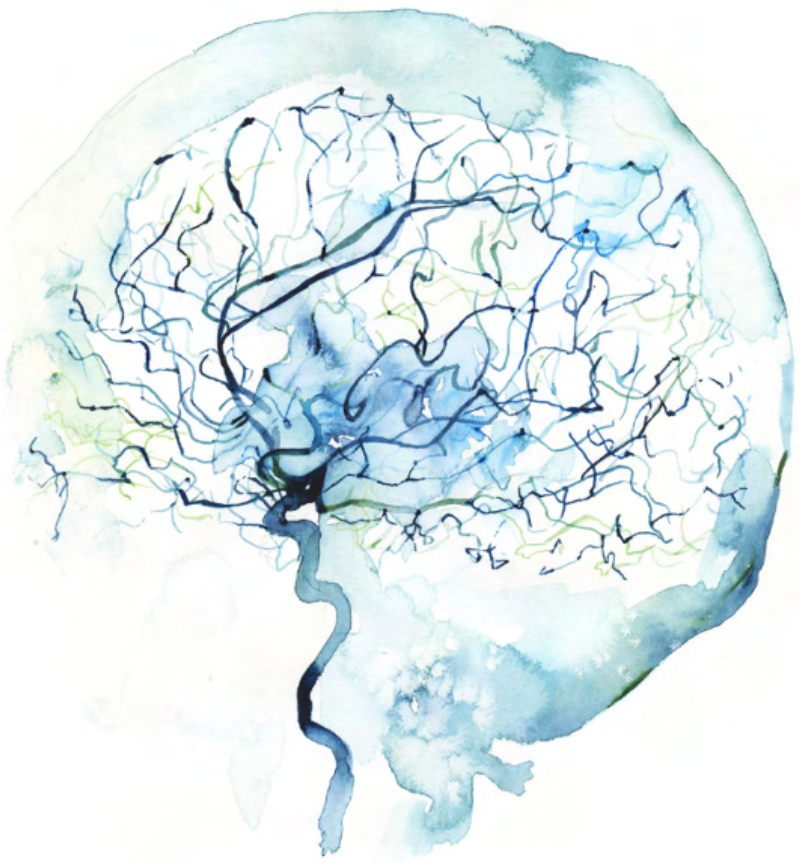
"Randomised multicentre clinical trial on early recurrence of stroke caused by mobile carotid plaques according to acute phase treatment"

The PLACA VIL Trial



END OF DEGREE PROJECT

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1. ABSTRACT

Title: Randomised multicentre clinical trial on early stroke recurrence associated with mobile carotid plaques according to acute phase treatment (The PLACA VIL Trial).

Authors: Yanire Altuzarra Foncea and Dr Joaquín Serena Leal.

Background: Stroke has a great impact on society, being the leading cause of adult disability and the second cause of death worldwide. Among the different etiopathogenetic mechanisms of ischemic stroke, atherothrombotic stroke accounts for 17-20%, the majority due to significant stenosis of the internal carotid artery. However, there is a relevant proportion of patients with atherothrombotic strokes associated with mobile carotid plaques (MCP), without significant carotid artery stenosis. These plaques seem to be associated with a high risk of recurrence but its prevalence and treatment is, nowadays, unknown and controversial.

Objective: The main objective of this study is to assess if patients with atherothrombotic ischemic stroke associated to MCP treated surgically in the acute phase (by Carotid Endarterectomy [CEA] or by Carotid Angioplasty with Stenting) have a lower risk of early recurrence than those treated with Best Medical Treatment (BMT). The secondary objectives aim to determine, if stroke recurrence at one month, three months and one year post-index stroke is associated with adjudicated treatment in acute phase (CEA/stent vs. BMT) and/or presence of cerebral microembolic signals (MEs). Finally, we will analyse outcome at month 3, using the modified Rankin Scale (mRS), in each group of treatment.

Design: This study was designed as a randomised, open-label, multicentered, prospective, controlled, parallel groups clinical trial, aiming to determine the optimal treatment in the acute phase for the mentioned patients. It will be a multicentre study with 23 potential participating centres belonging to the *Sociedad Española de Neurosonología (SONES), RICORS-Ictus* and *Proyecto Ictus*, all of which have neurosonology experts.

Participants: Patients admitted to the Stroke Unit (SU) for an ischaemic stroke caused by MCP detected in a high-definition colour Doppler ultrasound of the supra-aortic trunks.

Methods: 206 participants will be enrolled using a consecutive sampling method and the time of recruitment will be 1 year. Participants will be randomised following a 1:1 ratio into two groups: 1) Treated in the acute phase with CEA/stenting; 2) Treated in the acute phase with BMT. The subjects will be followed for 1 year after the index stroke. Major outcome variable will be early stroke recurrence (<72 hours post-admission).

Keywords: *Doppler ultrasound of supra-aortic trunks, early stroke recurrence, MCP, MEs.*

2. ABBREVIATIONS

ACA	Anterior Cerebral Artery
ACAS	Asymptomatic Carotid Atherosclerosis Study
AChA	Anterior Choroidal Artery
AF	Atrial Fibrillation
AHA/ASA	American Heart Association/American Stroke Association
ASA	Acetylsalicylic acid
RENISEN	Registro Nacional de Ictus de la Sociedad Española de Neurología
BMI	Body Mass Index
BMT	Best Medical Treatment
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
CCA	Common Carotid Artery
CEA	Carotid Endarterectomy
CEIC	Comité de Ética de Investigación Clínica
CI	Confidence interval
CNS	Central Nervous System
CREST	The Carotid Revascularization Endarterectomy versus Stenting Trial
CT	Computerised Tomography
CTA	Computed Tomography Angiography
DALYs	Disability-Adjusted Life-Years
DBP	Diastolic Blood Pressure

DOACs	Direct Oral Anticoagulants
DSA	Digital Subtraction Angiography
DWI	Diffusion-Weighted Imaging
ECA	External Carotid Artery
ECG	Electrocardiogram
ESUS	Embolic Stroke of Undetermined Source
FLAIR	Fluid-Attenuated Inversion Recovery
HbA1c	Haemoglobin A1c
HBP	High Blood Pressure
HR	Hazard ratio
HUDJT	Hospital Universitario Doctor Josep Trueta
ICA	Internal Carotid Artery
ID	Identification
INR	International Normalised Ratio
LDL	Low-Density Lipoprotein
m-CT	multimodal Computerised Tomography
MCA	Middle Cerebral Artery
MCP	Mobile Carotid Plaques
MEs	Microembolic signals
mp-MRI	multiparametric Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography

MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NASCET	The North American Symptomatic Carotid Endarterectomy Trial
NIHSS	National Institute of Health Stroke Scale
NNT	Number Needed to Treat
NOTCH3	Neurogenic Locus Notch Homolog Protein 3
P-commA	Posterior Communicating Artery
PCA	Posterior Cerebral Artery
PChA	Posterior Choroidal Artery
PFO	Patent Foramen Ovale
PT	Prothrombin Time
RF	Risk Factor
rt-PA	recombinant tissue Plasminogen Activator
SBP	Systolic Blood Pressure
SEN	Sociedad Española de Neurología
SOE	Source Of Embolism
SONES	Sociedad Española de Neurosonología
SPSS	Statistical Package for Social Sciences
SSS-TOAST	Trial of Org 10172 in Acute Stroke Treatment
SU	Stroke Unit
TCD	Transcranial Doppler

TEE	Transesophageal Echocardiography
TIA	Transient Ischaemic Attack
Tmax	Time to the maximum
TTE	Transthoracic Echocardiography
US	Ultrasound

3. INTRODUCTION

3.1. Stroke

3.1.1. Definition

According to the American Heart Association/American Stroke Association (AHA/ASA) (1) and following the new definition of stroke (ischemic and hemorrhagic) (2), this is defined as "brain, spinal cord, or retinal cell death attributable to ischemia, based on:

1. Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or
2. Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥1 hour or until death, and other etiologies excluded" (1).

It is, therefore, a neurological entity of vascular aetiology that results in the sudden onset of neurological focality that does not self-resolve.

3.1.2. Epidemiology

Stroke data reflect the great impact it has on many areas of the society. In Europe, its incidence varies across countries (3), but in our environment, the annual incidence of stroke is estimated at around 187.4 cases per 100,000 inhabitants (**72,000 new cases of stroke per year in Spain**), a data that is expected to increase by 35% until 2035 due to the ageing of the population. The prevalence is between 6-7% for those over 70 years of age, with a higher prevalence in men living in urban areas (4).

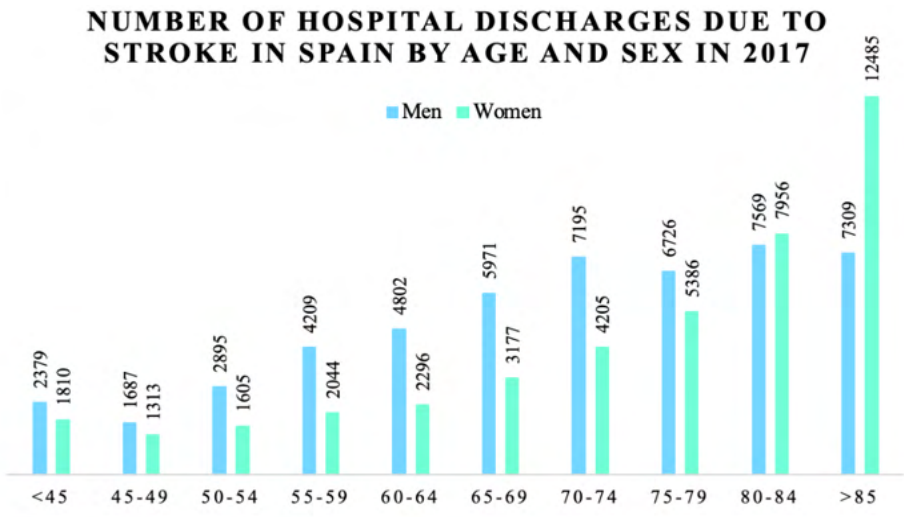

Figure 1. Number of hospital discharges due to stroke in Spain, by age and sex, in 2017 *(adapted from (4)).*

The **data rises with increasing age** and accumulation of **risk factors** (RF), especially in women (4). However, in people under 70 years of age, incidence and prevalence rates have increased by 22% worldwide (5). According to the Registro Nacional de Ictus de la Sociedad Española de Neurología (RENISEN)(6), strokes in patients between **20 and 64 years have increased by 25%** and one third of strokes occur in those under 65 years of age.

Vascular disease is one of the most frequent causes of death and disability worldwide. As a matter of fact, **stroke is the leading cause of disability in the world** in both sexes and the second leading cause of dementia after Alzheimer's disease (4). Worldwide, 143 million disability-adjusted life-years (DALYs) are due to stroke (5).

The consequences, both physical (loss of mobility, sensibility, vision, speech, etc.) and mental (cognitive, mood and behavioural disorders, etc.), significantly diminish the quality of life of the patient and the people around him/her.
It should be born in mind that, globally speaking, there are more than 25 million stroke survivors. This high figure is due to the fact that **every year the incidence of stroke increases, despite the fact that the mortality rate standardised by sex and age has been decreasing** (7,8). This has a great social, economic and health impact due to the significant consumption of resources involved in the rehabilitation and/or care of these patients (9). In Spain, stroke represents 3-4% of total healthcare expenditure, which amounts to around €20,000-40,000/patient/year if all the extra indirect costs it causes are taken into account (10).

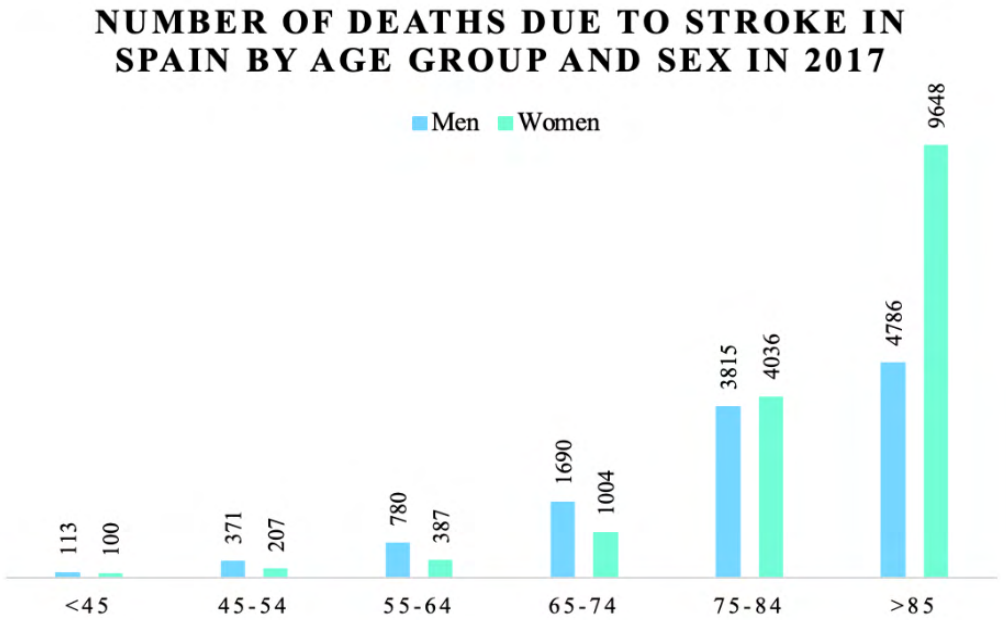

Figure 2. Number of deaths due to stroke in Spain, by age and sex, in 2017 *(adapted from (4)).*

In terms of mortality, **stroke is the second leading cause of death** in the general population after myocardial infarction (5), being responsible for 11% of total deaths (11). However, stroke is the **leading cause of death in women** (9).

Data show that 27,000 people die each year in Spain as a result of a stroke (4), a figure that is also expected to increase. In fact, this is due to the progressive ageing of the population and the exponential growth of unhealthy lifestyle habits that have a significant influence on the development of RF for stroke (diabetes mellitus, hypertension and hypercholesterolemia).

All of these data could be improved if the main RFs for stroke (to be discussed later) are effectively controlled, as **80% of strokes are preventable** (4).

3.1.3. Pathophysiology and Physiopathological Classification

The backbone of stroke is **vascular pathology**, as a sudden deficit in cerebral blood flow (hypoperfusion) causes neuronal damage. As the brain is an organ that lacks energy reserves, the reduction of oxygen and nutrients in the affected neurons leads to metabolic and biochemical disturbances and, thus, triggers their depolarisation, resulting in the onset of sudden focal neurological deficits (12).

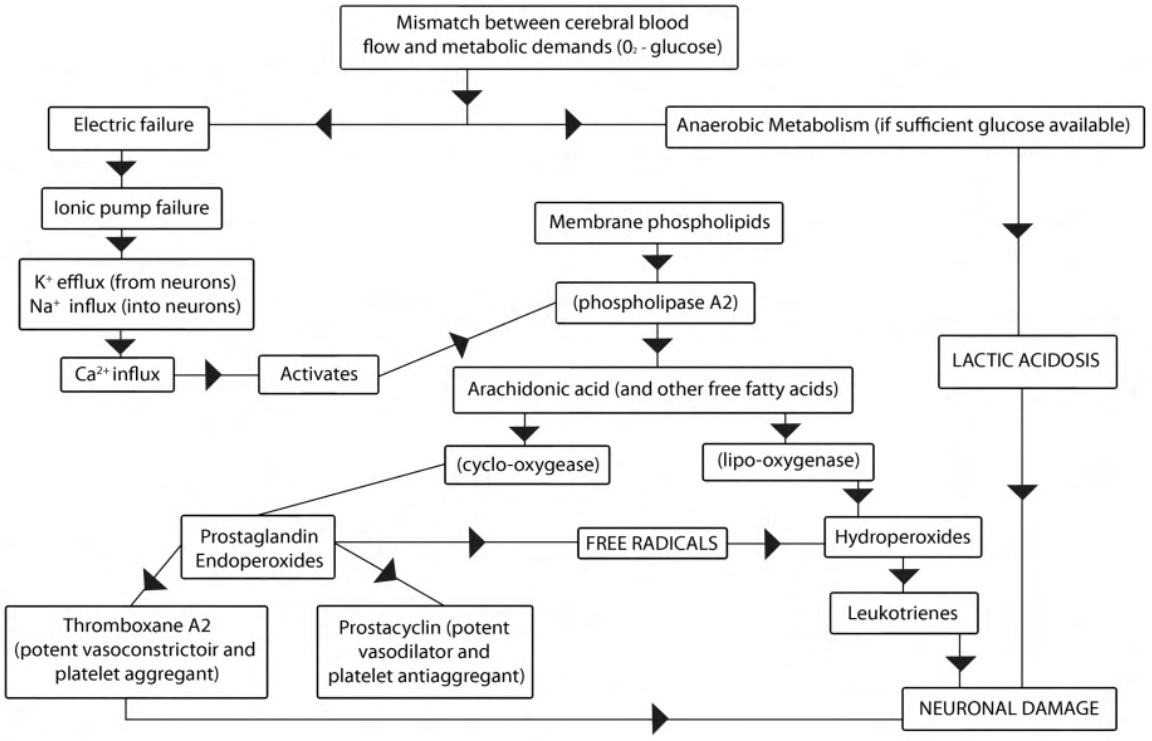

Figure 3. Stroke Pathophysiology *(13).*

The depolarised neuron causing the clinic can be viable for some time thanks to collateral circulation (oligoaemia or penumbra area seen on multimodal computerised tomography [m-CT] or in multiparametric magnetic resonance imaging [mp-MRI]). The speed of therapeutic action and the prognosis of the patient depend on the maintenance of this collateral circulation.

