Total cholesterol (mmol/L)	5.5(±1.1)
HDL cholesterol (mmol/L)	1.4(±0.4)
Active smoker	759(15.6%)
Past smoker	2636(54.0%)
Educational level	3[1,3]
ApoE4 one allele	1215(26.5%)
ApoE4 both alleles	112(2.4%)

Values are means (standard deviation) or numbers (percentage) or median [interquartile range]. Missing data: ApoE Alleles (318)

Table 2 shows the relation of demographic characteristics, several cardiovascular risk factors, hypertension treatment and ApoE4 allele with infarct types. Small cortical infarcts were associated with increasing age, male sex and smoking compared to persons without infarcts. Otherwise, the use of blood pressure lowering drugs was associated to less presence of small cortical infarcts.

Table 2. Association of infarct types with cardiovascular risk factors, hypertension treatment, education and ApoE4 alleles, using multinomial regression analysis.

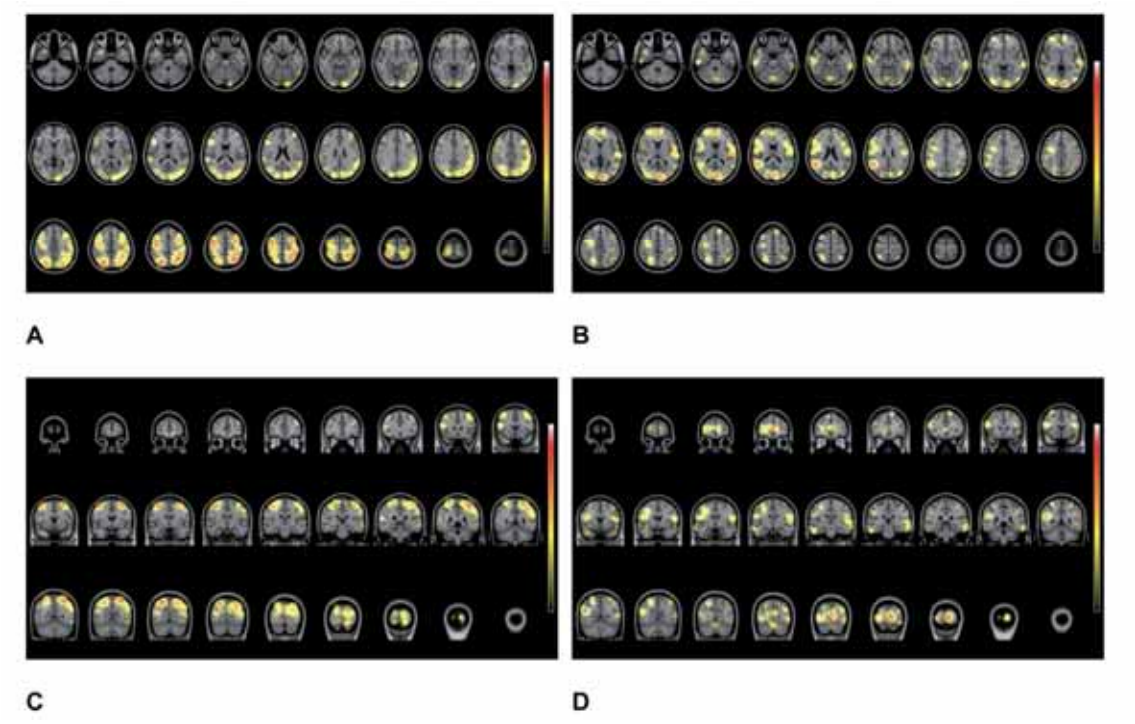
	Small cortical infarcts (N=54)	Large cortical infarcts (N=77)	Lacunar infarcts (N=224)	Combined infarct types (N=26)
Age per year increase	**1.06(1.02;1.09)**	**1.06(1.03;1.09)**	**1.07(1.05;1.08)**	**1.08(1.03;1.13)**
Sex, male	**1.98(1.01;3.92)**	**2.13(1.22;3.73)**	**1.78(1.26;2.50)**	0.62(0.24;1.62)
Systolic blood pressure per mmHg increase	1.01(0.99;1.03)	**0.98(0.96;0.99)**	1.01(0.99;1.02)	1.01(0.98;1.03)
Diastolic blood pressure per mmHg increase	0.98(0.95;1.01)	**1.04(1.01;1.07)**	1.01(0.99;1.03)	1.01(0.96;1.06)
Use of blood pressure lowering drugs	**0.49(0.26;0.93)**	**0.58(0.34;0.97)**	0.76(0.55;1.04)	0.98(0.40;2.43)
Diabetes mellitus	1.36(0.55;3.36)	1.53(0.64;3.66)	0.76(0.51;1.16)	**0.36(0.14;0.93)**
Total cholesterol per mmol/L increase	0.92(0.68;1.23)	0.92(0.72;1.18)	0.90(0.77;1.04)	**0.63(0.41;0.97)**
HDL cholesterol per mmol/L increase	0.62(0.26;1.48)	1.14(0.58;2.22)	1.16(0.77;1.73)	0.47(0.13;1.67)
Active smoker	**2.55(1.06;6.14)**	1.89(0.89;3.99)	**1.99(1.22;3.27)**	1.87(0.59;5.93)
Past smoker	0.98(0.46;2.07)	1.03(0.57;1.86)	1.24(0.86;1.80)	0.58(0.22;1.53)
Educational level	0.98(0.82;1.16)	0.88(0.76;1.02)	0.97(0.89;1.06)	1.22(0.95;1.57)
ApoE4 one allele	0.99(0.51;1.95)	0.76(0.42;1.39)	1.01(0.72;1.43)	2.21(0.93;5.25)
ApoE4 both alleles	1.98(0.46;8.57)	2.59(0.90;7.45)	1.99(0.92;4.30)	-

Values are OR and 95% CI. Reference category is no infarcts (N=4524). Significant values are bolded.

Analysis is adjusted by all covariates (age, sex, education, systolic and diastolic blood pressure, use of blood pressure lowering drugs, diabetes mellitus, Total and HDL cholesterol, smoking habit and ApoE4).

Figure 2 displays spatial distribution maps for all small and large cortical infarcts. Neither small nor large infarcts were uniformly distributed. The small ones were more frequently found in external border zone areas in frontal and parietal cortex. By contrast, large cortical infarcts were more frequently located in areas corresponding to large territorial zones of medial, anterior and posterior cerebral arteries.

Figure 2: Spatial distribution maps for small and large cortical infarcts. Backgrounds are T1 weighted MNI templates overlayed with the colored spatial distribution maps. Axial (A) and coronal (C) cross-section for small cortical infarcts showing accumulation of lesions in external borderzones. Axial (B) and coronal (D) cross-section showing accumulation of large cortical infarcts in temporoparietal cortex and left external occipital borderzone. Color scale, increasing probability of finding an infarct from below (transparency, lowest probability) to top (white, highest probability).