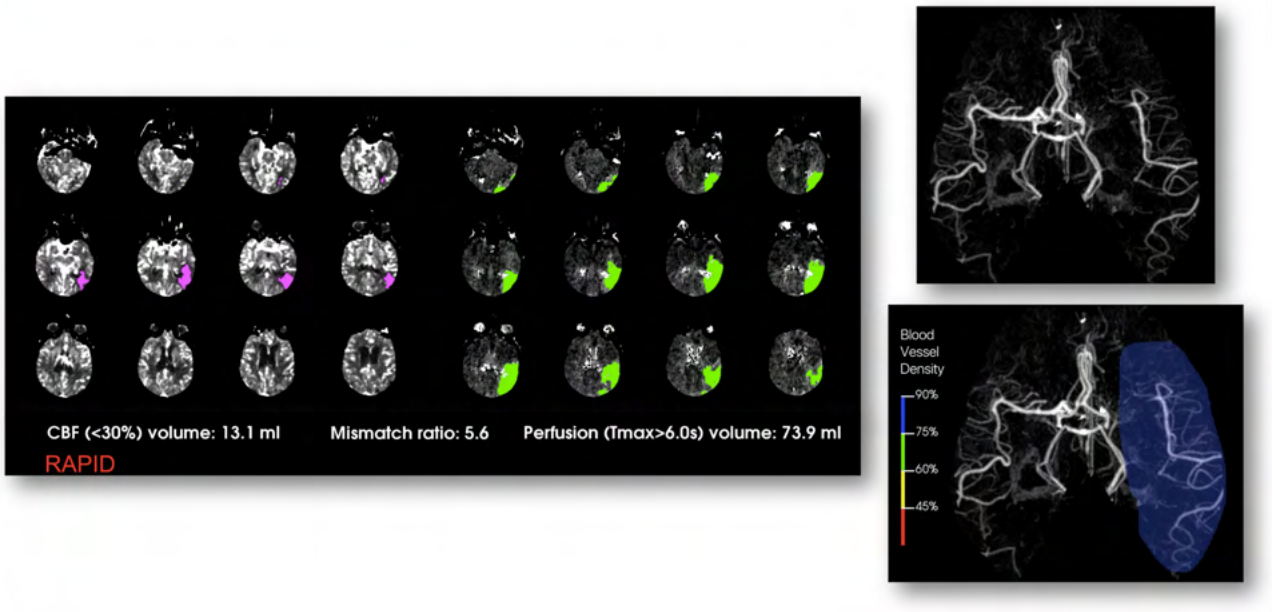

Figure 4. Computerised Tomography (CT) and Computed Tomography Angiography (CTA) images of a middle cerebral artery (MCA) stroke.

The CTA (photo on the right) shows the occlusion of the left MCA. The image on the left shows the established infarct area and the ischemic penumbra area. The established infarct area is shown in magenta, with a volume of 13.1 mL. Green area shows ischemic tissue that will evolve into an established infarct (Time to the maximum,Tmax >6") if blood flow cannot be restored. Its volume is 73.9 mL. It represents the ischemic penumbra or mismatch, in this case 5.6.

Courtesy of Dr Joaquín Serena.

Defining, understanding and knowing how to recognise a **neurological focality** is essential. Certain **functions** of the organism are encoded in determined areas of the **cerebral cortex**, known as Brodmann Areas. Lesions in these areas translate clinically into deficits in the functions encoded by each of the affected areas (neurological focality) (12), for example:

- Sudden alteration of sensation (paraesthesias, hypoesthesias, anaesthesias, etc.) of the face, arm and/or leg on the contralateral body side to the brain injury.
- Sudden loss of mobility and/or strength in the contralateral hemibody.
- Sudden loss of the ability to speak or understand (aphasia).
- Sudden partial loss of vision…

Extrapolating from stroke, each of the main cerebral arteries and their branches are responsible for irrigating specific areas of the brain. Therefore, knowing the predetermined distribution of neurological functions in the central nervous system (CNS), as well as the main vasculature of each of these areas, allows a **topographical diagnosis** of the injured artery to be made by the semiological examination of a patient affected by a stroke.

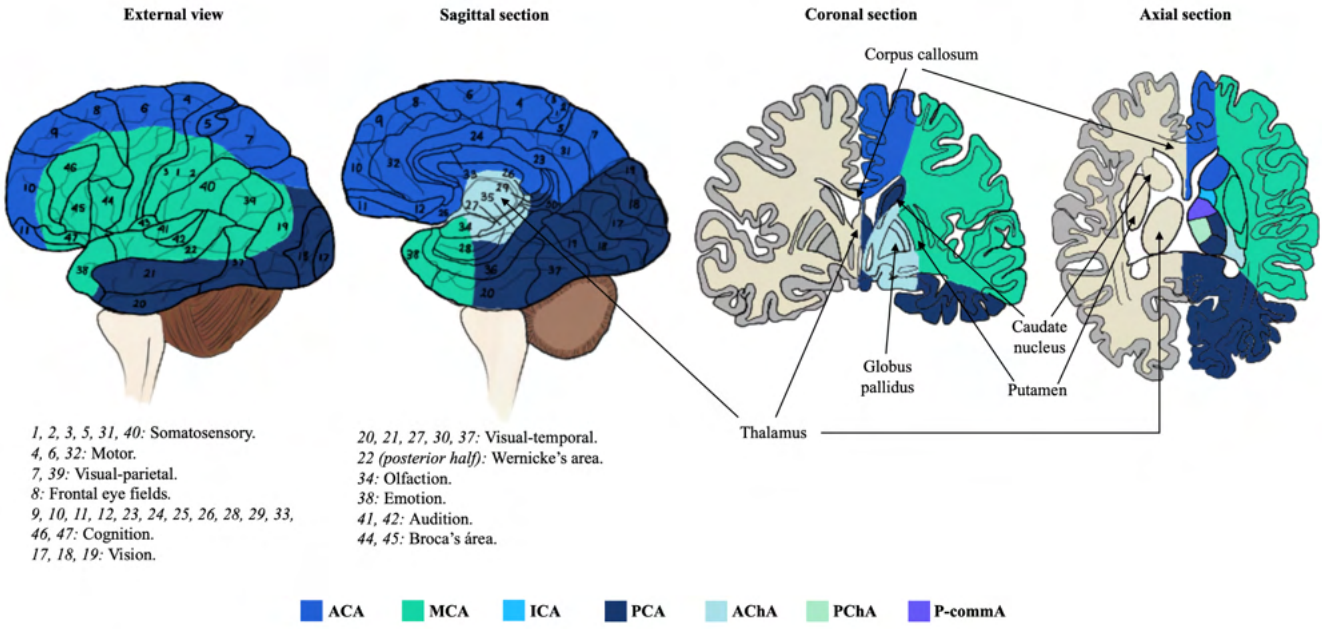

Figure 5. External view, sagittal, coronal and axial section of the brain showing Brodmann's areas, the main internal anatomical structures and the main irrigation of each area (approximately).

Anterior Cerebral Artery (ACA); Anterior Choroidal Artery (AChA); Internal Carotid Artery (ICA); Middle Cerebral Artery (MCA); Posterior Cerebral Artery (PCA); Posterior Choroidal Artery (PChA); Posterior Communicating Artery (P-commA).

The deficit in neuronal blood flow may be due to different pathological mechanisms, which are part of the **pathophysiological classification of stroke** (12):

- **Ischaemic stroke** (62.7% according to Feigin *et al.* (5)), is defined by the AHA/ASA as "an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction" (1). This is caused by a lack of blood supply to a certain area of the encephalic parenchyma, leading to tissue necrosis and, therefore, neurological clinic for ≥1 hour or leading to death. Computerised tomography (CT) neuroimaging usually shows a hypodense lesion in the acute moment. It can be subclassified according to aetiology, neuroimaging, vascular topography and evolution, as will be discussed later.

- When the duration of the episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia is less than 1 hour, with no signs of acute cerebral ischemia on diffusion-weighted imaging (DWI) sequences of magnetic resonance imaging (MRI), it is called a **transient ischaemic attack** or **TIA** (2).

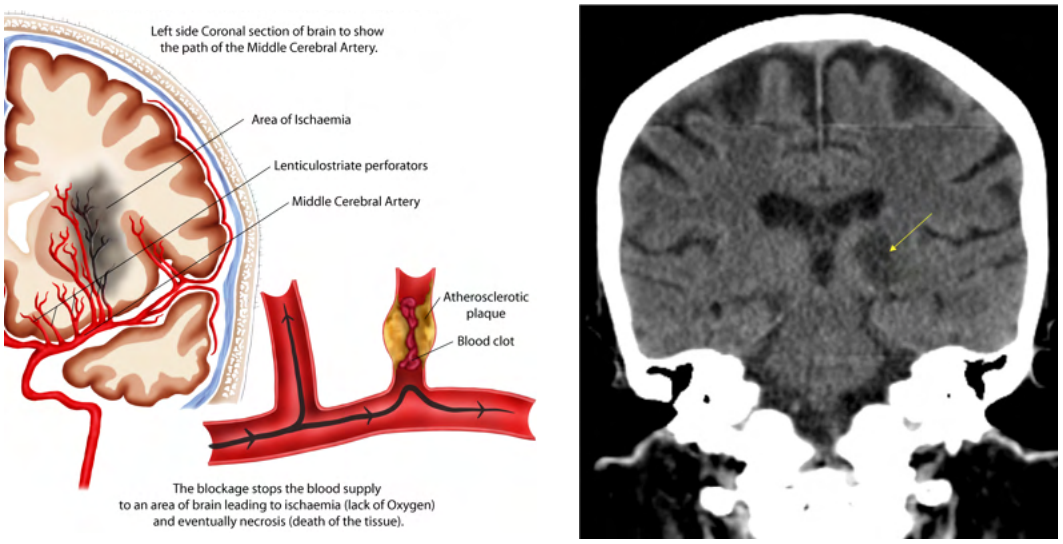

Figure 6. Schematic diagram of the pathophysiology of ischaemic stroke (left image, *adapted from (13))* ***and non-contrast computerised tomography (CT) scan of an acute ischaemic stroke (right image, yellow arrow,*** *adapted from(14)).*

- **Intracerebral haemorrhage** (27.9% according to Feigin *et al.* (5)), defined by the AHA/ASA as "rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma" (1). The collection of blood in the parenchyma (produced by the rupture of a cerebral vessel) is irritating, produces oedema and mass effect. Thus, it is more dangerous and has a worse prognosis than ischaemic stroke. It can be subdivided into lobar haemorrhagic stroke (more superficial) or deep haemorrhagic stroke. Its main RF is high blood pressure (HBP). CT neuroimaging usually shows a hyperdense lesion, with frequent mass effect on the adjacent parenchyma, as can be seen in *figure 7 (right image)*.

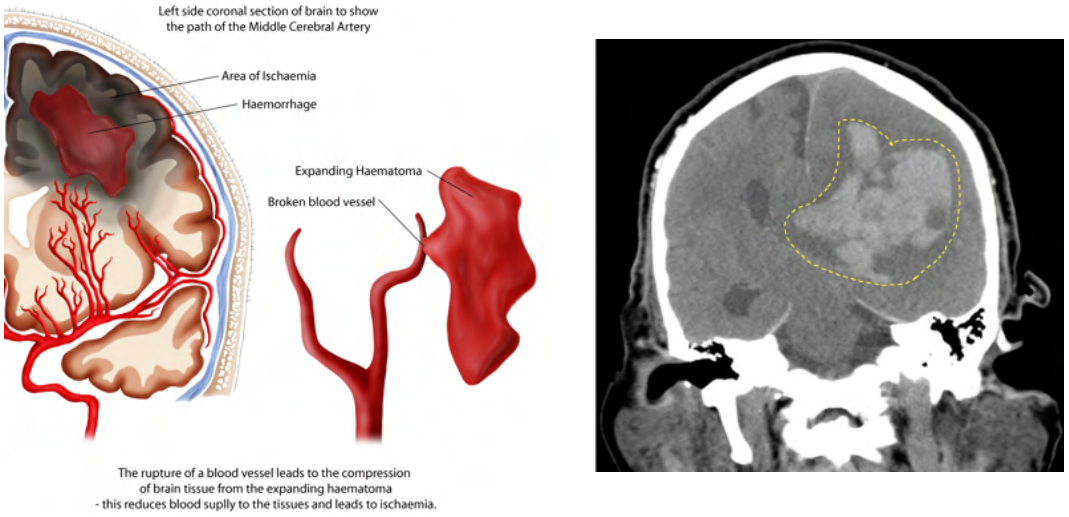

Figure 7. Schematic diagram of the pathophysiology of intracerebral haemorrhage (left image, *adapted from (13))* ***and non-contrast computerised tomography scan of an acute hemorrhagic stroke (right image, dotted circle,*** *adapted from (15)).*

- **Subarachnoid haemorrhage** (9.7% according to Feigin *et al.* (5)), defined by the AHA/ASA as "rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space, which is not caused by trauma" (1).

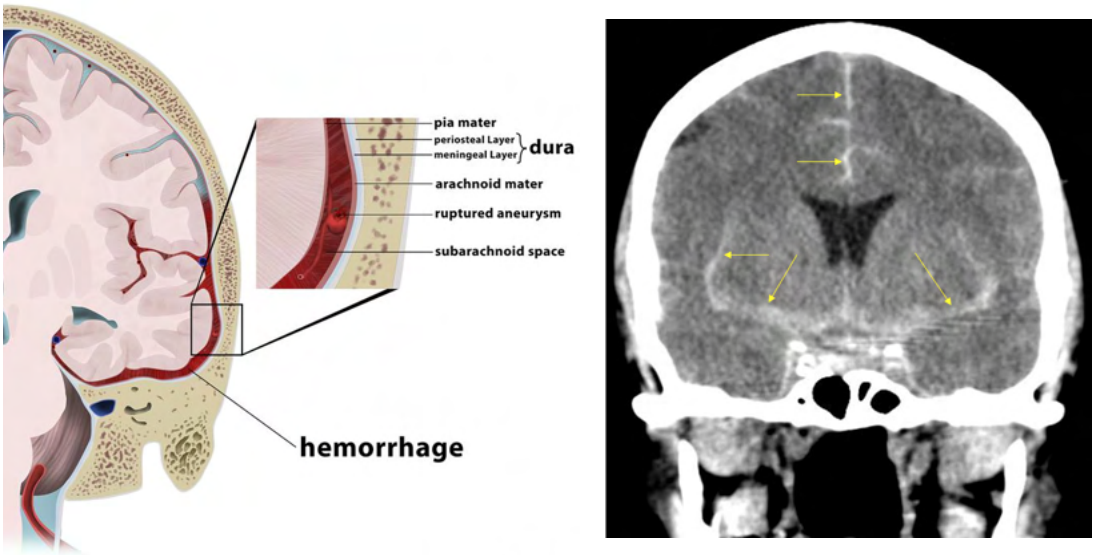

Figure 8. Schematic diagram of the pathophysiology of subarachnoid haemorrhage (left image, *adapted from (14))* ***and computerised tomography scan with contrast of a subarachnoid haemorrhage (right image, yellow arrows,*** *adapted from (14)).*

Clinically speaking, it is impossible to differentiate between ischaemic stroke, haemorrhagic stroke and subarachnoid haemorrhage, so additional tests are needed.

3.2. Ischaemic stroke

3.2.1. Etiopathogenesis

Ischaemic stroke (already defined in *section 3.1.3*) can be caused due to **multiple etiopathogenetic mechanisms**. The most important pathophysiological causes are (7):

- **Thrombotic etiopathogenesis:** caused by alterations in coagulation or by occlusion in the arteries supplying blood to the brain. The usual mechanism of strokes caused by thrombotic etiopathogenesis is small vessel disease (typical of elderly people with hypertension, diabetes, etc.).
- **Embolic etiopathogenesis:** due to obliteration of a vessel by a detached intraluminal fragment (embolus) in an artery proximal to the brain or in the heart. This is the most frequent underlying mechanism in stroke. If the embolus originates in venous territory and passes into the arterial circulation through an anomalous communication, it is called a paradoxical embolus.
- **Haemodynamic etiopathogenesis:** caused by inadequate collateral circulation in patients with proximal severe artery stenosis.

Other less frequent aetiopathogenesis of ischaemic stroke are **hyperviscosity** and **vasospasm.**

3.2.2. Risk factors

Due to the multifactorial aetiology of stroke, the **RF** involved are many and varied. Classically, RFs for stroke have been divided into *modifiable* and *non-modifiable*.
As mentioned in the *Epidemiology* section, most strokes are preventable. Up to 90% are due to modifiable RF and 80% of recurrent strokes can be prevented by proper control of modifiable RF. In addition, the role of secondary prevention is very important, as it reduces the risk of stroke recurrence, but also of suffering other vascular events such as acute myocardial infarction (7).
Recently, however, the role of new RFs (some of uncertain importance) has begun to be studied, leading to the creation of a new classification of stroke RFs. It divides RF into *Traditional* and *Non-traditional* (7).

Both classifications are shown combined in the next table:

Table 1. Stroke Risk Factors (RF) *(adapted from (7,16))*

	RF Modifiable	RF Non-modifiable
RF Traditional	**HBP** **Heart disease** (AF, valvular heart disease, prosthetic valves, previous myocardial infarction, congestive cardiomyopathy, ventricular hypertrophy, endocarditis, etc.). **Diabetes mellitus** **Dyslipidemia** **Arteriopathies** (asymptomatic carotid artery stenosis, peripheral artery disease) **Smoking** **Alcohol consumption** **Previous stroke** **Hyperhomocysteinemia** **Prothrombotic states** **Physical inactivity** **Oral contraceptives and hormonal therapy** **Drug abuse** **Migraine**	**Age** (directly proportional) **Sex** (men) **Genetic factors** (e.g. CADASIL disease, due to mutation in NOTCH-3) **Ethnicity** (African American) **Family history of stroke**
RF Non-traditional	**Obesity** (BMI ≥30 kg/m^2) **Metabolic syndrome** **Obstructive sleep apnoea syndrome** **Chronic inflammatory disease** (Crohn's disease, ulcerative colitis, autoimmune diseases, cancer in remission or active, etc.) **Dietary factors** **Depression** **Fatigue** **Infections**	**Type A personality** **Environmental pollution**

Atrial Fibrillation (AF); Body Mass Index (BMI); Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL); High Blood Pressure (HBP); Neurogenic locus notch homolog protein 3 (NOTCH3).