Regarding cognitive function, Tables 3 and 4 display the results for the relation of different infarct types with cognitive performance. Compared to persons without infarcts, those with small cortical infarcts showed lower scores in delayed recall in WLT (Table 3) and Stroop test (Table 4) after adjusting for age, education and gender (model 1). The pattern of association between small infarcts and cognition showed similarities with both lacunes (for Stroop test) and large cortical infarcts (for delayed memory in WLT and Stroop) as compared to persons without infarct. Large cortical infarcts and combined infarct type groups showed worse function on virtually all cognitive tests. Further correction for cardiovascular risk factors and ApoE4 genotype (model 2) did not change substantially the results, except for Stroop part 1 in large cortical infarcts and Stroop part 2 in small cortical infarcts that lost their significance (Table 4).

Table 3. Association of cognitive performance with brain infarcts, using analysis of covariance.

	Purdue both hands	Stroop 1	Stroop 2	Stroop 3	Cognitive G-factor
Small cortical infarct					
Model 1	0.12(-0.12;0.37)	**0.54(0.28;0.81)**	**0.27(0.01;0.54)**	**0.40(0.15;0.65)**	-0.22(-0.47:0.03)
Model 2	0.18(-0.13;0.37)	**0.48(0.21;0.75)**	0.21(-0.06;0.50)	**0.42(0.16;0.69)**	-0.22(-0.48;0.03)
Large cortical infarct					
Model 1	**-0.33(-0.54;-0.12)**	**0.27(0.04;0.50)**	**0.60(0.36;0.82)**	**0.50(0.29;0.71)**	**-0.46(-0.67;-0.24)**
Model 2	**-0.32(-0.53;-0.10)**	0.22(-0.01;0.45)	**0.54(0.30;0.77)**	**0.49(0.27;0.71)**	**-0.44(-0.66;-0.23)**
Lacunar infarct					
Model 1	**-0.32(-0.44;-0.20)**	**0.19(0.06;0.32)**	**0.21(0.08;0.34)**	**0.13(0.01;0.26)**	**-0.27(-0.39;-0.15)**
Model 2	**-0.34(-0.46;-0.21)**	**0.20(0.06;0.33)**	**0.21(0.07;0.35)**	**0.13(0.01;0.26)**	**-0.27(-0.40;-0.15)**
Combination of infarct types					
Model 1	**-0.67(-0.99;-0.35)**	**0.60(0.23;0.96)**	**0.78(0.41;1.15)**	**0.65(0.30;0.99)**	**-0.87(-1.18;-0.57)**
Model 2	**-0.61(-0.93;-0.28)**	**0.52(0.16;0.89)**	**0.68(0.30;1.05)**	**0.62(0.26;0.98)**	**-0.81(-1.12;-0.50)**

Values represent difference in Z score for cognitive tests for each type of infarcts, compared to reference category (no infarcts). Significant values are bolded.

Model 1: adjusted by age, education and sex.

Model 2: Additionally adjusted by systolic and diastolic blood pressure, Total and HDL cholesterol, diabetes, smoking, blood pressure lowering drugs, ApoE4.

Table 4. Association of cognitive performance with brain infarcts, using analysis of covariance.

	WFT	LDST	WLT immediate recall	WLT delay recall	WLT recognition
Small cortical infarct					
Model 1	-0.17(-0.42;0.07)	-0.24(-0.48;0.01)	-0.09(-0.35;0.17)	**-0.30(-0.56;-0.03)**	-0.21(-0.49;0.08)
Model 2	-0.20(-0.46;0.06)	-0.19(-0.44;0.07)	-0.11(-0.38;0.16)	**-0.31(-0.59;-0.04)**	-0.16(-0.45;0.14)
Large cortical infarct					
Model 1	**-0.28(-0.49;-0.07)**	**-0.38(-0.58,-0.19)**	-0.20(-0.42;0.02)	**-0.40(-0.61;-0.17)**	-0.08(-0.31;0.16)
Model 2	**-0.22(-0.44;-0.01)**	**-0.33(-0.54;-0.13)**	-0.19(-0.42;0.03)	**-0.37(-0.60;-0.14)**	-0.09(-0.33;0.15)
Lacunar infarct					
Model 1	-0.12(-0.25;0.01)	**-0.25(-0.37;-0.13)**	-0.11(-0.24;0.02)	-0.13(-0.26;0.01)	-0.05(-0.19;0.09)
Model 2	**-0.14(-0.27;-0.01)**	**-0.25(-0.37;-0.12)**	-0.07(-0.21;0.06)	-0.10(-0.24;0.04)	-0.05(-0.20;0.09)
Combination of infarct types					
Model 1	**-0.48(-0.83;-0.12)**	**-0.64(-0.97;-0.31)**	-0.30(-0.65;0.04)	**-0.51(-0.86;-0.16)**	-0.12(-0.50;0.025)
Model 2	**-0.39(-0.76;-0.02)**	**-0.59(-0.93;-0.24)**	-0.24(-0.60;0.12)	**-0.42(-0.80;-0.06)**	-0.08(-0.48;0.31)

Values represent difference in Z score for cognitive tests for each type of infarcts, compared to reference category (no infarcts). In the Stroop tests higher score means worse performance (longer time to complete the task). Significant values are bolded.

Model 1: adjusted by age, education and sex.

Model 2: Additionally adjusted by systolic and diastolic blood pressure, Total and HDL cholesterol, diabetes, smoking, blood pressure lowering drugs, ApoE4.

When directly comparing cognitive performance of persons with small cortical infarcts with those who had other types, results were in similar direction. People with small cortical infarcts had on average better cognitive function than persons with other infarct types, except in Stroop part 3 that they had worse perfomance than people with lacunar infarcts ($p<0.05$). These results are shown in Supplemental Figure I.

Repeating the analyses considering those participants who had both small and large cortical infarcts in the combination of infarcts category did not change the interpretation of results (data not shown).

After exclusion of participants with previous symptomatic stroke (n=28), the associations of cognitive scores with small cortical infarcts (compared with no infarct group) remained, even after adjusting for the covariates in model 2 (supplemental Tables I and II). However, virtually all the differences between infarct groups attenuated or disappeared (see supplementary figure II for G-factor, rest of data not shown).

Discussion

In this general population of non-demented elderly participants we found that over 14% of persons with MRI-defined brain infarcts exhibit only small-sized (≤ 15 mm) cortical infarcts (overall prevalence 1.1%). Our most important findings are that small cortical infarcts are located preferentially in the external border zone areas and share determinants with other infarct types. Besides, small cortical infarcts are associated with delayed memory deficit and worse scores in attention, information processing speed and interference of automated response tasks. Loss of cognitive function associated with small cortical infarcts is however less severe compared to large cortical infarcts, lacunes and combined infarct types.