According to the *Global Burden of Disease* analysis (5), the five most important RFs (from highest to lowest weight) are:

- **HBP**. It is the most important RF related to all types of stroke and multiplies the risk of stroke fourfold (7).
- **Body mass index (BMI).**
- **High fasting plasma glucose / Diabetes mellitus.**
- **Ambient particulate matter pollution.**
- **Smoking.**

3.2.3. Primary prevention

Primary prevention is based on the control of stroke RFs. It is founded on general recommendations (also applied in secondary prevention) to which targeted pharmacological treatment can be added. Some of these measures are shown in the diagram below (17,18):

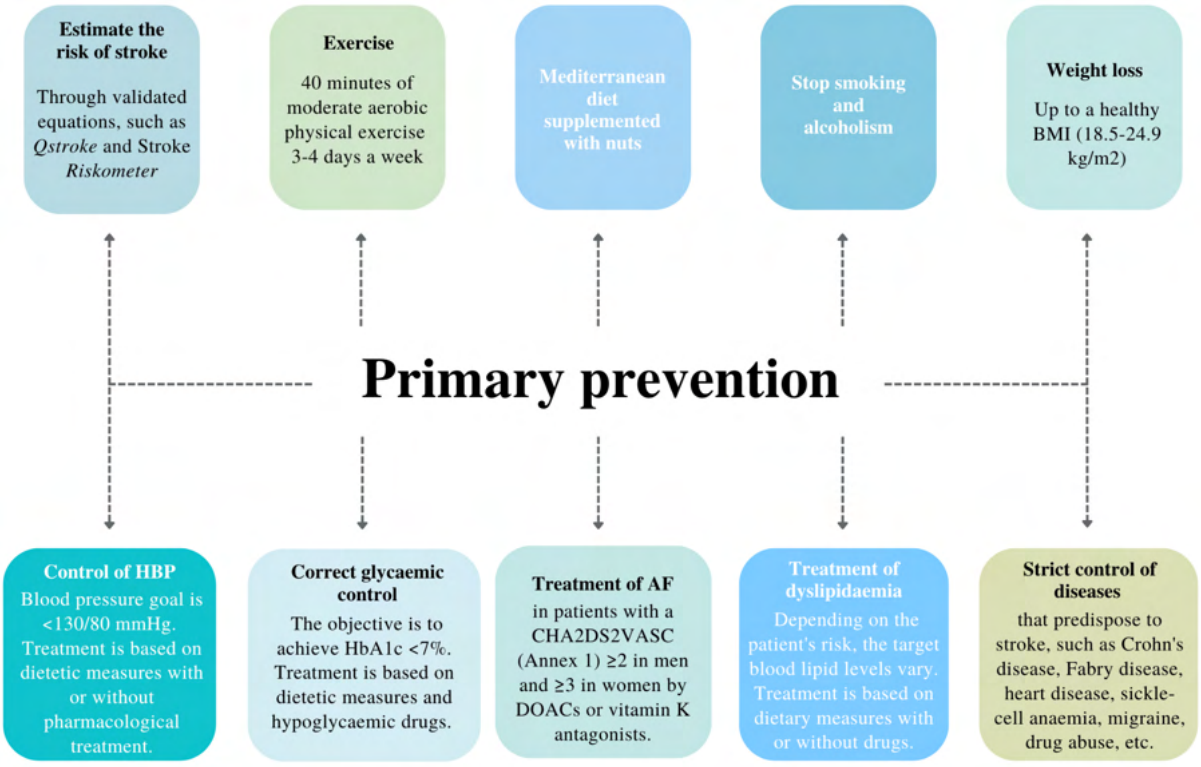

Figure 9. Strategy for primary prevention of stroke *(adapted from (17,18)).*
Body Mass Index (BMI); Direct Oral Anticoagulants (DOACs); Haemoglobin A1c (HbA1c); High Blood Pressure (HBP).

3.2.4. Sub-types of ischaemic stroke

The most widespread etiopathogenic classification of ischaemic stroke, with the highest interobserver agreement, is the classification of the Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) (Annex 2, (19)).

It differentiates 5 subtypes of ischaemic stroke (20): 1) **Large-artery atherosclerosis**; 2) **Cardioembolism (high-risk/medium-risk)**; 3) **Small-vessel occlusion (lacune)**; 4) **Stroke of other determined aetiology**; 5) **Stroke of undetermined aetiology.**

Furthermore, the SSS-TOAST classification divides each subtype (except for stroke of undetermined aetiology) into *"possible"* or *"probable"*, based on the results of complementary studies (20).

- The diagnosis is "probable" when clinical and neuroimaging data point to the same aetiology, as do other complementary studies. All other causes have been excluded.
- The diagnosis is "possible" when clinical and neuroimaging data point to the same aetiology, but no complementary studies have been performed.

The following figure shows a conceptual diagram of all subtypes and their frequency.

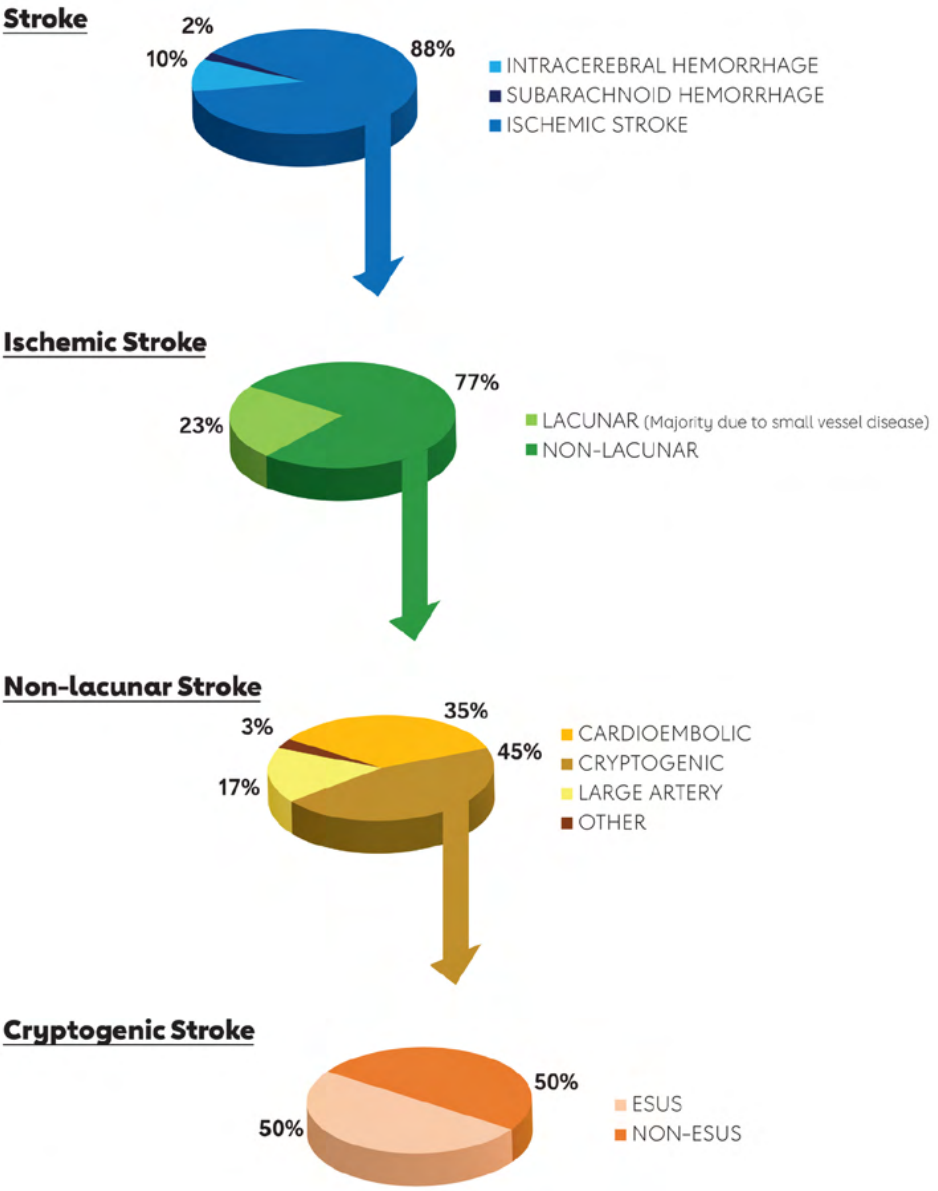

Figura 10. Conceptual diagram of stroke subtypes and their percentages of frequency *(21).*
Embolic Stroke of Undetermined Source (ESUS)

The following table shows the 5 subtypes of stroke in more detail according to the SSS-TOAST classification.

Table 2. Main features of the Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) classification *(adapted from (20)).*

		Large-artery atherosclerosis	**Cardioembolism (high-risk/medium-risk)**	**Small-vessel occlusion (lacune)**	**Stroke of other determined aetiology**	**Stroke of undetermined aetiology**
Origen		Significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis	Arterial occlusions presumably due to an embolus originating from at least one cardioembolic source: - *High-risk sources*: AF, mechanical prosthetic valve, atrial myxoma… - *Medium-risk sources*: foramen ovale, mitral valve prolapse, bioprosthetic cardiac valve…	Small vessel lipohyalinosis caused by HBP and/or diabetes mellitus.	Rare causes: - Nonatherosclerotic vasculopathies. - Hypercoagulable states. - Hematologic disorders, etc.	The cause of a stroke cannot be determined or there are two or more potential causes of stroke.
Pathological background		Intermittent claudication, TIAs in the same vascular territory, carotid bruit, diminished pulses, etc.	Previous TIA or stroke in more than one vascular territory or systemic embolism.	HBP, diabetes mellitus, etc.		It is possible to find any of the pathological antecedents just mentioned in other stroke subtypes.
Clinical features	**Cortical, brainstem or cerebellar focality**	+	+	-	+/-	+/-
	Lacunar syndrome: pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome, etc (22).	-	-	+	+/-	+/-
Neuroimaging features	**Cortical, cerebellar, brainstem or subcortical infarct >1,5 cm**	+	+	-	+/-	+/-
	Subcortical or brainstem infarct <1,5 cm	-	-	+/-	+/-	+/-
	Normal	+/-	+/-	+/-	+/-	+/-
Complementary tests	**Significant (>50%) stenosis or occlusion** of a major brain artery or branch cortical artery, presumably due to atherosclerosis	+	-	-	-	-
	Cardiac source of emboli	-	+	-	-	-
	Other abnormality on tests	-	-	-	-	+
Exclude other causes		Potential sources of cardiogenic embolism	Potential large-artery atherosclerotic sources	Cardiac sources of embolism and large-artery atherosclerosis		-

Atrial fibrillation (AF); High Blood Pressure (HBP); Transient ischaemic attack (TIA) **(22)**

3.2.5. Clinical diagnosis

Due to the severity of stroke, the diagnosis must be accurate and made as quickly as possible, so that appropriate treatment can be administered early (7).
Patients with TIAs should be evaluated in the same manner as patients with an ischemic stroke shown on neuroimaging (21).

As discussed above, the sudden onset of neurological focality raises the suspicion of stroke.
The **clinical diagnosis** of stroke is based on three pillars:

- **Anamnesis and medical history.**
- **Neurological and general examination.**
- **Complementary examinations.**

Anamnesis and medical history.
The medical history of the patient is fundamental, as it allows us to orientate the possible aetiology of the stroke as well as the previous frailty or disability of the patient. Special attention should be paid to personal and family history of vascular diseases as well as to vascular RF (7).

The relevant data that should be collected in a patient with a possible stroke is shown below. It allows us to orientate the diagnosis towards stroke and rule out other possible differential diagnoses (16,23):

- Current episode:
  - Symptoms at onset of the episode and their evolution.
  - Time of onset of symptoms or last seen asymptomatic if the exact time of onset is unknown. This is a key point, as it will determine the onset of the stroke and, depending on this time, one treatment or another will be applied. The patient and/or a witness should be interviewed.
  - Duration of symptoms.
  - Triggering circumstances.
- Personal history:
  - Previous stroke or TIA.
  - Recent history of: acute myocardial infarction, trauma, surgery, bleeding, infection, cancer, pregnancy, puerperium, etc.

    - RF of stroke and other comorbidities: HBP, atrial fibrillation (AF), valvular heart diseases, diabetes mellitus, alcoholism, smoking, dyslipidemia, thrombosis, drug abuse, history of dementia or cognitive impairment, migraine, other underlying diseases (heart disease, intermittent claudication, epilepsy, sickle cell anaemia, antiphospholipid syndrome, etc.).
- Family history: stroke, acute myocardial infarction, hereditary diseases predisposing to stroke (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [CADASIL] syndrome, sickle cell anaemia, etc.).
- Medication: antihypertensives, insulin, anticoagulants, antiplatelet drugs, oral contraceptives, hormone replacement therapy...
- Previous score on the modified Rankin Scale (mRS) (Annex 3, (24) and Dr Joaquín Serena courtesy): a simple scale that assesses the degree of disability of the patient. It has 7 stages (from 0 to 6), with 0 being a fully independent person and 6 being death. It is important to accurately determine, with the help of the patient and/or relatives, the baseline degree of disability, as one of the inclusion criteria for the activation of the stroke code is the score on this scale. Rapid action to initiate patient management or stroke code activation will not be taken if the patient has a high baseline mRS score (16).

Neurological and general examination.

Given the severity of the condition, the physical examination should start with the assessment of vital functions: cardiorespiratory function, heart rate, blood pressure, oxygen saturation, temperature and blood glucose (16).

Recognising the clinical signs of stroke in a patient is the most important step. To do this, a complete neurological examination of all brain functions must be performed (7). There are validated scales, such as that of the National Institute of Health Stroke Scale (NIHSS, Annex 4, Dr Joaquín Serena courtesy), which allow a rapid initial assessment, determine the severity and prognosis of the stroke, as well as the need or not for revascularization treatment (25).

The aspects that should be assessed in the neurological examination are (16):

- Mental functions:
    - Level of consciousness.

    - Orientation in space and time, assessed by answering simple questions on the subject.
- Language: assessing comprehension, response to simple commands and general expression.
- Cranial nerves.
- Oculocephalic deviation, which makes it possible to locate the affected territory. In hemispheric strokes, the patient's gaze deviates towards the side of the lesion, while in strokes of the trunk, the deviation is towards the plegic side (contralateral to the lesion).
- Motor deficit: complete (plegia) or incomplete (paresis).
- Sensory deficit contralateral to the lesion.
- Cerebellar alterations.
- Evaluation of meningeal signs.

When examining a patient, the most suspicious signs/symptoms or neurological focality of stroke, according to the Sociedad Española de Neurología (SEN) (16), are:

- Sudden motor deficits characterised by loss of strength, altered tone and first motor neuron signs (such as Babinski's sign) in the hemibody contralateral to the lesion, or in both hemibodies.
- Sudden onset alteration or loss of sensation in the face, arm or leg of one hemibody or in the whole body.
- Sudden difficulty in speaking or understanding others (aphasia, dysarthria...).
- Sudden loss of vision in one or both eyes.
- Loss of balance, coordination or difficulty walking.
- Intense and sudden headache of unknown cause.

Similarly, there are certain unusual clinical manifestations that do not indicate stroke at first: dizziness, loss of consciousness, amnesia, dysphagia, urinary or faecal incontinence, gradual progression of symptoms… (16).

Therefore, detecting these symptoms is crucial since they serve to activate the well-known "Stroke Code". The Servei Català de la Salut, in its latest update of the Instrucció 01/2013 that entered into force on May 6, 2022 (26), considers activation criteria of the code if:

- The symptoms have started less than 24 hours ago, or the onset is uncertain, or it is an awakening stroke.
- Sudden onset of focal symptoms (RAPID+, scale that allows the general population or healthcare providers to identify a stroke, Annex 5 (26)), including TIA.
- Autonomy for daily basic activities without important comorbidities (RANCOM-, tool used to quickly assess the previous functional situation of the patient, Annex 6, (26)).
- No age limit, lower or higher. In patients aged <15 years, the Pediatric Stroke Code will be activated.

A decision algorithm is attached in the Annex 7 (26), on suspicion of an acute stroke, for the activation of the Stroke Code.

In addition, a general physical examination should be performed, including cardiorespiratory, head-and-neck, abdominal, accessible arterial, and fundus examination (7).

Complementary examinations.

Complementary explorations allow the diagnosis to be confirmed and identify systemic conditions that may simulate a stroke (see *Differential diagnosis section*). For this reason, it is carried out systematically in all patients (7,21,27):

- Blood tests: blood count, blood glucose, electrolytes, platelet count, prothrombin time (PT), activated partial thromboplastin time, International Normalised Ratio (INR), renal profile, cardiac ischaemia markers (troponins) and fasting or nonfasting lipid profile.
- Electrocardiogram (ECG).
- Oxygen saturation.
- Neuroimaging: CT or MRI, usually including m-CT or mp-MRI information of plain CT scan (ischaemic vs. hemorrhagic), as well as established infarct volume, penumbra, mismatch and markers of hemorrhagic growth, if this is the case (as shown in figure 4).

On an individual basis, the complementary tests could be extended according to suspicion of other entities: liver profile, toxicological examination, blood alcohol test, pregnancy test, arterial blood gases, chest X-ray, lumbar puncture, electroencephalogram, etc. (27).

3.2.6. Differential diagnosis

There are a number of entities that can simulate a stroke, also known as *"stroke mimic"*. Theoretically, they are easy to differentiate with a correct anamnesis, physical examination and complementary tests, but in routine clinical practice this is not the case (16). In some series, up to 15-30% of patients with suspected stroke actually suffered from another pathology (28).