Strengths of our study are its population based-design and large sample size. Some limitations of our study should be considered. First, our study is cross-sectional and therefore we cannot establish causality. Second, we did not separately rate infratentorial infarcts that might influence cognitive functions. [20]. Third, also in absence of a clear definition of small and large infarcts, we chose a cut off based on the size distribution in our own population and on literature on small cortical infarcts in subacute stroke.[17]

Prevalence of small cortical infarcts in our study was 1.1% of the whole cohort. That is lower than non-demented microinfarct autopsy-based studies (range from 6-43%) and microinfarct prevalence assessed by high field 7-T MRI in the control groups of clinical setting (range 27-45%).[9, 10] But it is similar to large cortical infarcts in our cohort (1.6%) and to prevalence estimates of small-sized and larger cortical infarcts found in other community-based studies assessed by 1.5 and 3-Tesla MRI (size range ≥3 to ≥16 mm, prevalence range 2.7 to 6.4%).[4-6] Small cortical infarcts were associated with male sex and increasing age similar to large cortical and lacunar infarcts. Besides, they shared determinants with large cortical infarcts and also with lacunar infarcts.

The different spatial distribution of small and large cortical infarcts suggests a different pathophysiological mechanism, but studying the disease mechanisms is beyond the objectives of our general population analysis. However, despite having similar risk factors, large cortical infarcts were frequently found in the territories of large intracranial vessels suggesting atherosclerosis of these vessels or embolism while small ones were frequently seen in external borderzone areas suggesting hypoperfusion or embolic mechanism. [21] Similarly, previous studies have found that microinfarcts were preferentially located in watershed areas of pure Alzheimer's disease autopsy cases [22] and etiology was suspected to be hypoperfusion.[23]

Previous groups have also published associations between cognitive performance and brain infarcts. However, some did not take into account cortical or subcortical localization,[24] and most did not take into account lesion size[2, 4, 5] or included only a limited number of participants[5, 6]. To our knowledge this is the first study that evaluates small cortical infarcts in a large sample of not demented individuals. It shows that despite the limited size of these infarcts they have an adverse effect in cognition.

Compared to healthy individuals, those with small cortical infarcts had a worse cognitive performance in delayed memory recall and executive function (attention, processing speed and answer inhibition). Besides, their decreased performance in both domains is similar to the one achieved by people with large cortical and lacunar infarcts although of different magnitude. When directly comparing with any infarct groups, task performance is better for small cortical infarcts in most tests suggesting an intermediate affection of these smaller lesions. However, the effects on cognition of small cortical infarcts might be also partly due to their different lobar localization that is beyond the objectives of this study.

We observed that exclusion of participants with previous symptomatic stroke did not alter the fact that persons with small cortical infarcts had worse cognitive function than controls. Moreover, differences in cognitive performance between infarct groups disappeared or attenuated. This suggests that despite the silent clinical course of small cortical infarcts they might be playing a covert role in cognition, which is to some extent similar to silent large cortical infarcts or silent lacunes.

In summary, small cortical infarcts in non-demented old people are frequently found in watershed areas and are associated with deficits in cognitive function by affecting memory and executive function. Our results suggest that small cortical infarcts share cardiovascular risk factors and cognitive correlates with large infarcts, but also with lacunar infarcts.

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Conflicts of interest None

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Supplemental Table I. Association of cognitive performance with brain infarcts after excluding prevalent stroke.

	WFT	**LDST**	WLT immediate recall	WLT delay recall	WLT recognition
Small cortical infarct	-0.20(-0.47;0.07)	-0.16(-0.42;0.10)	-0.08(-0.36;0.20)	**-0.32(-0.61;-0.04)**	-0.17(-0.47;0.12)
Large cortical infarct	-0.14(-0.39;0.10)	**-0.23(-0.46;-0.01)**	-0.02(-0.27;0.24)	-0.24(-0.50;0.01)	0.09(-0.18;0.37)
Lacunar infarct	**-0.14(-0.27;-0.01)**	**-0.25(-0.37;-0.12)**	-0.07(-0.21;0.06)	-0.10(-0.23;0.04)	-0.05(-0.20;0.09)
Combination of infarct types	-0.19(-0.59;0.21)	**-0.41(-0.78;-0.04)**	0.06(-0.34;0.45)	-0.21(-0.61;0.19)	0.13(-0.30;0.56)

Values represent difference in Z score for each type of infarcts, compared to reference category (no infarcts). In the Stroop tests higher score means worse performance (longer time to complete the task). Significant values are bolded.

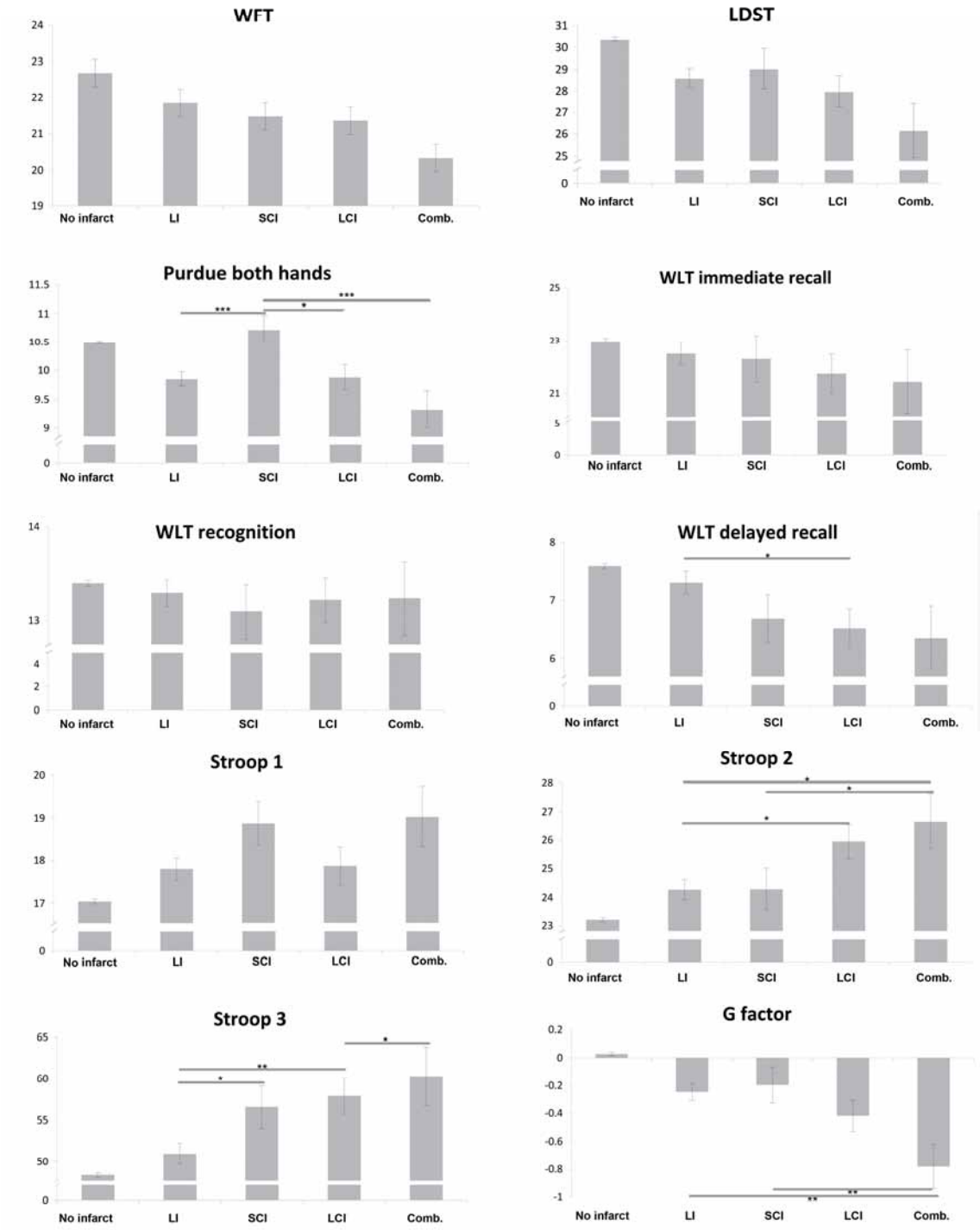
Each regression model adjusted by age, education, gender, SBP, DBP, smoking, total cholesterol, HDL cholesterol, diabetes, blood pressure lowering drugs, Apoε4.