The entities that most frequently simulate a stroke and should be ruled out are (16):

- **Seizures or post-ictal period**, as they can present hemiparesis, aphasia, hemianopsia, etc. It is the pathology that most frequently simulates a stroke, affecting 5% of patients with suspected stroke (SEN guide).

- **Migraine with aura**: characterised by headache with or without visual disturbances (aura) or sensory or motor deficits. In this case, the symptoms are more gradual.

- **Hypoglycaemia**: may cause focal symptoms and signs that mimic a stroke (whereas hyperglycaemia in patients with stroke is associated with a worse prognosis). Therefore, in all patients with neurological focality, hypoglycemia should be ruled out by blood glucose measurement.

- **Hypertensive encephalopathy:** a condition presenting with headache, delirium and/or neurological focality caused by HBP. It is a diagnosis of exclusion, after having ruled out stroke.

- **Conversion disorder:** neurological entity in which the patient unconsciously develops neurological symptoms following a traumatic event, with normal imaging tests.

- **Others:** subdural haematomas, abscesses, tumours and brain metastases, trauma, drug abuse, alcoholic encephalopathy, systemic infections or multiple sclerosis... etc.

3.2.7. Treatment

Ischaemic stroke is a life-threatening emergency. The prognosis and subsequent disability depend, to a large extent, on the speed with which revascularizing treatment is established.

Currently, only two types of recanalization treatment are available in the acute phase of stroke, and they can be administered individually or in combination (21):

- **Endovenous fibrinolysis with recombinant tissue plasminogen activator (rt-PA).**
- **Endovascular treatment with mechanical thrombectomy.**

Mechanical thrombectomy cannot delay the administration of rt-PA, but neither should endovascular treatment be delayed to complete the systemic perfusion of fibrinolytic (7,27).

As can be seen, the treatment options in the acute phase of ischaemic stroke are very limited. Moreover, they have a narrow temporal therapeutic window and a wide range of contraindications and potential complications, which greatly reduce the population of patients who can benefit from them. In addition, mechanical thrombectomy can only be done if an occluded vessel is evident by neuroimaging. Furthermore, it is not available in all centres and is only performed in hospitals with experienced professionals (7). For this reason, some patients with ischemic stroke may not receive any revascularization treatment.

The following table lists the main indications and contraindications of these treatments, according to the medical guide of the Societat Catalana de Neurologia (7).

	rt-PA	Mechanical thrombectomy
Indications	• Stroke with symptom onset time of less than 4.5 hours (in individualized cases, it can be administered up to 9 hours after the onset of symptoms, or in the wake-up stroke) • ≥18 years. • Individualise in patients with Rankin >2. • Strokes that are mild (NIHSS <4) or that are improving rapidly as long as the deficits are considered disabling or there is evidence of intracranial occlusion. • Awakening stroke or stroke with unknown time of onset of symptoms but with mismatch between diffusion signal involvement and absence of FLAIR signal involvement on brain MRI.	• Ischaemic stroke of less than 24 hours' duration with proximal large vessel occlusion in the anterior territory (intracranial internal carotid or segment 1 of the middle cerebral artery). • Stroke due to occlusion of the intracranial internal carotid or segment 1 of the middle cerebral artery between 8 and 24 hours of evolution with moderate-severe neurological deficit and a small infarct seen by neuroimaging. • Tandem occlusions of the intracranial and extracranial carotid circulation. • Certain contraindications to rt-PA administration: history of intracranial haemorrhage, recent ischaemic stroke, recent surgery or arterial puncture, recent systemic haemorrhage, mild platelets (>30,000/ µL), anticoagulation in therapeutic and infectious range. • Patients with mild neurological deficits (NIHSS <6) especially if there is fluctuation of neurological symptoms. • Attempt to perform without general anaesthesia.
Contraindications	Absolute contraindications: • Major head trauma, ischaemic infarction, intracranial or intra-spinal surgery in the previous 3 months. • Hypodensity on cranial CT suggestive of established ischaemic infarction > 1/3 of the cerebral hemisphere. • History of previous intracranial haemorrhage. • Active internal haemorrhage or within the previous 21 days. • Signs or symptoms of intracerebral or subarachnoidal haemorrhage. • Acute haemorrhagic diathesis. • Platelets <100,000/mm3. • Treatment with heparin at full doses within 48 hours. • Treatment with Acenocoumarol/Warfarin with an INR >1.7 or PT >15 seconds. • Treatment with direct thrombin inhibitors or direct factor Xa inhibitors. • Arterial puncture at a non-compressible site within the previous 7 days. • Intra- or extracranial neoplasm, arterio-venous malformation or aneurysm. • Uncontrollable high blood pressure (SBP >185 and/or DBP >110 mmHg). • Blood glucose <50 mg/dl (2.7 mmol/L) or >400 mg/dl that cannot be corrected during the therapeutic window of fibrinolysis. • Stroke secondary to infective endocarditis. • Concomitant aortic dissection. Relative contraindications (individualise): • Mild or rapidly improving deficits. • Pregnancy. • Have given birth in the previous 14 days. • Major surgery or major trauma (not head injury) within the previous 14 days. • Recent gastrointestinal or urinary tract bleeding (outside the previous 21 days). • Recent acute myocardial infarction (within the previous 3 months). • Previously known multiple microbleeds on brain MRI. • Small aneurysms (<10 mm) or untreated cerebral arteriovenous malformations with no history of previous rupture.	• Treatment-resistant hypertension (SBP >185 and/or DBP >110 mmHg) • Severe coagulation disturbances or supratherapeutic levels of anticoagulation (e.g. INR>3, thrombocytopenia <30,000/µL) • Extreme blood glucose levels. • Severe renal insufficiency (creatinine >3 mg/dl) • Patients with a history of severe allergy to iodinated contrast or components of thrombectomy devices. • Individualise in patients with stroke of a few hours of evolution and absence of extensive established lesion in occlusions of other intracranial arteries, such as segments 2 and 3 of the middle cerebral artery, anterior, posterior, vertebral or basilar cerebral arteries, or in isolated extracranial carotid occlusions. • Individualise in patients with previous disability. • Individualise in patients with extensive established lesions, especially if other patient factors suggest functional improvement as a result of reperfusion.

Table 3. Indications and contraindications for fibrinolytic therapy and endovascular treatment *(adapted from (7)).*
Computerised tomography (CT); Diastolic blood pressure (DBP); Fluid-attenuated inversion recovery (FLAIR); International normalised ratio (INR); Magnetic resonance imaging (MRI); National Institute of Health Stroke Scale (NIHSS); Prothrombin time (PT); Recombinant tissue plasminogen activator (rt-PA); Systolic blood pressure (SBP).

3.2.8. Etiological study

The aetiological diagnosis consists of performing a series of tests on the patient according to the suspected aetiology that has caused the stroke. One of the reasons why the SSS-TOAST classification is very important is because it allows the patient to be classified according to a first etiopathogenic suspicion of stroke (20). Depending on this, certain tests will be carried out to identify possible cardioembolic sources, thromboembolism due to atherosclerosis of large vessels, hypercoagulable states, etc.

This aetiological study allows, not only to categorise the type of stroke, but also to administer the optimal treatment in the acute phase and to establish a secondary prevention strategy according to the findings (7,21).

The following list shows the AHA/ASA recommendations on the aetiological study of ischaemic stroke (21):

1. In case of doubts about the diagnosis of stroke due to a negative initial neuroimaging or suspicion of TIA, a cranial MRI could be performed since a quarter of acute strokes with a negative initial cranial CT will have MRI evidence of acute/subacute infarction (29). In patients with posterior circulation stroke, MRI can also be used to confirm the diagnosis (30).

2. Perform a blood test as described in section *3.2.5 (Complementary examinations)*. It allows to identify metabolic and/or haematological alterations and to stratify patients according to the risk of recurrence.

3. Perform an ECG to diagnose AF or detect other comorbidities such as acute myocardial infarction.

4. A vascular study must be performed in all patients, such as transcranial Doppler (TCD) ultrasound and of both of the supra-aortic trunks, computed tomography angiography (CTA) or magnetic resonance angiography (MRA). Arteriography is the gold standard, but it is rarely performed as it is an invasive procedure.

5. Detecting symptomatic intracranial atherosclerotic disease and symptomatic intra- or extracranial vertebrobasilar stenosis allows to classify patients at high risk of recurrence. Furthermore, the study of collateral circulation and cerebral hemodynamic reserve can be performed. It is, therefore, important to perform non-invasive studies, such as transcranial Doppler ultrasound, to identify them and indicate the appropriate secondary prevention treatment.

6. In patients with suspected cardioembolic stroke or without evident stroke aetiology, it is advisable to perform echocardiography to identify cardioembolic sources with a possible treatment. Transthoracic Echocardiography (TTE) is preferred for the study of left ventricular thrombi, while Transesophageal Echocardiography (TEE) is more sensitive to the detection of left atrial thrombi, aortic atheromatous plaques, native or prosthetic valve abnormalities, atrial septal abnormalities or cardiac tumours.

7. In patients with stroke of unknown aetiology, after performing the aforementioned studies, prolonged cardiac monitoring (2-3 weeks), especially Holter ambulatory monitoring, has been shown to detect high rates of unknown AF. Cardiac CT has a very good specificity (95%) but lower sensitivity (72%) to the detection of embolic sources in strokes of unknown origin (21). The role of cardiac MRI is also scarce in this type of patients.

8. If rare causes of stroke are suspected, additional testing should be performed based on diagnostic suspicion guided by medical history, physical findings, and basic test results.

The following figure summarises what has just been presented: the diagnostic algorithm from the time a stroke is suspected in a patient until its aetiology is found.

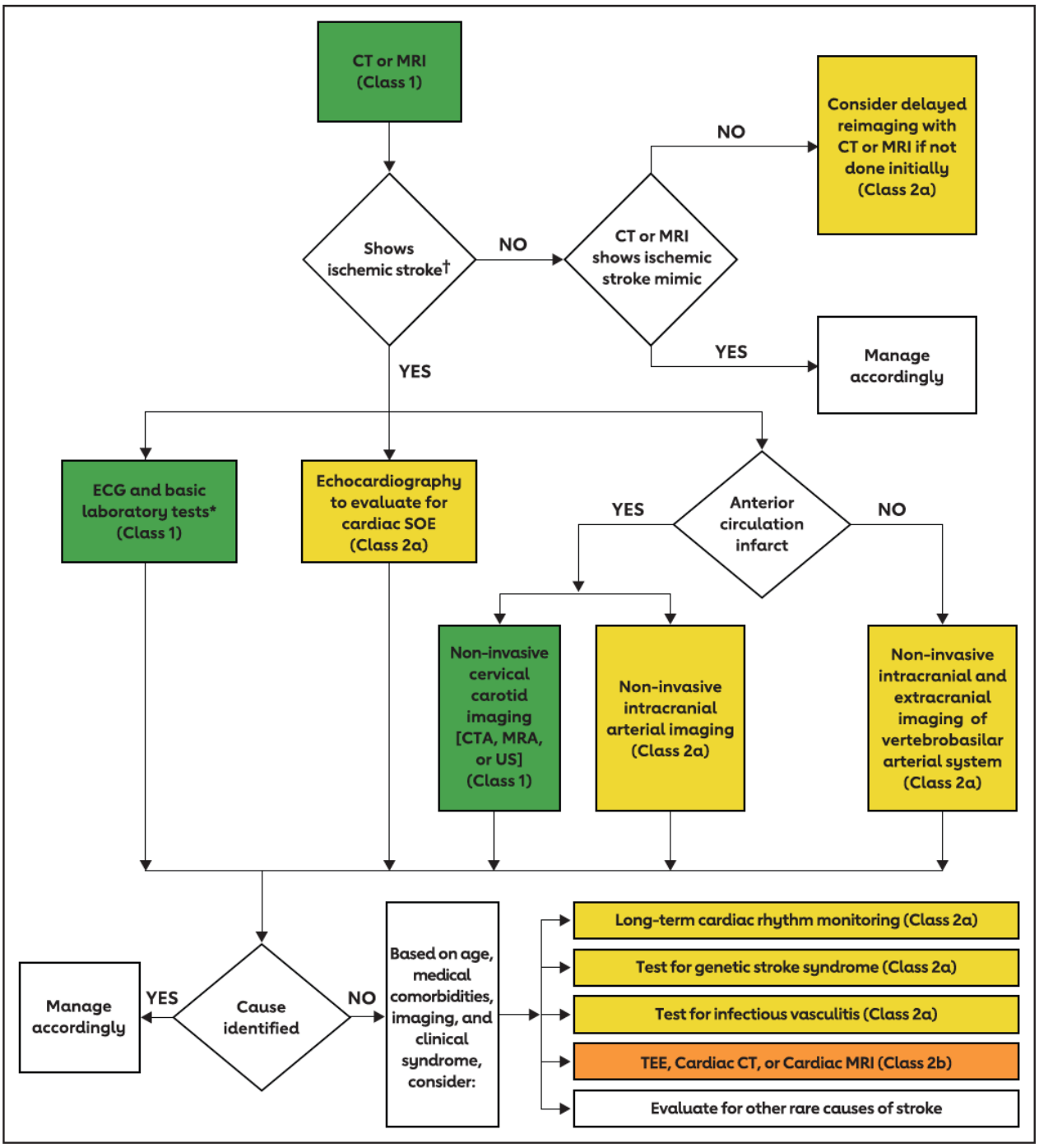

***Figure 11. Algorithm for the diagnosis of stroke and the detection of its possible aetiology. Colours correspond to Class of Recommendation in Anexo 8** (21).*

Computerised tomography (CT); Computed tomography angiography (CTA); Electrocardiogram (ECG); Magnetic resonance angiography (MRA); Magnetic resonance imaging (MRI); Patent foramen ovale (PFO); Source of embolism (SOE); Transcranial Doppler (TCD); Transesophageal echocardiography (TEE); Transthoracic echocardiography (TTE); Ultrasound (US).

3.2.9. Secondary prevention

Secondary prevention should include the same general recommendations as mentioned for primary prevention (17,18).

In addition, depending on the aetiology that caused the stroke according to the results of the aetiological study tests, specific recommendations will be made for each type of stroke. Below is a brief summary (21):

- Atherothrombotic strokes (31), lacunar strokes and strokes of undetermined aetiology: high doses of statins and antiplatelet aggregation therapy (in some specific cases, double antiplatelet therapy for 21 days).
- Cardioembolic strokes:
    - Non-valvular aetiology: anticoagulant treatment.
    - Valvular aetiology: antiplatelet or anticoagulant treatment depending on the specific aetiology.

3.2.10. Recurrence of Atherothrombotic Stroke

As previously mentioned, atheromatous disease and carotid atherosclerosis are important causes of stroke and, therefore, morbidity and mortality. Thus, it is crucial to determine and explore different parameters that are predictors of a new stroke recurrence.

If these risk markers were known and detected in each patient, a more or less aggressive treatment could be implemented depending on their risk of recurrence. In this way, a better selection of patients would be made who, due to their risk of stroke recurrence, must undergo surgical treatment, which *a priori* has more risks, or who simply need to undergo intensive medical treatment (10).

Currently, clinical, neuroimaging and analytical markers are available (e.g. plaque vulnerability biomarkers), and could help in predicting this risk of recurrence.

The following table lists the main clinical, hemodynamic, and neuroimaging parameters that may be useful in daily clinical practice to predict this risk of recurrence. As can be seen in *figure 12*, the parameters that indicate a higher risk of recurrence are those that benefit more from revascularization treatment, that is, surgery (carotid endarterectomy [CEA] or carotid angioplasty with stenting).

	Greater net benefit if revascularization	Lower net benefit if revascularization
HR 1.73, 95% CI 1.06-2.84	ICA stenosis >70% (>85%)	ICA stenosis 50-69%
	Male	Female
HR 1.25, 95% CI 1.02-1.53	<70 years old	>75 years old
	Not diabetic	Diabetic
	Stroke	TIA or asymptomatic
HR 3.8, 95% CI 1.5 to 9.5	Hemispheric symptoms	Amaurosis fugax (HR, 95% CI, 0 [0.0–0.6])
OR 3.66 (2.77-4.95)	Plaque characteristics (hypoechoic, irregular, ulcerated, high volume, progression)	Calcified plaque
HR 4.1, 95% CI 1.3-13.1	Decreased CVR. Poor collateral circulation	Good collateral circulation
HR 6.56, 95% CI 1.6–26.8	MES +	MES -

Figure 12. Clinical, haemodynamic, and neuroimaging parameters useful in routine clinical practice *(10). Cerebrovascular reactivity (CVR); Confidence interval (CI); Hazard ratio (HR); Internal carotid artery (ICA); Microembolic signals (MES); Transient ischaemic attack (TIA).*

As can be seen, *microembolic signals (MEs)* are the most powerful predictor of recurrence risk, with a hazard ratio (HR) of 6.56. The next most powerful marker is *plaque characteristics*, with a HR = 3.66. That is why both entities are key points of this clinical trial.

In a prospective observational study published in The Lancet Neurology (32), the presence of MEs detected by transcranial Doppler ultrasound of the MCA was studied for at least 1 hour at baseline and at 6, 12, and 18 months, as shown in the following figure.

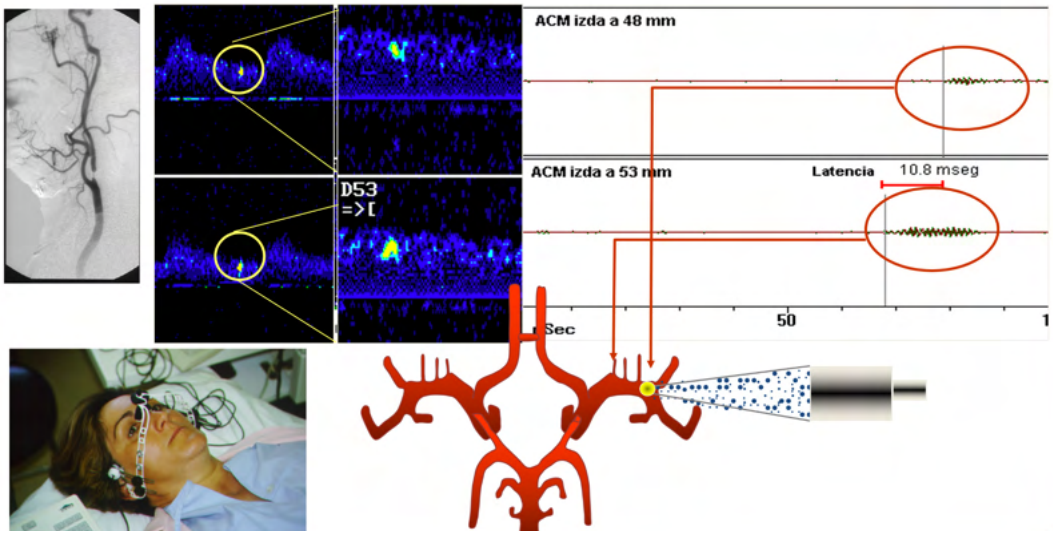

Figure 13. Detection of cerebral microemboli signals (MEs) in unstable plaques by transcranial Doppler. *The typical detection of MEs is shown, as well as their spectral identification in the middle cerebral artery (MCA, shown in the picture as ACM) ipsilateral to the carotid stenosis, with detection at 2 different depths (53 mm and 48 mm) while the microembolism travels through the cerebral artery (DWL detection software). Courtesy of Dr Joaquín Serena.*

This prospective study concluded that the absolute annual risk of ipsilateral stroke or transient ischemic attack was 3.62% in patients with MEs and 0.70% in patients without MEs.

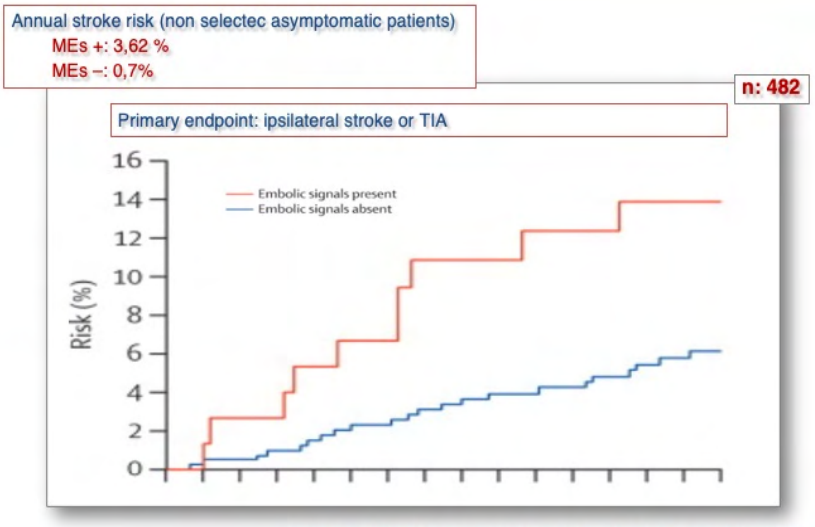

Figure 14. Annual stroke risk according to the presence or absence of cerebral microemboli signals (MEs). *Courtesy of Dr Joaquín Serena, adapted from (32).*

Therefore, the detection of MEs can be used to identify patients who are at increased risk of stroke and TIA, as well as those who are at low risk of recurrence. Consequently, it would be useful to select patients who would possibly benefit from surgical treatment of said carotid atheroma plaque (CEA or stenting) (32).

3.3. Mobile carotid plaques

3.3.1. Definition and background

As previously mentioned (section *3.2.8. Etiological study*), in patients with possible atheromatous stroke, it is advisable to perform an ultrasonographic study of the supra-aortic trunks to detect possible carotid stenosis.

This is why, for some years now, more and more cases of **carotid atheromatous plaques with mobile characteristics** have been reported (33), both in stenotic and non-stenotic plaques (34).

Mobile carotid plaques (MCP) are defined as abnormal plaque motion in all or part of the plaque, identified by ultrasonographic study (35). Furthermore, it has been suggested that

MCP are associated with high risk of stroke and recurrence, in spite of absence of relevant carotid stenosis (34).

According to the characteristics of each of the MCP on carotid ultrasound, they are classified into 5 types (36,37) (figures 19, 21, 22, 24 and 25):

- **Jellyfish-type plaque.**
- **Streaming-band-type plaque.**
- **Mobile-thrombus-type plaque/Carotid free-floating thrombus.**
- **Fluctuating-ulcer-type plaque.**
- **Snake fang-type plaque.**

However, it is still a largely unknown area, as the scarce literature is mostly based on case series. Therefore, both the natural history of these MCP and their management and treatment are highly controversial (33,38).

Further adding to the uncertainty is the lack of precise description (39). Many authors refer to them as "mobile plaques or floating plaques" (36,40,41), but others use the term "carotid free-floating thrombus" (33,42), that is only one subtype of mobile plaques. This makes the literature and knowledge on this topic disparate.

3.3.2. Epidemiology

As the characterisation and detection of these plaques is not yet fully elucidated, the epidemiology is uncertain, and numbers vary widely.
According to Kotval (43), there is an estimated prevalence of 1 MCP per 2000 carotid ultrasound scans. More recent studies estimate that 12.8% of strokes associated with external carotid atherosclerosis are due to MCP (36).

3.3.3. Diagnosis

The optimal method for diagnosing MCP also differs to some extent, with some authors using Doppler ultrasound of the supra-aortic trunks, others using CTA, MRA or even digital subtraction angiography (DSA) (33).

Although MCP can be detected by any of the previously mentioned techniques, **eco-Doppler ultrasound of the supra-aortic trunks,** a widely available and non-invasive method, is increasingly used to assess plaque morphology and content.

Furthermore, ultrasound is the only method that provides information about plaque mobility, the main anatomical feature associated with increased stroke risk in MCP (33,44).

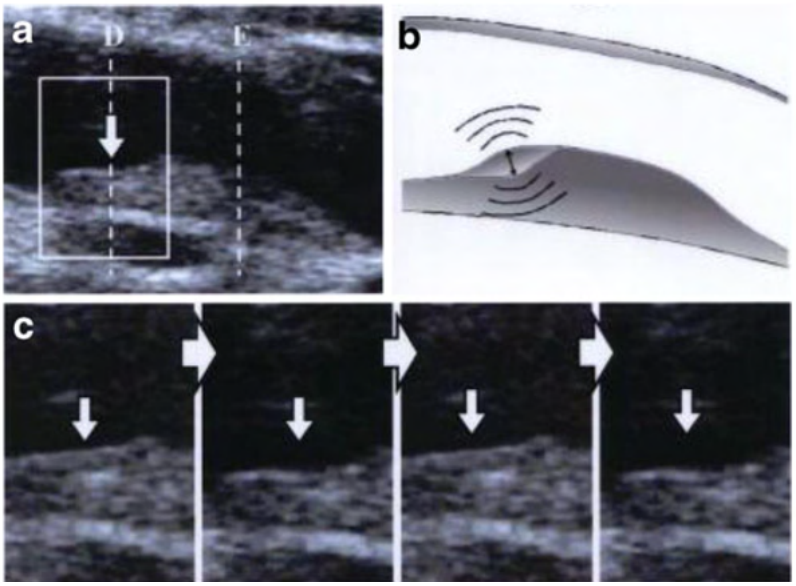

Figure 15. Movement of a Mobile Carotid Plaques (MCP).

Image A shows a longitudinal B-mode ultrasonography of the cervical internal carotid artery (ICA) with the jellyfish sign (square D). Image B shows a scheme of this ultrasonography. Image C is a montage of the movement of this mobile carotid plaque (arrows) (44).

3.3.4. Histologic characteristics

In Annex 9 (45) we include the classic and accepted histopathological characteristics associated with unstable plaque or vulnerable plaque. In their management, there is consensus on the indication for intensive medical treatment, while surgical treatment (stent or CEA) is not indicated, in spite of the well known increased risk of stroke associated with the characteristics of vulnerable plaques.

In terms of the anatomopathology of MCP, the histological features of these plaques have been found to be different from those of symptomatic non-MCP (44).

In particular, **the necrotic core of MCP was found to be significantly larger** than in non-MCP. A higher frequency of mural thrombus and a lower median minimum fibrous cap thickness were also observed in MCP compared to non-MCP, although the relationship was not significant (46).

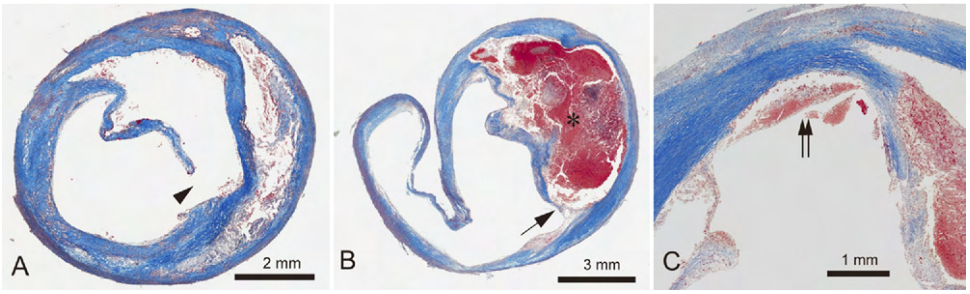

Figure 16. Histology of a Mobile Carotid Plaques (MCP) (I).
Masson's trichrome stained image of a carotid bifurcation showing A) complete disruption of the fibrous cap (arrow); B) cross section showing a large necrotic core with intraplaque haemorrhage (*) covered by a thin fibrous cap (arrow); C) intramural fibrin deposition, indicating a mural thrombus (double arrow) (46).

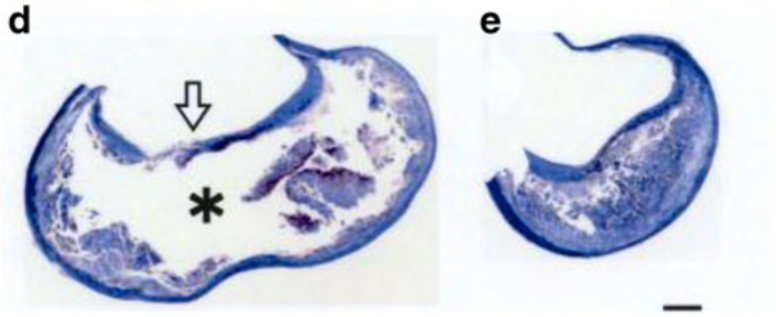

Figure 17. Histology of a Mobile Carotid Plaques (MCP) (II).
Masson's trichrome stain of a carotid plaque showing the mobile plaque area (D), with thinning and rupture of the fibrous caps overlying the plaque; and the non-mobile plaque area (E), with a thickened fibrous capsule overlying the plaque (44).

3.3.5. Implications

Despite the apparent low prevalence of these plaques, the main interest in their study is the **high rates of acute-phase stroke recurrence** that have been observed. In the study conducted by Ogata *et al.* (36), 33.3% of patients with MCP had early stroke recurrences compared to 7.3% in patients with non-MCP. Similar results have been recorded in other studies (33), as seen in *figure 18*. This high recurrence implies increased neurological focality in acute phase and greater short- and long-term neurological disability.

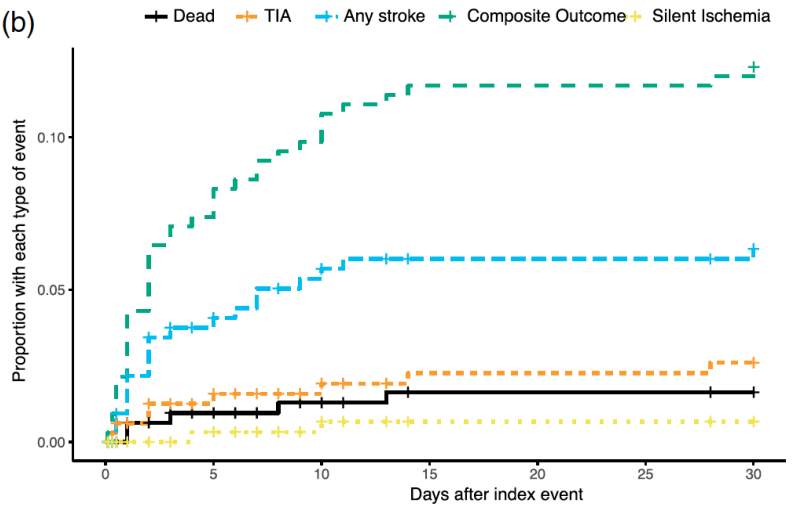

Figure 18. Kaplan-Meier plot for 30-day outcomes in stroke patients with mobile carotid plaques *(33).*

Transient ischaemic attack (TIA).

Although the reason for these behaviour of the MCP is not completely known, as their natural history is unknown, it is hypothesised that the histological characteristics of these plaques could explain, to a large extent, the high risk of stroke recurrence in patients with MCP (46).
It also appears that the mean **degree of stenosis measured by Doppler ultrasonography is significantly lower in stroke patients with MCP** compared to patients with non-MCP (34,36). This could be related to the lower neurological deficit in stroke patients with MCP at admission compared to patients with non-MCP (median NIHSS 1 vs. 4) (36).

Ulcer formation in atheromatous plaques is a well known marker of vulnerability and of aggressive behaviour. **Ulcer formation in MCP has been found to be more frequent** (58.3%) than in non-MCP (11%) (36).

All of these studies were based on samples with very few patients, so data on the prevalence or early recurrence of stroke for each plaque subtype require further study.

3.3.6. Subtypes of mobile plaques

As mentioned above, there have been described **5 subtypes of MCP.** This classification has been carried out mainly by the work of Ogata *et al.* (36), but also by the studies of Tateishi *et al.* (37).

Jellyfish-type plaque:

The Jellyfish-type plaque is characterised by upward and downward mobility of the fibrous cap with the heartbeat, a feature that gives it its name, due to the similarity in its movement with the tentacles of a jellyfish (36,40). In the Ogata *et al.* study (36) it was found to be the most common carotid plaque subtype and the one with the highest rate of early stroke recurrence.

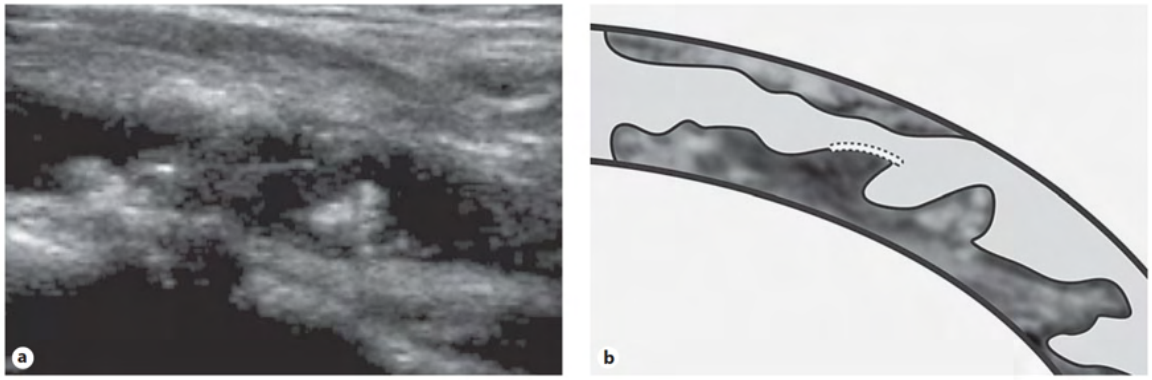

Figure 19. Jellyfish-type plaque seen by supra-aortic trunk ultrasound (A) and its scheme (B) *(36).*

It appears that such mobility is due to thinning and rupture of the fibrous cap of the plaque. This could result in the continuous release of embolic material, leading to new early ischaemic events. Jellyfish-type plaques have, therefore, been identified as an important predictor of ischaemic stroke recurrence and a sign of high-risk plaque vulnerability (44).

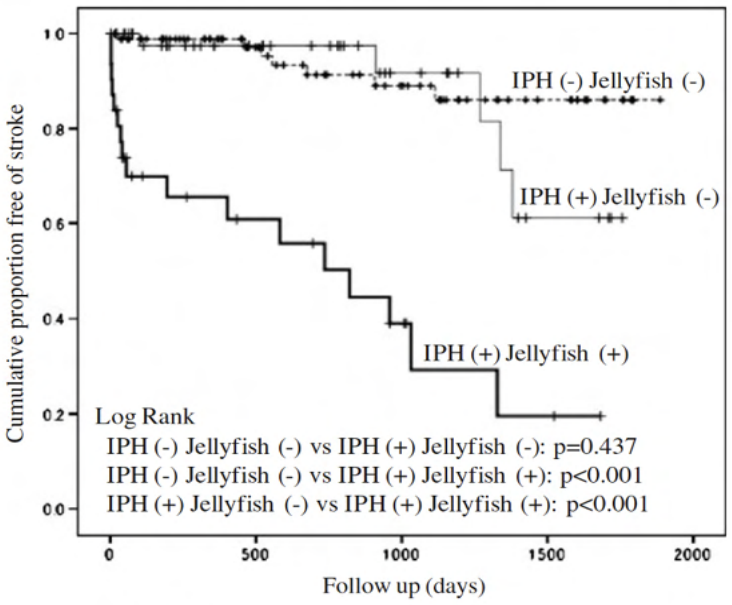

Figure 20. Kaplan–Meier survival estimation of the proportion of patients remaining free of ipsilateral ischemic stroke event for subjects of the three groups: IPH(−); IPH(+)JF(−); and IPH(+)JF(+) *(44).*
Intraplaque haemorrhage (IPH); Jellyfish sign (JF).