Supplemental Table II. Association of cognitive performance with brain infarcts after excluding prevalent stroke.

	Purdue both hands	Stroop 1	Stroop 2	Stroop 3	G-factor
Small cortical infarct	0.12(-0.13;0.38)	**0.51(0.23;0.79)**	0.22(-0.06;0.50)	**0.46(0.19;0.73)**	-0.23(-0.49;0.04)
Large cortical infarct	**-0.25(-0.50;-0.01)**	0.062(-0.19;0.31)	**0.36(0.10;0.62)**	**0.44(0.20;0.68)**	**-0.31(-0.55;-0.06)**
Lacunar infarct	**-0.33(-0.46;-0.21)**	**0.20(0.06;0.33)**	**0.21(0.07;0.35)**	**0.13(0.01;0.26)**	**-0.27(-0.39;-0.15)**
Combination of infarct types	**-0.48(-0.83;-0.12)**	0.23(-0.17;0.63)	**0.46(0.05;0.87)**	0.36(-0.03;0.76)	**-0.51(-0.85;-0.17)**

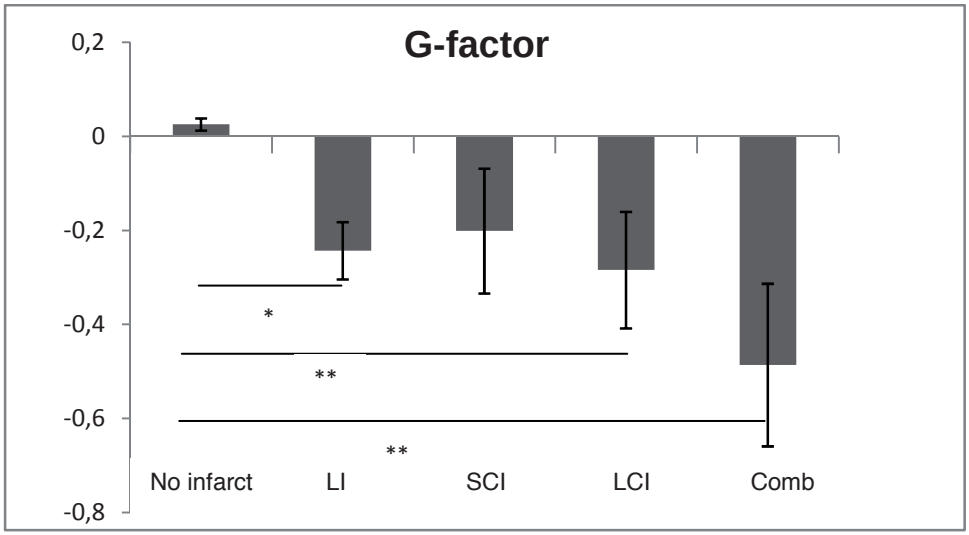
Values represent difference in Z score for each type of infarcts, compared to reference category (no infarcts). In the Stroop tests higher score means worse performance (longer time to complete the task). Significant values are bolded.

Each regression model adjusted by age, education, gender, SBP, DBP, smoking, total cholesterol, HDL cholesterol, diabetes, blood pressure lowering drugs, Apoε4.



Supplemental Figure 1: Mean and standard error of the mean for each neuropsychological test among different infarct groups after adjustment for covariates of model 2 (age, sex, education, systolic and diastolic blood pressure, diabetes mellitus, total and HDL cholesterol, smoking, blood pressure lowering drugs and ApoE4). In the Stroop tests higher positive values mean greater time to achieve the objective (worst performance). Asterisk represents statistically significant comparisons between groups with infarcts: *p≤0.05, **p≤0.005, ***p≤0.001

SCI: small cortical infarcts, LCI: large cortical infarcts, LI: lacunar infarcts, Comb: combination of infarct types



Supplemental Figure II: Mean and standard error of the mean of G-factor among different infarct groups after excluding prevalent stroke. Adjustment for covariates of model 2 (age, sex, education, systolic and diastolic blood pressure, diabetes mellitus, total and HDL cholesterol, smoking, blood pressure lowering drugs and ApoE4). *p≤0.05, **p≤0.005

SCI: small cortical infarcts, LCI: large cortical infarcts, LI: lacunar infarcts, Comb: combination of infarct types

E. SÍNTESIS DE LOS RESULTADOS Y DISCUSIÓN

E.1. La enfermedad cerebrovascular silente. Prevalencia y determinantes de los infartos cerebrales silentes (ICS) y de los espacios perivasculares dilatados (EPVD) en hipertensos.

E.1.1. Prevalencia de los ICS

Nuestros resultados muestran que la prevalencia de ICS es del 10.1%,(125) aunque sabemos que un 8.1% (0.8% en el global de participantes) no fueron realmente silentes tras una nueva entrevista centrada en posibles síntomas del infarto cerebral detectado en la resonancia.(126) Esto se puede deber a una falta de reconocimiento o a pasar por alto síntomas leves o atípicos de ictus por parte del paciente, familia o personal sanitario. Creemos que en los casos en los cuales se ha mostrado una relación entre los síntomas y la imagen radiológica ya no podemos seguir hablado de infarto cerebral silente y sería mejor usar términos como “no reportado”, “encubierto” o “subclínico”.(127)

Si nos centramos en la prevalencia de los ICS vimos que ésta es en nuestra cohorte inferior a la media de la prevalencia en hipertensos.(125) Esto se puede deber a las características de la muestra (selección al azar a partir de población hipertensa en atención primaria vs. selección en clínicas especializadas) y de los participantes (la mayoría están en tratamiento hipotensor y las cifras de la PA son más bajas que en otros trabajos en hipertensos).