Streaming-band-type:

According to Ogata *et al.*'s description (36), this subtype of MCP is characterised by mobility at its edge, which appeared wavy, like a "flow band" due to rupture of the fibrous capsule.

It is the second most frequent subtype and has a lower risk of stroke recurrence than the Jellyfish-type plaque.

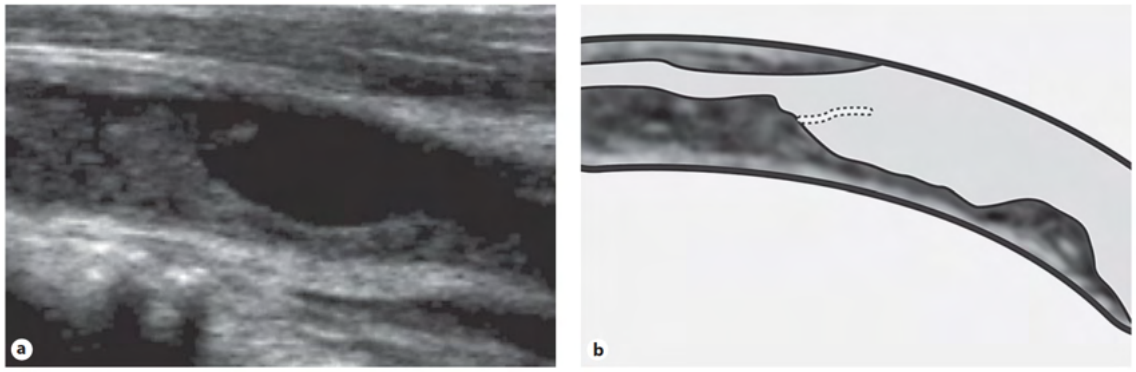

Figure 21. Streaming-band-type seen by supra-aortic trunk ultrasound (A) and its scheme (B) *(36).*

Mobile-thrombus-type plaque or carotid free-floating thrombus:

This subtype appears to be caused by the formation of a thrombus on a previously ruptured atheroma plaque (36). Thus, the thrombus attached to the plaque shows mobility in all its parts. Although none of the patients in Ogata *et al.*'s study with this plaque subtype showed recurrence (36), other studies have linked this subtype to an increased risk of early stroke recurrence (33). As already mentioned, this is the subtype of MCP that creates confusion in terms of nomenclature, since many authors use the term “MCP” or “free-floating thrombus” interchangeably, actually being different terms.

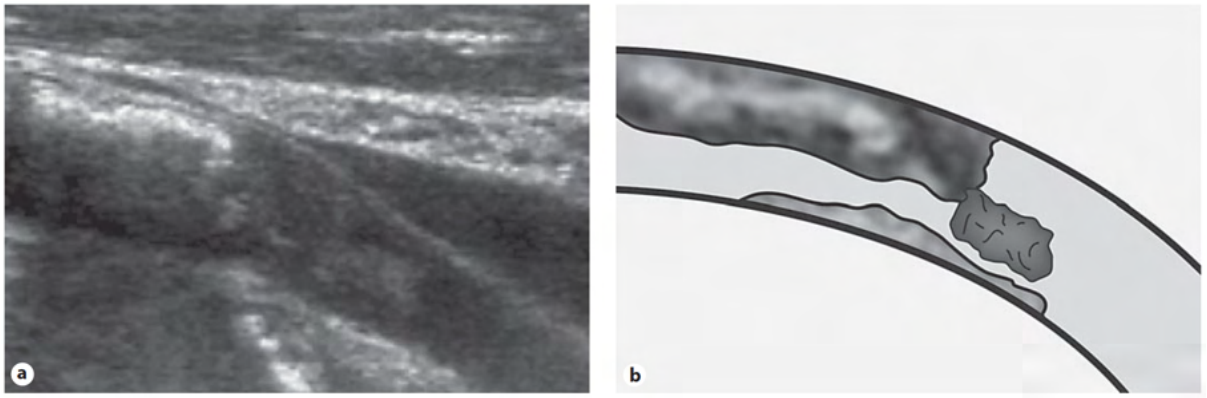

Figure 22. Mobile-thrombus-type seen by supra-aortic trunk ultrasound (A) and its scheme (B) *(36).*

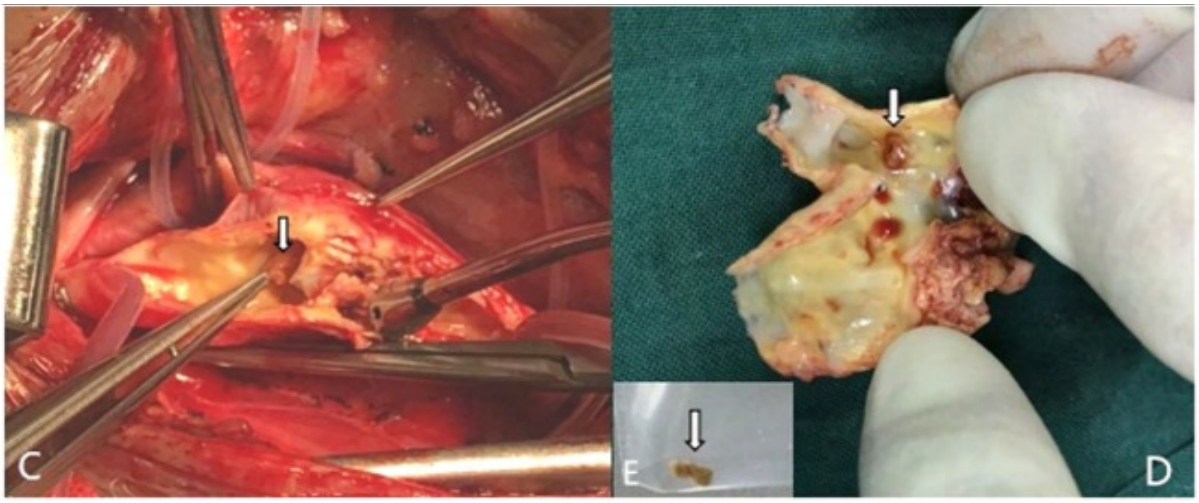

Figure 23. Mobile-thrombus-type seen during a carotid endarterectomy (CEA) *(41).*

Fluctuating-ulcer-type plaque:

This subtype of plaque is characterised by mobility at the bottom of an ulcer in the carotid plaque (36). This mobility is caused by a mobile substance that appears to move out of the ulcer and back in with each heartbeat. Patients studied by Ogata *et al.* (36) with this subtype of plaque had no stroke recurrences.

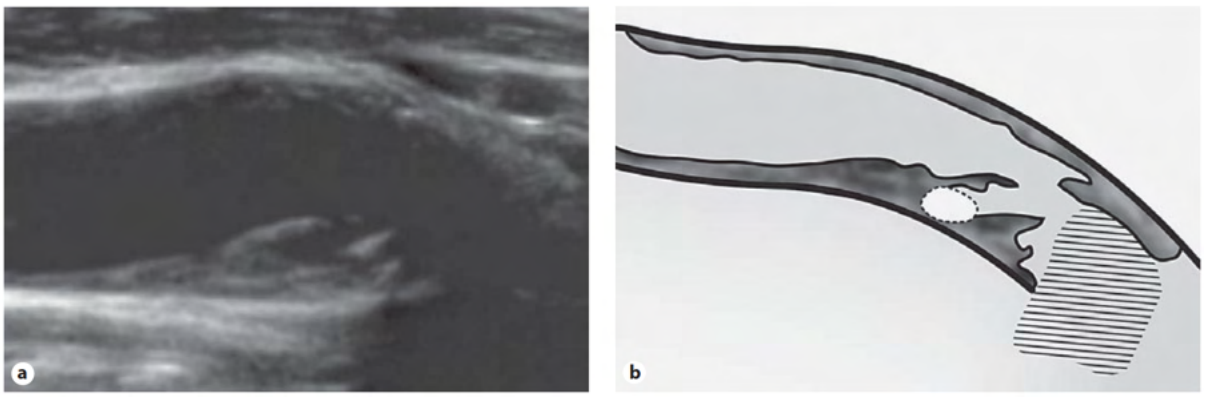

Figure 24. Fluctuating-ulcer-type plaque seen by supra-aortic trunk ultrasound (A) and its scheme (B) *(36).*

Snake fang-type plaque:

This subtype is characterised by the presence of floating thrombi in the distal region of small carotid atheromatous plaques without significant stenosis or plaque vulnerability (37). This is called *"snake fang sign"*, as it resembles the fangs of a snake, as seen in *figure 25.*

Floating thrombi in plaques produce a vortex flow, which is conducive to the formation of embolic material.

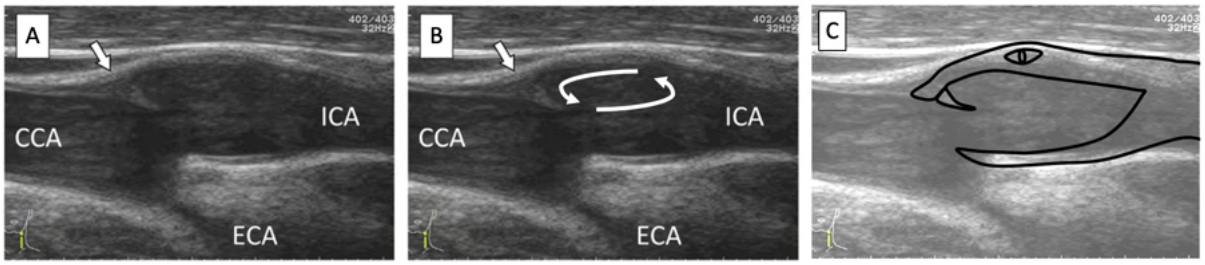

Figure 25. Snake fang-type plaque seen by ultrasound of the supra-aortic trunk (A), vortex flow (B) and its outline (C) *(36).*

Common carotid artery (CCA); External carotid artery (ECA); Internal carotid artery (ICA).

3.3.7. Treatment

Regarding the management of MCP, there is no consensus on their treatment in symptomatic patients suffering from an acute ischaemic stroke or a TIA (33,36,44). Furthermore, no studies have been conducted to determine the optimal treatment in these patients.

It is unclear whether best medical treatment (BMT) or interventional/surgical treatment is better. Within medical treatment, it is also unclear whether the use of anticoagulation is superior to antiplatelet therapy or viceversa. The same applies to interventional treatment with stents or CEA (33).

In a recent systematic review focusing on carotid free-floating thrombus (33), there were no differences in outcomes for any anticoagulation regimen or when to perform the surgical/interventional revascularization procedure. However, the evidence is of very low quality and warrants a large-scale randomised clinical trial in floating carotid thrombi and other MCP subtypes.

4. JUSTIFICATION

As mentioned in the *Introduction* section, the epidemiology of stroke reflects its major impact on society and health systems. Therefore, research into its prevention, diagnosis, treatment and risk reduction of sequelae is a priority.

Among the different aetiologies of ischaemic stroke, atherothrombotic stroke accounts for 17-20% of the total (21). Hence, its proper management is crucial to reduce the morbidity and mortality associated with it.

In atherothrombotic stroke, internal carotid artery (ICA) significant stenosis or intracranial artery stenosis of atheromatous origin are the main source of distal embolic stroke. The embolism is due to a local clot or to a piece of ruptured plaque that is carried by the bloodstream (embolus) and oclude a distal intracranial artery.
Treatment of carotid stenosis, particularly symptomatic stenosis, is well established (7).

However, several studies (33,36,44) have shown that, in a high proportion of patients, the aetiology of atherothrombotic ischaemic stroke is associated with non-significant stenosis atheromatous plaques in the ICA (33,34), often with malignant features described as **mobile carotid plaques or MCP** (17-33.3% of increased stroke risk, according to some authors (33,36)).

The epidemiology of these MCP is scarce and uncertain, as the literature has low quality and its mostly based on case series with very few patients. Furthermore, the imprecise description of these plaques makes it difficult to reach a consensus on their management, as the terminology of "mobile plaques" and "floating thrombi" is often used interchangeably (39,47). To date, only one systematic review on the subject is available, but it only focuses on the study of floating thrombi (a subtype of MCP), establishing a prevalence of 1.53% of stroke patients and a 30-day risk of stroke recurrence or death of 17.1% (33).

What the literature strongly suggests (33,36,44) is that these MCP have been associated with an increased risk of atherothrombotic ischaemic stroke and early stroke recurrence. However, further scientific evidence studies are required to demonstrate this.

The definition criteria, subtypes, diagnosis and treatment of these MCP are not well established, due to the limited conclusive literature available. In addition, its prevalence is probably underestimated, as suggested by recent studies (27), since its diagnosis has increased in recent years due to the increased use of early noninvasive vascular imaging, particularly of high-definition Doppler ultrasound of the supra-aortic trunks.

Therefore, given the lack of knowledge in this area, as well as the increased risk of stroke and early recurrence, it is important to investigate its optimal diagnosis, early clinical course, and, above all, its most appropriate treatment.

As mentioned, the risk of stroke recurrence from these MCP is high and early (17-33.3%) (33,36), while the risk derived from a surgical or interventional carotid treatment (carotid endarterectomy [CEA] or stent) is very low (<1%) (48), so considering this intervention in a clinical trial would be justified.

For this reason, it seems reasonable in this scenario of lack of knowledge, to propose a randomised clinical trial that studies the efficacy of CEA/stent as treatment in the acute phase of ischemic stroke caused by MCP, and its possible superiority with respect to the best medical treatment (BMT) for atherothrombotic stroke, not analysed until now.

5. HYPOTHESIS

Main hypothesis.

- Surgical treatment (carotid endarterectomy [CEA] or stenting) is superior to the best medical treatment (BMT) in preventing early stroke recurrences in patients with mobile carotid plaques (MCP), and it is associated with a better functional outcome.

Secondary hypothesis

- Cerebral microembolic signals (MEs) will be detected more frequently on the 5th day (±24 hours) post-randomization in patients with MCP-associated stroke treated in the acute phase with BMT than in those treated with CEA/stent.

- The risk of recurrence at one month, three months and one year post-stroke will be lower in the group of patients with MCP whose treatment in the acute phase was surgical (CEA/stent), compared to the arm treated with BMT.

- The degree of dependence at three months, measured using the modified Rankin Scale (mRS), will be lower in the group of patients with MCP whose treatment in the acute phase was surgical (CEA/stent) compared to the arm treated with BMT.

6. OBJECTIVES

Main objective

- To determine the risk of early recurrence (<72 hours post-admission) by adjudicated acute phase treatment (carotid endarterectomy [CEA]/stenting vs. best medical treatment [BMT]).

Secondary objectives

- To determine the presence of cerebral microembolic signals (MEs) in strokes associated with mobile carotid plaques (MCP), evaluated on the 5th day (± 24 hours) post-randomization, according to the treatment awarded in the acute phase (CEA/stent vs. BMT).

- To determine the risk of stroke recurrence at one month, three months and one year post-index stroke, according to the treatment administered in the acute phase (CEA/stent vs. BMT).

- To establish the degree of disability at 3 months, using the modified Rankin Scale (mRS), per adjudicated treatment (CEA/stent vs. BMT).

7. MATERIALS AND METHODOLOGY

7.1. Study design

To study the main objective of this project, a **randomised, open-label, multicentered, prospective, controlled, parallel groups, clinical trial** is designed.

The study is designed to compare, as its main objective, the risk of early recurrence of ischemic stroke in patients with MCP according to the treatment received in the acute phase (CEA/stenting vs. BMT) and, thus, determine the optimal treatment for this type of patients. All patients will be treated following the current protocol, but they will be randomised in a ratio 1:1 into one of the following two groups:

- Group 1: Patients with an ischaemic stroke caused by MCP **treated in the acute phase with CEA/stenting.**
- Group 2: Patients with an ischaemic stroke caused by MCP **treated in the acute phase with BMT.**

It is important to clarify that what we are studying is treatment in the acute phase. However, all patients who suffer an atherothrombotic stroke (including those in this study), as soon as they are admitted to the Stroke Unit (SU), should receive secondary prevention medical treatment (BMT) in accordance with current guidelines (21), although individualised according to the specific characteristics of each patient.
Therefore, this BMT will be considered acute phase treatment and secondary prevention treatment in the group of patients belonging to the BMT arm. However, the other arm (CEA/stent group) will have CEA/stent as acute phase treatment and medical therapy (BMT) as secondary prevention treatment.
In summary, both arms of the clinical trial will receive secondary preventive medical treatment (BMT).

This process is schematized in the following figure.

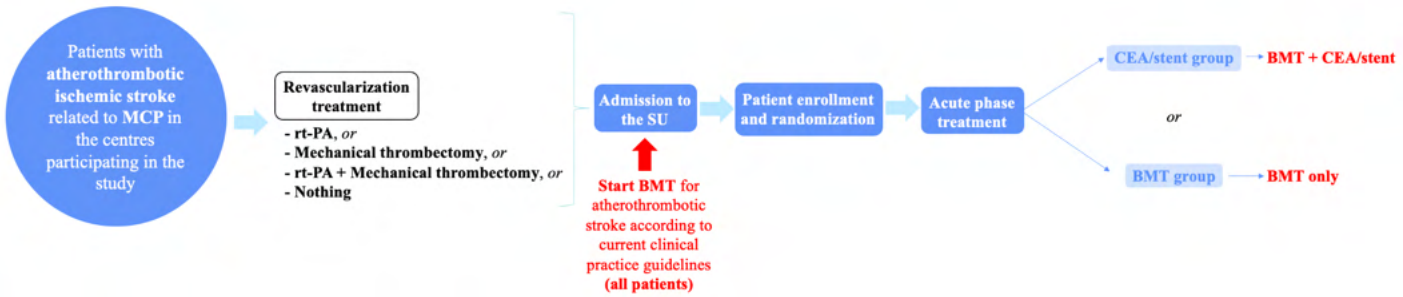

Figure 26. Explanatory diagram on the acute phase treatment and secondary prevention treatment of the patients who will enter this study.

Best Medical Treatment (BMT); Carotid Endarterectomy (CEA); Mobile Carotid Plaques (MCP); recombinant tissue Plasminogen Activator (rt-PA).

Regarding the masking method, an open-label method was chosen because the different interventions (CEA/stenting vs. BMT) are very obvious to both participants and researchers.

Since this clinical trial focuses on the study of MCP, plaques with a very aggressive behaviour, the name of the study will be **"The PLACA VIL trial"**, an acronym in Spanish for "PLAca CArotídea móVIL".

7.2. Study setting

Given the low prevalence of MCP, this project will be multicentre, with the collaboration of, at least, 13 centres among the 23 potential participating centres belonging to the *Sociedad Española de Neurosonología (SONES)*, *RICORS-Ictus* and *Proyecto Ictus*. All of these centres have vascular neurologists with expertise in neurosonology and a SU similar to the one of the Hospital Universitario Doctor Josep Trueta (HUDJT), that also belongs to these three organisations. The list of hospitals belonging to these networks that will participate in the study is attached in Annex 10.

The participating centres not only have experience in doing collaborative research projects, but also have similar technical characteristics. All of them have equipment for CT, CTA, Doppler ultrasound of the supra-aortic trunks, transcranial, and specific software for the analysis of cerebral MEs.

As mentioned, the SUs are also very similar. The SU of each centre consist of:

- Health professionals specialised in stroke, which allows a multidisciplinary approach of the patient.
- Non-invasive continuous monitoring equipment (ECG, heart rate, respiratory rate, oxygen saturation) and continuous video surveillance from the nursing control. These integrate a predictive system of hidden causes responsible for stroke (e.g. AF).
- Each room has mobilisation cranes on the ceiling and adapted spaces capable of starting an early rehabilitation.

7.3. Subjects selection

The population of this study will consist of consecutive patients admitted to the SU of the participating centres belonging to the *SONES*, *RICORS-Ictus* and *Proyecto Ictus* Annex 10 for an ischaemic stroke caused by MCP detected in a high-definition colour Doppler ultrasound study of the supra-aortic trunks, according to criteria defined in the *Introduction* section. Patients must have previously read and understood an information sheet (Annex 11) about the study as well as having signed the informed consent form (Annex 12).

7.3.1. Inclusion criteria

Patients who meet all of the following requirements may enter the present study:

1) **Acute neurological deficits** compatible with cerebrovascular event which meet the following criteria:
   - Clinical duration of less than 1 hour, with no signs of acute cerebral ischaemia on CT. This is defined as **TIA**. It is evaluated by a vascular neurologist.
   - Clinical duration greater than 1 hour and/or evidence of acute cerebral ischaemia on CT. This is defined as **Acute Ischaemic Stroke.**

2) Patients with an ischaemic stroke of **possible large-artery atherosclerosis** aetiology, according to SSS-TOAST criteria.

3) Consecutive patients with **extracranial MCP** (according to the criteria defined in the *Introduction* section) shown on high-definition colour echo-Doppler study of the supra-aortic trunks.

4) Patients with a pre-admission **mRS ≤ 3.**

5) Adult male or female **patients ≥ 18 year.**

6) **Follow-up** of the patient contemplated by this study (**1 year**) after the index stroke.

7) Accepted and signed **informed consent form** (Annex 11 and 12**).**

7.3.2. Exclusion criteria

Patients will be definitively excluded from the study if they meet any of the following criteria:

1) Patients with an ischaemic stroke of **possible or probable small-artery disease, cardioembolic stroke, stroke of other determined aetiology and/or stroke of undetermined aetiology, according to the SSS-TOAST classification.**
2) Patients with internal carotid stenosis ≥ 50% (**probable large-artery atherosclerosis** according to SSS-TOAST criteria).
3) Patients with **atherosclerosis of the intracranial carotid** artery, **anterior** cerebral artery, **middle** cerebral artery (MCA) or involvement of the **posterior cerebral territory.**
4) **Total occlusion** of a cerebral **vessel ipsilateral** to the lesion.
5) Patients with a pre-admission **mRS >3.**
6) Patients with **severe neurological** deficit after index stroke **(mRS ≥4)**
7) Patients with **haemorrhagic stroke** or **subarachnoid haemorrhage** shown by neuroimaging.
8) **Stroke mimic**.
9) **Pregnancy or breastfeeding.**
10) Patients who, for whatever reason, **do not understand the study** and, therefore, do not have the autonomy to make the decision to participate or not.
11) **Life expectancy** (except for stroke) **< 3 months.**
12) Patients who **do not give informed consent.**

7.2.3. Withdrawal of the study

Patients who agree to participate in the clinical trial must commit to the follow-up established in the protocol and the investigators must encourage them to do so. However, patients may withdraw from the study if a number of situations are met.

Each participant loss must be declared and recorded in a *"Loss Record"*, adding the patient's data and the reason for withdrawal from the study. The data obtained up to the time of the participant's withdrawal will be used for the study.

Participants may withdraw from the study if any of the following situations occur:

- Voluntary decision to leave the clinical trial by means of the *"Application for Withdrawal of Consent to Study"* (Annex 13). The decision to be excluded from the study should preferably be recorded in writing.
- Patients that at any time of the clinical trial meet an exclusion criteria because it was developed after their inclusion.
- Loss of patient follow-up, if the patient does not show up for one of the activities included in the protocol.

7.3. Sampling

7.3.1. Sample size

The risk of early recurrence has been shown to be 0.03% in patients who undergo CEA/stenting (48). However, the risk of recurrence in the BMT group is very imprecise since, according to different authors, it varies from 17.1% to 33.3% (33,36). We consider these figures to be very high and variable. Therefore, assuming a worse scenario, we establish that the risk of recurrence in the group assigned to BMT is 8%.

In a two-sided test with a significance level (α risk) of 5%, a statistical power (1-β) of 80%, foreseeing a moderate risk and a 5% of losses, we will need **206 patients.**
This 5% loss has been established since, in previous clinical trials carried out by this research group and its collaborators, the losses of participants with similar characteristics to those of the patients included in the present study, were less than 3%.

Therefore, to find statistically significant differences between the two groups, we will need: **103 subjects** in the group of patients **treated with CEA/stenting** and **103 subjects** in the group of patients **treated with BMT.**

The computations were carried out with the Prof. Marc Sáez' software, based on the "pwr" package of the free statistical environment R (version 4.2.2.).

7.3.2. Sample collection

As previously mentioned, the sampling method selected for the study will be a **non-probabilistic consecutive sampling**. The choice to enter the study will be offered to patients admitted to the SU of the centres belonging to the *SONES*, *RICORS-Ictus* and

Proyecto Ictus (Annex 10) who meet all the inclusion criteria and none of the exclusion criteria. The number of patients recruited in each hospital will be proportional to the number of eligible patients. Eligible patients shall be provided with an understandable explanation of the study (Annex 11) and shall be given and sign the informed consent form (Annex 12). The sampling collection will be conducted until the sample size is fully achieved.

Regarding sample collection, each hospital will be responsible for the recruitment and follow-up of its own patients. All data from each individual will be reviewed by the principal researcher to determine the patients who will finally be included in the final sample, depending on whether they meet the inclusion criteria and have no exclusion criteria. It is the data from these patients that will be analysed.

7.3.3. Sample recruitment time

According to data obtained from the HUDJT Neurology Service (courtesy of Dr. Joaquín Serena), it attends an approximate average of 600 ischemic strokes/year. The rest of the potentially participating hospitals are reference hospitals for a number of inhabitants, on average, similar to the HUDJT. In fact, there are certain hospitals with a higher volume of patients. Thus, they attend a greater number of ischemic strokes per year.

The data regarding the prevalence of MCP are very variable, since there are authors, such as Fridman *et al.* (33), who report a prevalence of MCP associated with stroke of 1.53%, while others, such as Ogata *et al.* (36), up to 12.8%. However, the first data refers to a single subtype of MCP, the carotid free-floating thrombus (the disparity in the nomenclature of these plaques has already been previously commented). For this reason, and placing ourselves in a worse scenario than the one reported by Ogata *et al.* (36), we consider a conservative prevalence of MCP in patients with ischemic stroke of 3%.

Hence, it is estimated that it will be necessary to recruit patients for **1 year** to achieve the sample size indicated in the Sample size section.

This time is an estimation based on data from the HUDJT but, surely, since several hospitals have much more admissions per year than the reference centre for this study (HUDJT), the sample size will probably be reached prematurely.

7.4. Variables

7.4.1. Independent variable

The independent variable for this study is "*Type of treatment"*. It will be expressed by *CEA/stenting* or *BMT*. It is a qualitative dichotomous variable.

7.4.2. Dependent variable

The dependent variables of the study are set out below:

- **Dependent variable of the main objective:** "*Early recurrence (<72 hours post-SU admission for stroke)".* Recurrence is considered to be the experience of a new stroke, TIA or death of the patient. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

  This variable will be determined by death of the patient due to stroke or a new onset of clinical criteria of sudden neurological focality, assessed by expert vascular neurologists. This may or may not be accompanied by neuroimaging tests (such as CT or MRI), where the occurrence of a new cerebral ischaemic lesion will be assessed.

- **Dependent variables of the secondary objectives:**
  - Dependent variable of the presence of cerebral microembolism study: *"Presence or absence of cerebral microembolic signals (MEs) on the 5th day (± 24 hours) post-randomization"*. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

    The analysis of this variable will be carried out by transcranial Doppler ultrasound performed on the 5th day (± 24 hours) post-randomization, using a specific software for the detection and identification of cerebral MEs, with continuous bilateral monitoring of both MCAs (Multi-Dop X of DWL®, Sipplingen), for at least 1 hour.

  - Dependent variable of the recurrence at month 1: "*Recurrence during the first month post-admission"*. As in the main dependent variable, recurrence includes the occurrence of a new stroke, TIA or death of the patient. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

    This variable will be determined by death of the patient due to stroke or a new onset of clinical criteria of sudden neurological focality, assessed by expert

vascular neurologists. This may or may not be accompanied by neuroimaging tests (such as CT or MRI), where the occurrence of a new cerebral ischaemic lesion will be assessed.

- Dependent variable of the recurrence at month 3: "*Recurrence during the third month post-admission"*. As before, recurrence includes the occurrence of a new stroke, TIA or death of the patient. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.
  This variable will be determined by death of the patient due to stroke or a new onset of clinical criteria of sudden neurological focality, assessed by expert vascular neurologists. This may or may not be accompanied by neuroimaging tests (such as CT or MRI), where the occurrence of a new cerebral ischaemic lesion will be assessed.

- Dependent variable of the long term recurrence study: *"Recurrence during the first year post-admission"*. Recurrence includes the occurrence of a new stroke, TIA or death of the patient. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.
  This variable will be determined by death of the patient due to stroke or a new onset of clinical criteria of sudden neurological focality, assessed by expert vascular neurologists. This may or may not be accompanied by neuroimaging tests (such as CT or MRI), where the occurrence of a new cerebral ischaemic lesion will be assessed.

- Dependent variable of the dependency study: *"Degree of dependency in activities of daily living three months after admission to the SU"*.
  This variable will be measured using the mRS scale (Annex 3). It is a qualitative dichotomous variable, since it will evaluate the performance of a *good outcome (mRS ≤2)* vs. a *bad outcome (mRS >2)*.

7.4.3. Covariates

- **Age**: at the moment of the first stroke episode. It is a discrete quantitative variable. It will be measured in *years*.

- **Sex**: categorised as *Male* or *Female*. It is a qualitative dichotomous variable.

- **rt-PA**: variable that analyses whether the patient received intravenous fibrinolysis (rt-PA) as recanalization treatment. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

- **Mechanical thrombectomy**: variable that analyses whether the patient underwent a mechanical thrombectomy as a recanalization treatment. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

- **Previous myocardial infarction**: determined by the presence or absence of a previous diagnosis of acute myocardial infarction in the patient's computerised medical history. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

- **HBP**: it is defined as a systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg, or history of medical treatment of hypertension (49). It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

- **Diabetes mellitus,** it is defined as (50):
  - A haemoglobin A1c (HbA1c) ≥6,5%, or
  - A fasting serum glucose (no caloric intake for at least 8 hours) of ≥126 mg/dL, or
  - A serum glucose ≥200 mg/dL after 2 hours of a glucose oral tolerance test, or
  - A serum glucose ≥200 mg/dL in any moment of the day in patients with classical symptoms of hyperglycemia or hyperglycemic crisis.

  It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

- **Dyslipidemia**: it is defined as a total cholesterol ≥250 mg/dL, a low-density lipoprotein (LDL) ≥130 mg/dL, a triglyceride level ≥200 mg/dL, or the use of a

lipid-lowering agent (51). It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

- **Smoking**: it will be expressed by *smoker* (if the patient is a current or former smoker) or *non-smoker* (if the patient has never smoked). It is a qualitative dichotomous variable.

- **Intermittent claudication**: it is a mode of presentation of peripheral arterial disease. It is defined as the onset of muscle pain triggered by physical activity of low-to-moderate intensity, which requires rest for relief. It is a qualitative dichotomous variable. It will be expressed by *yes* or *not*.

- **Previous mRS**: degree of dependency of the patient prior to the stroke index. It will be expressed by the *score on the mRS scale* (Annex 3). It is a qualitative dichotomous variable, since it will evaluate the performance of a *good outcome (mRS ≤2)* vs. a *bad outcome (mRS >2)*.

- **BMI**: following the BMI cut-off points (52), this variable will be categorised as *under-normoweight* (<25 kg/m^2), *overweight* (25-30 kg/m^2) and *obese* (≥30 kg/m^2). It is a qualitative polytomous ordinal variable.

- **MCP subtype**: determined by the morphological characteristics found in the high definition Doppler ultrasound of the supra-aortic trunks. It will be expressed as: *Jellyfish-type plaque*; *Streaming-band-type plaque*; *Mobile-thrombus-type plaque/Carotid free-floating thrombus*; *Fluctuating-ulcer-type plaque* or *Snake fang-type plaque*. It is a qualitative polytomous nominal variable.

Table 4. Summary of study variables, measurement method and categories.

	VARIABLES	DESCRIPTION	MEASUREMENT	CATEGORIES
Independent	**Type of treatment**	Qualitative dichotomous	Computerised medical history or anamnesis	- CEA/stent - BMT
Dependent – Principal	**Early recurrence (<72 hours post-stroke)**	Qualitative dichotomous	New onset of clinical criteria of sudden neurological focality ± neuroimaging tests	- Yes - No
Dependent – Secondary	**Presence of MEs 5 days (±24 h) post-randomization**		Transcranial Doppler ultrasound	
	Recurrence 1 month post-stroke		New onset of clinical criteria of sudden neurological focality ± neuroimaging tests	
	Recurrence 3 months post-stroke			
	Long-term recurrence (1 year post-stroke)			
	Degree of dependency (3 months post-stroke)		mRS score	- mRS ≤2 - mRS >2
Covariates	**Age**	Discrete quantitative	Computerised medical history or anamnesis	≥18
	Sex	Qualitative dichotomous		- Male - Female
	rt-PA			- Yes - No
	Mechanical thrombectomy			
	Previous myocardial infarction			
	HBP		Clinical criteria	
	Diabetes mellitus		Analytical ± clinical criteria	
	Dyslipidemia		Analytical criteria	
	Smoking		Computerised medical history or anamnesis	- Smoker - Non-smoker
	Intermittent claudication		Clinical criteria	- Yes - No
	Previous mRS		mRS score	- mRS ≤2 - mRS >2
	BMI	Qualitative polytomous ordinal	Clinical criteria	- Under-normoweight (<25 kg/m^2) - Overweight (25-30 kg/m^2) - Obese (≥30 kg/m^2)
	MCP subtype	Qualitative polytomous nominal	Doppler ultrasound of supra-aortic trunks	- Jellyfish-type plaque - Streaming-band-type plaque - Mobile-thrombus-type plaque/Carotid free-floating thrombus - Fluctuating-ulcer-type plaque - Snake fang-type plaque

Best Medical Treatment (BMT); Body mass index (BMI); Carotid endarterectomy (CEA); High blood pressure (HBP); Microembolic signals (MEs); Mobile Carotid Plaques (MCP); Modified-Rankin scale (mRS); recombinant tissue Plasminogen Activator (rt-PA).

7.5. Study intervention

7.5.1. Enrollment

In the *Subjects selection* section, the population of this study has already been stated. The enrollment process will begin with consecutive patients who attend the neurological emergency services of the centres participating in the study with symptoms suggestive of stroke. The first thing to do is to make a clinical diagnosis as detailed in the *Introduction* section. An anamnesis will be carried out on the patient or the relative/witness, and also a neurological and general examination. In addition, a blood test will be performed to help rule out other causes of the symptoms as well as to determine if it would be possible to perform an intravenous fibrinolysis based on analytical values in case of ischaemic stroke (e.g. INR values). Upon arrival at the hospital, the patient will undergo a CT to rule out cerebral haemorrhage and confirm or not the presence of ischemic lesion in the brain parenchyma that explains that neurological focality. In the same way, a CTA will also be performed to determine if there is occlusion of any vessel that is candidate for mechanical thrombectomy.

Based on the results, the most appropriate revascularizing treatment for each patient will be decided: *rt-PA* or *mechanical thrombectomy* or *rt-PA + mechanical thrombectomy* or *nothing*.
The patient will be admitted to the SU of the centre in question, where he or she will be monitored by measuring ECG, heart rate, respiratory rate, oxygen saturation, urine volume, video surveillance from the nursing control and through periodic visits by the nursing and medical staff. It is, at this time, that all patients will start treatment with BMT, as specified in the Study design section.
This is so since, the first hours after the stroke, are those with the highest risk of early recurrence (53). In atherothrombotic stroke, the risk is higher in the first 72 hours, decreasing progressively afterwards. For this reason, the main objective of this clinical trial is focused on determining the risk of early recurrence, studied during the first 72 hours post-admission.