En cuanto al sexo, la probabilidad de tener un ICS en hombres es más del doble que en las mujeres, independientemente de otros FRV. El análisis estratificado por sexo ya mostró diferencias importantes en los FRV y en el REGICOR, todos excepto las medidas de obesidad y la PAS fueron significativamente más elevadas en el hombre que en la mujer. Por lo tanto, los hombres tenían en general más FRV lo cual se ha relacionado con anterioridad con tener ICS.

E.1.2. Prevalencia de los EPVD

Prácticamente todos los hipertensos tienen EPVD (sólo 1.7% no muestran EPVD en centro semioval y 1.1% no tienen EPVD en ganglios de la base). Si consideramos tener >10 EPVD, un 40.0% los tienen en centro semioval y un 23.3% en ganglios de la base. Tener más EPVD en centro semioval que en ganglios de la base podría relacionarse con el hecho de que los espacios perivasculares en centro semioval están recubiertos por una sola capa leptomeningea, la cual les podría conferir mayor vulnerabilidad a la HTA y dilatarse antes que los espacios a nivel de ganglios de la base que constan de dos capas leptomeningeas.(128) La prevalencia de EPVD extensos es superior en esta cohorte de hipertensos que en la población general pero inferior a la población con ictus clínico. Este hallazgo quizás nos esté indicando una afectación intermedia de los EPVD asociada a la HTA.

E.1.3. Determinantes de los ICS y EPVD

Los determinantes de ambas lesiones son diferentes. Aunque el REGICOR está asociado a ambas lesiones en el análisis univariante (EPVD extensos en centro semioval y ICS), en el análisis multivariante sólo se mantiene en el caso de los ICS.(125) Además, los que tienen ICS tienen significativamente más antecedentes de enfermedad cardiovascular que los que no tuvieron ICS, cosa que no sucede entre los que tienen EPVD extensos en centro semioval o en ganglios de la base comparado con los que no los tienen.

Por otro lado, la microalbuminúria (un marcador de daño subclínico renal) dobla de manera independiente la probabilidad de tener ICS, mientras que no es un factor independiente de EPVD. El hecho de que los ICS estén asociados al daño subclínico renal podría indicar que el mecanismo fisiopatológico a nivel cerebral y renal es similar. Ambos comparten que son órganos de baja resistencia y tienen una mayor vulnerabilidad a la pulsatilidad del flujo que aumenta con la HTA y el envejecimiento.(105) No estar asociados

a EPVD quizás indique un mecanismo fisiopatológico diferente o un estadio previo de la enfermedad en aquellos con EPVD pero todavía sin daño cerebral mayor (o ICS).

En resumen, los ICS se asocian a una enfermedad cardiovascular más avanzada ya que se asocian en general a un mayor riesgo cardiovascular y a más enfermedad clínica y subclínica de los órganos diana de la HTA. Por lo tanto, los ICS sugieren probablemente una enfermedad hipertensiva más avanzada que los EPVD. El estudio longitudinal de esta cohorte nos posibilitará averiguar la progresión de las diferentes lesiones radiológicas estudiadas y sus relaciones causales.

Por último, los EPVD extensos tanto en centro semioval como en ganglios de la base cerebrales están relacionados con la presencia de ICS de tamaño lacunar, y en el caso de los EPVD en ganglios de la base también con las extensas HSB profundas independientemente de las otras lesiones radiológicas y del REGICOR. Por lo tanto, estamos de acuerdo con los estudios previos que mostraron que los EPVD constituyen un marcador de enfermedad de pequeño vaso cerebral.(37, 129)

E.2. Prevalencia, FRV y localización de los infartos corticales en población general

En el caso de la población general, sólo el 1.1% muestran infartos corticales pequeños y el 1.6% tienen infartos corticales grandes. Esta prevalencia es la misma que en otro estudio en la comunidad.(130) Pero es menor a la encontrada en otros estudios que incluyeron personas con una edad media más elevada o con más FRV.(131, 132)

Hemos encontrado que los FRV asociados independientemente a los infartos corticales pequeños son similares a los de los otros tipos de infarto. Nos parece especialmente interesante destacar que los infartos corticales pequeños comparten características con los infartos corticales grandes y con los infartos lacunares. El sexo masculino casi dobla la probabilidad de tener infarto cortical pequeño como sucede con el infarto cortical grande y el infarto lacunar. También los fumadores tuvieron dos veces más probabilidad de infarto

cortical pequeño e infarto lacunar. En cambio el uso de medicación hipotensora disminuye la probabilidad de cualquier infarto cortical.

Lo que nos sorprendió más fue encontrar una distribución desigual para los infartos corticales pequeños (predominan en el territorio limítrofe externo entre las zonas de irrigación de las arterias cerebrales anteriores y medias y entre las arterias cerebrales medias y posteriores) y grandes (que son más frecuentes en territorios de de las grandes arterias cerebrales: arteria cerebral media de los dos lados y arteria cerebral posterior izquierda). Esto podría indicar que la fisiopatología de ambas lesiones es diferente. Sabemos que los infartos en territorio frontera son causados por hipoperfusión o embolia o por la combinación de ambos mientras los infartos territoriales corticales son de etiología aterosclerótica o embólica.(133) En esta cohorte sería necesario esclarecer si existen estenosis intra o extracraneales que justifiquen la hipoperfusión además de de otros mecanismos como la hipotensión o si existen fuentes embolígenas a nivel cardiaco, placas ateroscleróticas a nivel extra o intracraneal con posibilidad de embolizar.

Por lo tanto, parece que los infartos corticales pequeños no son meramente lesiones corticales de pequeño tamaño sino que podrían tener una fisiopatología diferente respecto los infartos corticales grandes y unos FRV ligeramente diferentes.

Sería interesante determinar si estas lesiones son un estadio independiente o intermedio entre los microinfartos corticales y los infartos corticales grandes. Los estudios longitudinales pueden esclarecer esta y otras cuestiones planteadas.

E.3. La función cognitiva normal en hipertensos

El estudio de la función cognitiva normal y la obtención de datos normativos es imprescindible de cara al posterior estudio de la función cognitiva en una población dada.

La obtención de datos normativos para nuestra población fue una necesidad y requisito previo al estudio del estado cognitivo ya que no se disponía de datos normativos

comparables para la DRS-2. Por ello, en ausencia de otro test de cribado o batería cognitiva se tuvieron que excluir numerosos participantes (n=239) que presentaban alguna causa que podría haber interferido con la cognición o con el proceso de normalización. Queremos destacar que excluimos participantes con enfermedad clínica que podían interferir con su estado cognitivo (p.ej. personas con infarto cerebral subclínico, traumatismo cráneo-encefálico severo, insuficiencia renal crónica, déficit sensorial severo, etc.) y personas que presentaban mal control metabólico (p.ej. hemoglobina glicosilada >7%).

Encontramos que la edad y la escolaridad influían en los resultados obtenidos en el Total y en las subescalas de la DRS-2, como sucede con las puntuaciones en otros test neuropsicológicos.(48) Vimos que la puntación cruda Total de la DRS-2 fue significativamente peor en las mujeres que en los hombres. Es de destacar que las mujeres tenían menos años de escolarización que los hombres en nuestra cohorte, esto fue significativo para las de edad más avanzada (más de 63 años). Tras la corrección por años de escolaridad y edad esto se corrigió para la puntuación Total y ya no hubo diferencias entre grupos.

Además, hallamos que el 17.5% (n=140) de participantes puntuaron por debajo del punto descrito para deterioro cognitivo (≤8 puntos en DRS-2 Total ajustado por edad y escolaridad). Esta cifra está ligeramente por debajo del porcentaje original (28-19%) descrito para la puntuación del Total ≤8 ajustado por edad y escolaridad.(120)

El resto de los participantes tenían un resultado por encima del punto de corte de deterioro cognitivo en la DRS-2 y fueron considerados cognitivamente normales.

E.4. La prevalencia del Deterioro Cognitivo Ligero y su relación con los factores de riesgo vascular y con las lesiones cerebrovasculares

En el penúltimo trabajo, mostramos que la prevalencia de DCL fue de 8.9% en nuestra cohorte de hipertensos de edad comprendida entre 50-71 años. Esta es similar a la

encontrada en los estudios de base comunitaria en Norte América y Europa, aunque existen diferencias importantes con nuestra cohorte, los estudios comunitarios incluyen hipertensos y no hipertensos y la edad recogida es a partir de los 60 años.(87)

La educación como esperábamos por la literatura previa, se mostró como factor independiente de DCL en todos nuestros análisis. En cambio, en cuanto a los FRV clásicos no hubo diferencias estadísticamente significativas entre el grupo de DCL y el grupo con envejecimiento cognitivo normal (ECN).

En cuanto a las lesiones cerebrovasculares, vimos que tanto los EPVD extensos en GGBB como los ICS y los infartos lacunares y las HSB profundas se relacionaron con el DCL. El efecto fue independiente de los factores de riesgo vascular para EPVD extensos en ganglios de la base y para HSB profundas extensas. No obstante la única lesión que se relacionó de forma independiente tras ajustar por el resto de lesiones cerebrovasculares con el DCL fueron las HSB profundas extensas. En estudios previos también se mostró que las HSB están asociadas al DCL en la comunidad. Algunos grupos usaron la misma escala visual semi-cuantitativa (u otras) y otros midieron el volumen de lesión que se encontró en cualquier caso correlacionado con el DCL. (87, 134) En cuanto a la localización de las HSB, muchos estudios encontraron relación con HSB periventriculares y otros con HSB profunda.

Siguiendo las recomendaciones de los expertos, en próximos trabajos se debería estudiar el efecto conjunto de la acumulación de las diferentes lesiones cerebrovasculares en el declive cognitivo (siendo esta recomendación también válida para el ictus).(35)

E.5. La función cognitiva y su relación con las lesiones cerebrales

E.5.1 Los infartos corticales en la población general y su relación con las funciones cognitivas

En la cohorte del estudio Rotterdam vimos que aquellos con infartos corticales tanto pequeños como grandes tienen peor memoria diferida y peor función ejecutiva

(incluyendo velocidad de procesamiento y atención) que los que no tenían infartos independientemente de FRV, tratamientos y ApoE4.

No obstante hay ciertas diferencias cuando comparamos los individuos con infartos corticales pequeños con los que tienen otro tipo de infarto. Los que tienen cualquier otro tipo de infarto realizan la tarea motora (medida por el Test de Purdue Pegboard) peor que los que tienen infartos corticales pequeños. Los que tienen infarto lacunar realizan peor la tarea de interferencia (Stroop parte 3) y tienen una peor puntuación global que los que tienen infartos corticales pequeños. Por lo tanto, tienen una afectación cognitiva moderada respecto a otros tipos de infarto.

Grupos previos también observaron que había una asociación perjudicial entre los infartos corticales y la función cognitiva en la población general. En una población general de EUA se observó que aquellos que tenían infartos corticales tuvieron significativamente peor resultado en tareas de memoria y en velocidad de procesamiento (aunque esto último no se mantenía al ajustar por los FRV, HSB y atrofia).(131) En su caso, los resultados fueron similares para aquellos que tenían infartos en subcórtex y los peores resultados en afectación de memoria, función ejecutiva y velocidad de procesamiento los obtuvieron aquellos que tenían infartos en ambas localizaciones.

La localización de los infartos corticales pequeños en las zonas limítrofe de la vascularización de grandes vasos a nivel frontal podría explicar en parte sus manifestaciones cognitivas. El córtex prefrontal es el encargado del control de las funciones ejecutivas.(135) Los infartos en territorio de la arteria cerebral anterior y media causan disfunción ejecutiva y por tanto es lógico esperar que las lesiones en estas aéreas aunque sean pequeñas causan similares disfunciones de menor magnitud. El córtex prefrontal está conectado con el lóbulo temporal mesial y se ha relacionado con un síndrome amnésico con dificultad para recuperar y falsos reconocimientos.(136) No

obstante, en los participantes con infartos corticales pequeños sólo observamos un déficit en la memoria diferida con reconocimiento similar a aquellos que no tienen infartos.

No evaluamos en este trabajo la función visuoespacial que se relaciona que la integridad del córtex occipital, el cual también está afectado por los pequeños infartos corticales en nuestra cohorte.

E.5.2 Las lesiones cerebrovasculares silentes en hipertensos y su relación con las funciones cognitivas

En nuestro trabajo en hipertensos del estudio ISSYS hemos mostrado que las diferentes funciones cognitivas evaluados con la DRS-2 se relacionaban de forma inversa con la presencia de lesiones extensas de HSB profundas. En cambio en el caso de los infartos ICS, no había diferencias entre el grupo con ICS lacunares y el que no tenía ICS lacunares en cuanto a las funciones cognitivas.

E.6. La rigidez arterial y su relación con las funciones cognitivas y el Deterioro Cognitivo Ligero

En nuestro último trabajo mostramos como la función cognitiva, en concreto la atención se relaciona de manera inversa a la rigidez arterial medida por Presión de Pulso (PP) diurna (beta=-0.22, IC 95% -0.41,-0.03) después de corregir por FRV, tratamientos y lesiones de enfermedad de pequeño vaso cerebral (EPVC). Esta relación de la PP y la atención ya fue descrita anteriormente, (137) por lo tanto parece que existen funciones cognitivas más vulnerables al daño por la rigidez arterial que otras. Nos parece interesante destacar que estos resultados suceden independientemente de las cifras de PA, las cuales han sido históricamente más estudiadas que otros parámetros hemodinámicos de la PA como es la rigidez arterial.

Igualmente, encontramos que la presión de pulso (PP) fue mayor en todos casos (en la clínica y ambulatoria en los diferentes periodos) para los que tenían DCL que los que tenían ECN. Por lo tanto, coincidimos en afirmar que la rigidez arterial y en concreto la PP se asocia al DCL como mostraron previamente otros grupos.(100)

Es interesante señalar que la PP nocturna fue un factor independiente de DCL tras ajustar por FRV, EPVC y tratamientos. Especialmente la HTA nocturna y menos consistentemente los patrones anómalos de PA durante el sueño se han relacionado con la presencia de ictus y enfermedad cardiovascular.(138) En el caso del deterioro cognitivo los grupos que han estudiado la relación con la PA nocturna o otros parámetros de la PA han sido muy pocos.(139)

La PP como el resto de componentes de la PA sigue un ritmo circadiano, en el cual durante el periodo nocturno los estímulos ambientales son menores debido al sueño y el organismo depende más de sus propios sistemas regulatorios de la PA como el sistema renina-angiotensina-aldosterona. Por lo tanto, encontrar parámetros de la PA del periodo nocturno asociados con el DCL simplifica los parámetros a tener en cuenta en posteriores investigaciones.

En este último trabajo también observamos que la PP se relaciona con las lesiones de EPVC (ictus lacunar silente, HSB) y ambas se relacionaron con el DCL. Faltaría no obstante averiguar si la PP y la EPVC tienen una relación entre ellas y esto es lo que causa DCL. Por la literatura previa, hemos visto que esta puede ser una explicación plausible. Es decir, la fisiopatología de este hallazgo se podría relacionar con el daño que causan las fluctuaciones de alta PA (o alta PP) a la microvasculatura cerebral (remodelado de la pared del vaso y estrechamiento de su luz) que ocasiona hipoperfusión y finalmente conduce a infartos cerebrales o HSB.(28, 140) Por otro lado, sabemos que la función cognitiva atención se localiza a nivel frontal y tiene conexiones subcorticales.(47) Así pues, la

existencia de HSB profunda podría estar interrumpiendo las conexiones cortico-subcorticales de esta red.

Se necesitarían otro procesamiento de las RM (p.ej. segmentación de la sustancia blanca y análisis por áreas) y estudios prospectivos para evaluar si realmente la relación de las función cognitiva y el DCL con la rigidez arterial se debe a las lesiones cerebrovasculares en nuestra cohorte.

E.7. Estudio ISSYS: Fortalezas, limitaciones y objetivos futuros

El estudio ISSYS es un estudio de base poblacional, prospectivo en hipertensos de mediana edad que pretende averiguar la prevalencia, los determinantes y el pronóstico de las lesiones cerebrovasculares y del Deterioro Cognitivo Ligero.

Además pretende identificar factores clínicos, biológicos, hemodinámicos y genéticos asociados a la presencia y la progresión de las lesiones cerebrovasculares y el deterioro cognitivo.

En la fase de *seguimiento* del estudio nos permitirá estudiar nuestros dos objetivos principales: observar que pacientes se mantienen como DCL o progresan a demencia y cuáles revierten y por tanto no tienen deterioro cognitivo y cuáles presentan un ictus incidente.

En las visitas de seguimiento se están recogiendo cada año (por teléfono y con apoyo en la historia clínica) la aparición de eventos vasculares (AIT, ictus isquémico y hemorrágico, endarterectomía o stent carotideo, infarto de miocardio, angor pectoris que requiera hospitalización, cirugía de revascularización coronaria, , claudicación intermitente, cirugía de revascularización periférica y muerte de causa cardiovascular), la aparición de quejas cognitivas, la evaluación de la función cognitiva (MMSE), cambios en el tratamiento y cumplimiento terapéutico de los hipotensores. A los 3 años se realizará una nueva visita

presencial, muy similar a la visita basal, para determinar la incidencia de lesiones cerebrovasculares silentes y declive cognitivo.

El estudio de las lesiones cerebrovasculares silentes, función cognitiva y deterioro cognitivo en hipertensos libres de ictus o demencia tiene su interés por múltiples motivos entre los que destacamos:

a) Se desconoce la prevalencia de lesiones cerebrovasculares silentes en población Mediterránea, la que se considera de menor riesgo cardiovascular y en la que hay menos frecuencia de ictus comparado con población de EUA o Asiática.
b) Tampoco se conoce la prevalencia del DCL en nuestro país en el grupo seleccionado de los hipertensos.
c) El estudio de población subclínica tanto para ictus como para demencia es ventajosa ya que nos permite estudiar la fisiopatología de la enfermedad y estudiar cual es la mejor estrategia de prevención primaria para estos individuos.
d) La población en riesgo asintomática (aquellos con ICS, HSB, EPVD) o paucisintomática (DCL) es un grupo ideal para estudiar qué pacientes tienen mayor riesgo de evolucionar a ictus y demencia.
e) Conocemos bastante bien el pronóstico de los ICS y las HSB, se asocian tanto a ictus clínico como a demencia en el futuro. En cambio desconocemos el significado pronóstico de otras lesiones como la EPVD será el mismo o diferente.
f) También conocemos bastante bien el pronóstico del DCL en la población general. Pero el pronóstico del DCL vascular o DCL en grupos de población con alto riesgo vascular como son los hipertensos es desconocida en nuestro medio.

El estudio ISSYS intentará dar respuesta a varias de las anteriores cuestiones. Entre otros en esta Tesis hemos mostrado el resultado para los dos primeros puntos.

Además la evaluación de las lesiones de órgano diana de la hipertensión (índice tobillo-brazo, hipertrofia de ventrículo izquierdo, microalbuminuria, velocidad de la onda de pulso carótido-femoral, etc.) y la recogida de fluidos orgánicos para estudio de biomarcadores y genes asociados a estas patologías permitirá estudiar el valor de estos en la enfermedad subclínica y descubrir nuevos biomarcadores o replicar los existentes y comprobar si son los mismos que para el ictus clínico y la demencia.

Las *fortalezas* principales del estudio ISSYS son su diseño y el uso de técnicas disponibles para estudios en la comunidad. El tamaño muestral es el adecuado para la consecución del objetivo principal del estudio (determinar la prevalencia de ICS). La población fue elegida al azar y aleatorizada por edad y sexo según la presencia esperada de HTA. Esto disminuye la presencia de sesgos y ayuda a que los resultados se puedan generalizar. El estudio a nivel cerebral es extenso y también se incluye el estudio de otros órganos que se pueden afectar de manera precoz en la HTA. Además, se ha hecho un esfuerzo clínico adicional para estudiar si los participantes con infarto en la RM cerebral realmente no recordaban tener síntomas.

Las *limitaciones* del estudio están relacionadas con la sensibilidad y especificidad de las técnicas usadas para el estudio de las lesiones cerebrales y el deterioro cognitivo. Usar una RM con mayor resolución facilitaría la detección de estas pequeñas lesiones y su diagnostico diferencial con otros marcadores similares. Asimismo, evaluar a toda la cohorte con una amplia batería neuropsicológica, estudiar de forma sistemática las quejas cognitivas y las AIVD habría disminuido los falsos positivos que obtuvimos con el test de cribado y también habría disminuido los falsos negativos que posiblemente estén incluidos

dentro del grupo de envejecimiento cognitivo normal. El escaso número de participantes con DCL limita el poder estadístico en algunos de los análisis.

CONCLUSIONES

1) Hemos incluido 1037 participantes con hipertensión arterial esencial de 50-71 años en el estudio observacional y prospectivo ISSYS para el estudio de las lesiones cerebrovasculares silentes y deterioro cognitivo.

2.1) La población de mediana-avanzada edad hipertensa española tiene una prevalencia de infarto silente cerebral del 10.1%.

a. Los hombres muestran más frecuencia de FRV y de infartos cerebrales silentes en esta población.
b. El riesgo cardiovascular global medido por REGICOR (ecuación de Framingham para población de nuestro entorno) es un factor independiente para los infartos silentes cerebrales.
c. La microalbuminúria también es un predictor independiente que dobla la probabilidad de tener infarto silente cerebral.
d. De los infartos cerebrales silentes hay una porcentaje no desdeñable (8.1% en nuestra cohorte) que son identificados como infartos clínicamente sintomáticos tras la nueva entrevista con el participante.

2.2) Los espacios Perivasculares dilatados (EPVD) son prácticamente ubicuos tanto en centro semioval (CSO) como en ganglios de la base (GGBB) en hipertensos.

a. La prevalencia de EPVD extensos (>10 lesiones) en hipertensos es mayor en CSO (40.0%) que en GGBB (23.3%).

b. Los EPVD se relacionan con la edad, el riesgo cardiovascular (REGICOR) y el resto de lesiones cerebrovasculares de enfermedad de pequeño vaso cerebral (EPVC).

c. La asociación de los EPVS con el Deterioro Cognitivo Ligero no es independiente de la presencia de otras lesiones de EPVC.

3) Los infartos corticales pequeños (<15 mm) se encuentran en un 1.1% de los individuos de la población general.

a. Los infartos cerebrales pequeños tienen FRV similares a los otros infartos cerebrales (corticales grandes, lacunares y ambos).

b. Los infartos cerebrales pequeños se asocian con déficits cognitivos en memoria verbal diferida, atención y función ejecutiva de forma independientemente a los FRV, gen ApoE4 y al tratamiento hipotensor. Los resultados son similares cuando consideramos sólo los individuos sin infarto previo.

c. Los infartos corticales pequeños se acumulan en las zonas de irrigación limítrofe anterior y posterior, mientras los infartos corticales grandes se distribuyen mayoritariamente en los territorios de irrigación de las grandes arterias cerebrales.

4) Creamos un protocolo de evaluación cognitiva y obtuvimos datos normativos para la escala de cribado de demencia Dementia Rating Scale (DRS-2) de 798 participantes hipertensos.

a. A pesar de que las mujeres obtuvieron significativamente peor puntuación Total en la DRS-2, tras la corrección por edad y años de escolaridad no hay diferencias entre sexos.

b. Un 17.5% de los participantes con datos normativos obtuvieron un puntuación en la DRS-2 Total por debajo de lo esperado según su nivel educativo y edad.

5) Un 8.9% de los participantes con datos normativos del estudio ISSYS cumplen criterios de Deterioro Cognitivo Ligero (DCL).

a. El DCL se asoció de manera independiente a la baja escolaridad y no hubo diferencias significativas en los FRV clásicos entre el grupo de DCL y el grupo con envejecimiento cognitivo normal.

b. El DCL en población hipertensa se asoció de manera independiente (de FRV, lesiones cerebrovasculares y tratamientos) a las extensas hiperintensidades de sustancia blanca de localización profunda.

6) Las mediciones de rigidez arterial (Presión de Pulso –PP-) de 24 horas se relacionan con la función cognitiva y el estatus cognitivo.

a. Una mayor PP diurna se asocia de manera independiente (de FRV, lesiones cerebrovasculares y tratamiento hipotensor) a una peor puntuación en el subtest de atención de la DRS-2.
b. En cambio, una mayor PP nocturna se asocia de manera independiente a la presencia de DCL.

CONCLUSIONS

1) We enrolled 1037 participants aged 50-71 with essential hypertension in an observational and prospective study to study cerebrovascular silent lesions and cognitive impairment.

2.1) Middle and older aged Spanish hypertensive individuals had a silent brain infarct (SBI) prevalence of 10%.

a. Men show higher frequency of vascular risk factors and more SBIs than women.

b. Cardiovascular risk assessed by means of REGICOR (Framingham calibrated risk score for Spain) is an independent factor of SBIs.

c. Microalbuminuria is also an independent factor that doubled the odds of having SBIs.

d. There is a percentage of SBIs (8.1% in our cohort) that are considered as clinically symptomatic after MRI and re-interviewing of the participant.

2.2) Enlarged perivascular spaces (EPVS) are almost ubiquitous in centrum semiovale (CSO) and basal ganglia (BBGG) in hypertensive individuals.

a. Prevalence of extensive EPVS (>10 lesions) is higher in CSO (40.0%) than in BBGG (23.3%).

b. EPVS are related with higher age, cardiovascular risk (assessed by REGICOR) and other small vessel disease lesions (lacunar infarcts and white matter hyperintensities).

c. The association of EPVS with Mild Cognitive Impairment is not independent of other small vessel disease lesions.

3) Small cortical infarcts (<15mm) prevalence is 1.1% in the general population.

a. Those with small cortical infarcts have similar risk factors to those that have other infarct types (large cortical infarcts, lacunar infarcts and combination of previous types).

b. Those with small cortical infarcts have worse delayed memory, executive function and attention than people without infarcts (independent of vascular risk factors, hypertension treatment and ApoE4 alleles). Similar results are obtained when prevalent stroke is excluded.

c. Small cortical infarcts are more frequent in anterior and posterior borderzone areas as compared to large cortical infarcts that are more frequent in the arterial irrigation territories of big brain arteries.

4) We created a cognitive protocol evaluation and obtained normative data in 798 hypertensive individuals for Dementia Rating Scale 2 (DRS-2).

a. Women obtained worse Total DRS-2 raw score than men. After correction by age and education no differences are seen between sexes.

b. 17.5% of our cohort obtained a Total DRS-2 score that is lower than expected by age and education years.

5) 8.9% of the ISSYS participants with DRS-2 normative data were diagnosed of Mild Cognitive Impairment.

a. MCI is independently associated with low education and no differences are seen in classical vascular risk factors between MCI and normal cognitive aging.

b. MCI is independently associated with deep extensive white matter hyperintensities in hypertensive individuals (independent of vascular risk factors, small vessel disease lesions and treatments).

6) Arterial stiffness (assessed by 24 hours Pulse Pressure -PP-) is related to cognitive function and MCI.

a. Higher diurnal PP is associated independently (of vascular risk factor, small vessel disease lesions and hypertension treatment) with lower attention score in DRS-2.

b. However, higher nocturnal PP is independently associated with MCI.

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