Although, according to the symptoms, RF and comorbidities of the patient, there is already an etiological suspicion (and for this reason the BMT was started from the first moment of admission to the SU), the etiological study will be carried out (as mentioned in the *Etiological Study* section), which will help to choose the patients for our sample. This is because one of the most important inclusion criteria is that the index stroke is of atherothrombotic aetiology.

Within the first 24 hours post-admission, all patients will undergo a Doppler ultrasound of the supra-aortic trunks in order to detect not only stenosis of the carotid lumen, but also the presence or absence of MCP. If MCP are not detected in that ultrasound, the patient will be excluded from the study. On the contrary, if any subtype of MCP is diagnosed, it will be at that moment that the present clinical trial will be explained to the patient and, also, the information sheet (Annex 11) and the informed consent form (Annex 12) will be given.

7.5.2. Randomization

Once the patient has understood the study, its stages, follow-up, possible complications derived from the treatment, agreed to enter in it and signed the informed consent form (Annex 11), it will be the moment in which the patient will be randomised in a ratio 1:1 into one of the following two groups using a randomization computer program:

- Group1: Consecutive patients with an ischaemic stroke caused by MCP **treated in the acute phase with CEA/stenting.**
- Group 2: Consecutive patients with an ischaemic stroke caused by MCP **treated in the acute phase with BMT.**

Therefore, randomization will occur within the first 24 hours post-admission.

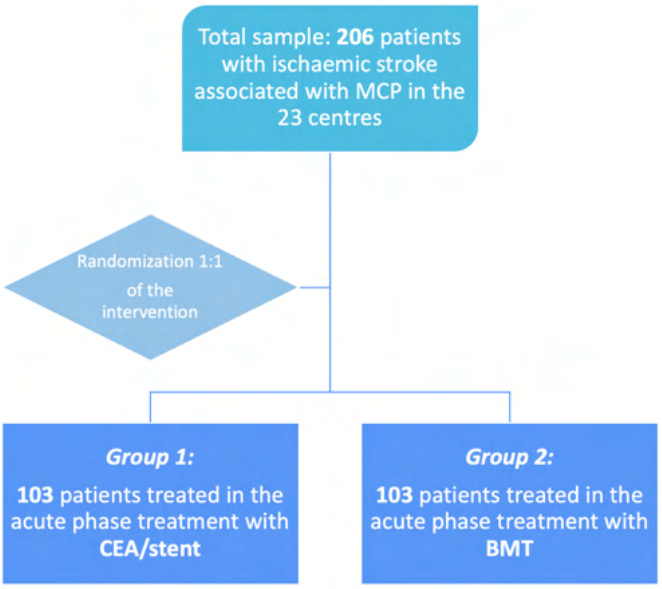

Figure 27. Randomization of the intervention

Best Medical Treatment (BMT); Carotid Endarterectomy (CEA); Mobile Carotid Plaques (MCP).

In addition, it should be made clear that patient data, including name, phone number, address, and medical history information, will be anonymized. Each patient will be given an identification (ID) code number.

7.5.3. Intervention

All patients participating in the study, and belonging to both arms of the clinical trial, will be studied for the presence of MEs. It will be carried out by continuous bilateral monitoring of the MCA with a transcranial Doppler ultrasound and a specific software for the detection of cerebral MEs, for at least 1 hour, during the first 24 hours post-stroke.

During their stay in the SU, data on the recurrence of the participating subjects will be collected during the first 72 hours post-stroke.

Patients who have been randomised to the BMT group will continue medical treatment just after the randomization process. Patients who have been randomised to the CEA/stent group will undergo the intervention over the next 3 days (and continue with the BMT).

7.5.3.1. Carotid endarterectomy (CEA)/Stent

Patients who are randomised to the CEA/stent acute phase treatment arm will undergo a surgical procedure within the first 3 days post-index stroke to prevent early recurrent strokes. They are, therefore, prophylactic interventions, since they reduce the emboli generated in the atheromatous plaque of the carotid bifurcation (54).
This period of time has been chosen to carry out the intervention since, the longer the time between the stroke and the CEA/stent, the higher the risk of recurrence and the greater the number needed to treat (NNT) to prevent a stroke (NNT=5 in <2 weeks vs. NNT = 125 in ≥2 weeks) (55).

There are 2 options to restore normal carotid flow: CEA or carotid stenting. In most of the patients in our study, the chosen method will be stent placement, although surgical treatment (CEA) is also allowed if there are centres that prefer one or the other, or cannot perform stent placement. This is so since both procedures are comparable (55) and, as will be discussed later, they have similar risk of complications. In addition, the stent is a less invasive method, faster and without the need of general anaesthesia. However, the choice of treatment for each patient must be individualised at criteria of each centre and investigator.

The patient should be told that, before undergoing a CEA/stent, they should receive standard medical treatment and management antiplatelet therapy (BMT), have an ECG, blood tests, urine tests, and chest X-ray. The patient should not smoke before surgery, as well as fasting

for a minimum of 8 hours (55). After the intervention, the patient usually remains in the hospital for 1 to 3 days.

CEA consists of the surgical removal of the atheromatous plaque, intima layer, and part of the media layer of the stenosed carotid area. In addition, prosthetic graft is usually implanted to further increase the carotid lumen (54).

After the results of "The North American Symptomatic Carotid Endarterectomy Trial" (NASCET) (56), it was determined that it is only beneficial to perform a CEA in two scenarios:

- If the stenosis is ≥70% but asymptomatic, treatment consists of CEA in selected cases. The "Asymptomatic Carotid Atherosclerosis Study" (ACAS, (57)) demonstrated that, in this type of patients undergoing CEA, there is a significant 5-year reduction in the risk of stroke.
- If the stenosis is ≥50% but symptomatic, treatment with CEA or stenting will be done. It is considered symptomatic if the patient has had an ipsilateral stroke, a TIA manifested as unilateral or bilateral amaurosis fugax, hemiparesis and/or episode of language disorder. As already mentioned, most of the patients in our study would meet this requirement.

CEA can be performed using two main surgical techniques (55):

- *Classic/conventional method:*

  An incision is made along the medial aspect of the sternocleidomastoid muscle until reaching the carotid arteries. The flow of the ICA is temporarily stopped in order to open it lengthwise. Prior to plaque removal, a shunt is placed to divert blood around the endarterectomy site, which will be removed once the plaque has been removed and the carotid sutured.

- *Eversion method:*

  In this method, the internal carotid artery is cut obliquely at the base of the bifurcation of the Common Carotid Artery (CCA). The plaque is divided, and removed, and the artery is then sutured.

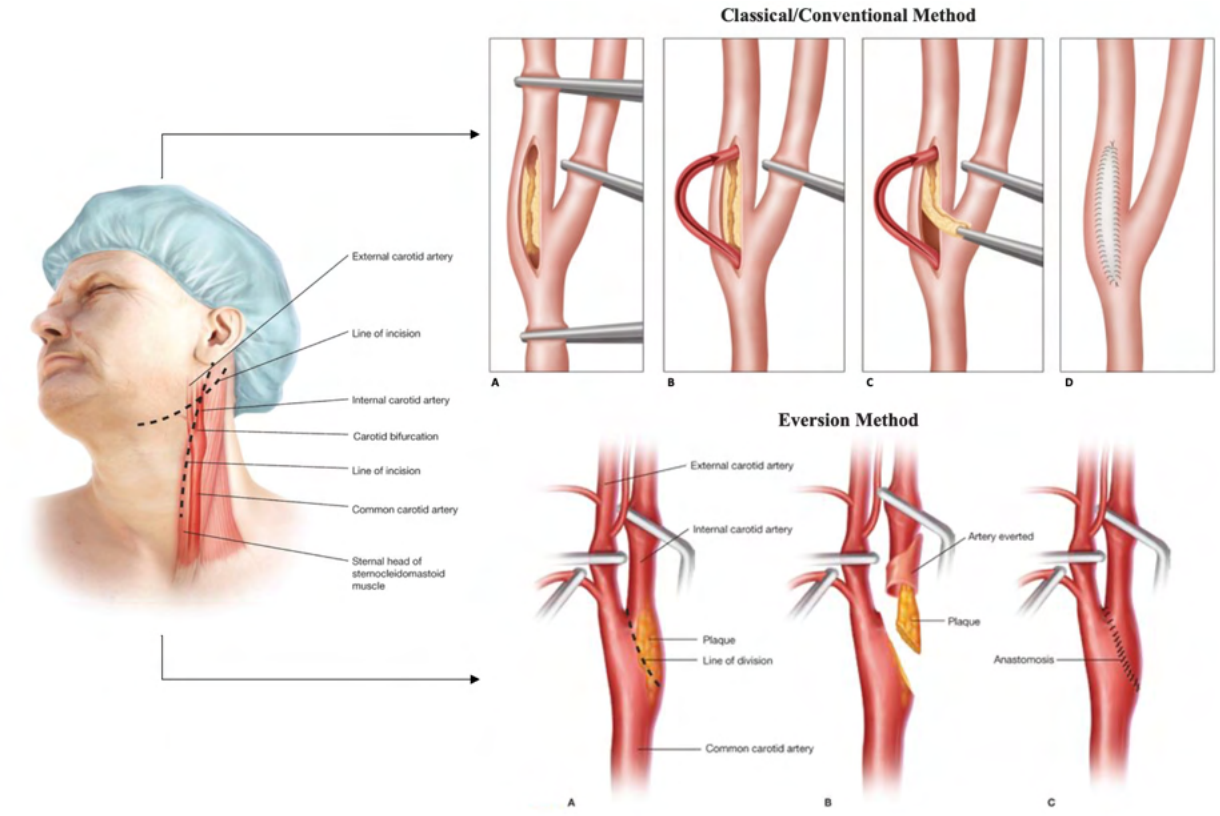

Figure 28. Scheme of the Classic/conventional method (up) and Eversion method (down) of a carotid endarterectomy (CEA) *(adapted from (58,59))*

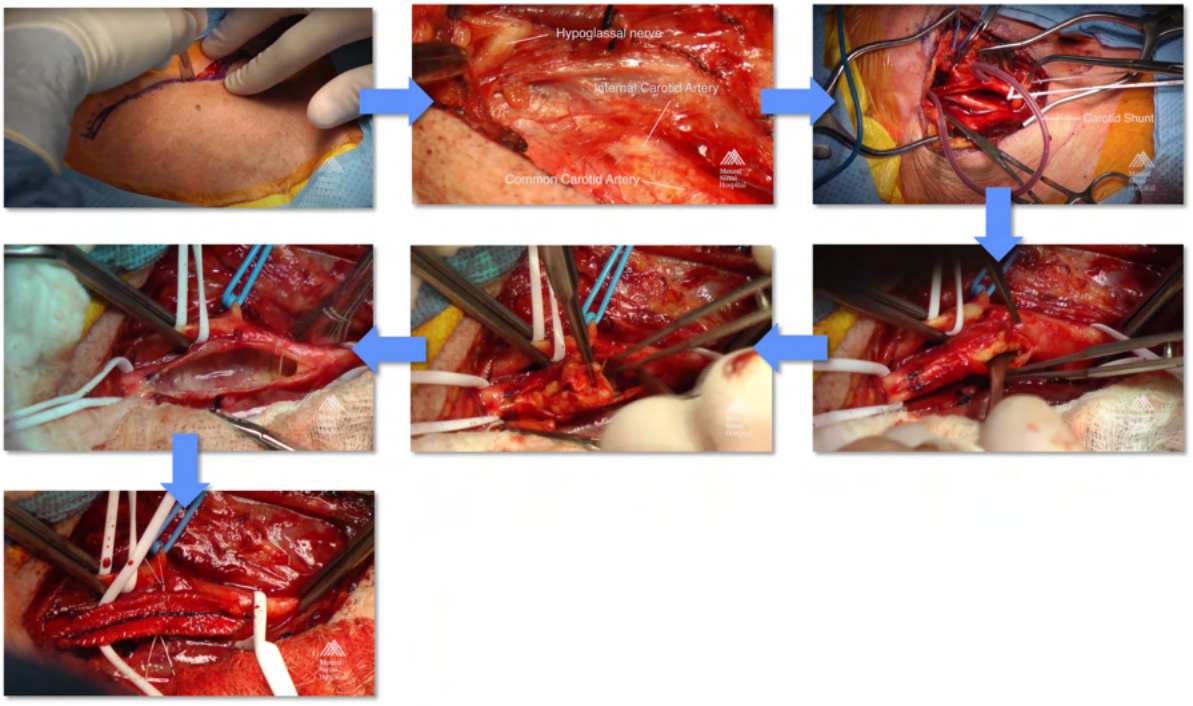

Figure 29. Actual surgical procedure of a Carotid endarterectomy (CEA), extracted from The Mount Sinai Surgical Film *(60)*

However, instead of undergoing CEA, the patient could also undergo a minimally invasive procedure such as **Carotid Artery Angioplasty with Stenting**. To do this, the carotid artery must be accessed through a catheter that can be introduced through a femoral, brachial/radial or carotid access (55). Intraoperative angiography is performed to visualise the catheter track. This catheter reaches the carotid plaque where a balloon is inflated (angioplasty) to open the lumen of the vessel and then, a stent (tubular metal mesh), is placed to decrease the possibility of the artery narrowing again.

It is more commonly used in patients with multiple comorbidities, at high risk of complications from general anaesthesia (as in this intervention is not required), patients with radiation/anterior neck dissection, or tracheostomy.

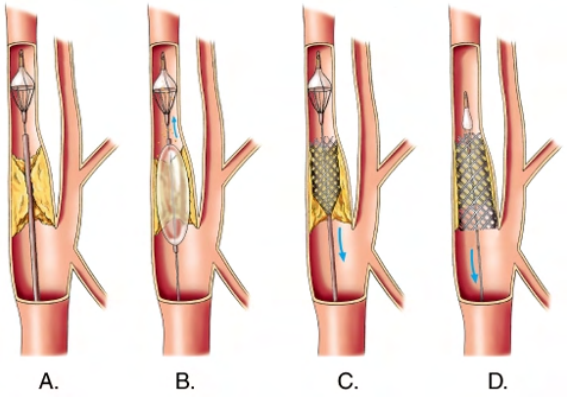

Figure 30. Scheme of a carotid angioplasty with stenting *(61)*

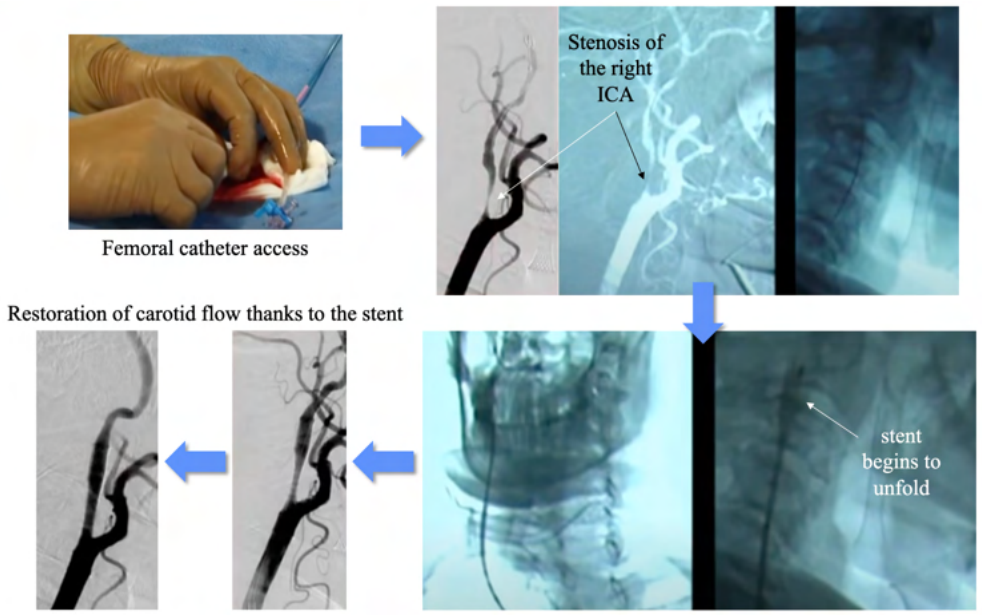

Figure 31. Actual surgical procedure of a Carotid endarterectomy (CEA), extracted from Agrim Stroke & Neurointervention *(62).*

Internal Carotid Artery (ICA).

7.5.3.2. Best Medical Treatment (BMT)

Currently, the optimal treatment or **BMT** for atherothrombotic stroke recommended by most clinical practice guidelines (21,63) consists of:

- Antiplatelet treatment:
  - Acetylsalicylic acid (ASA) 100 mg/day.
  - In minor stroke (NIHSS ≤3) or TIA: treatment with dual antiplatelet therapy, ASA 100 mg/day + Clopidogrel 300 mg loading dose, followed by 75 mg/day, for 21 days (to reduce the risk of recurrence in the first 90 days after stroke, since it is the period with the highest risk of recurrence). After the 21 days, the normal regimen of ASA 100 mg/day is followed.
- High potency statins: Atorvastatin 80 mg/day, with target LDL of <55 mg/dL or decrease ≥50% if the baseline LDL was between 70-135 mg/dL.
- Strict control of classic cardiovascular RF:
  - Antihypertensive treatment if SBP ≥140 mmHg and/or DBP ≥90 mmHg (e.g. Enalapril, with target SBP <130 mmHg and DBP <90 mmHg).
  - Hypoglycemic treatment if the patient is diabetic. The HbA1c target is <7% (<6.5% being optimal).
  - Lose weight if overweight or obese, with a goal of BMI <25 kg/m^2.
  - Mediterranean diet (high in potassium, low in salt [<1.5 g/day] and saturated fat).
  - Increase physical activity (moderate-intensity aerobic exercise for 40 minutes, 4 days a week, or 150 minutes/week).
  - Stop smoking and moderate alcohol consumption.

As mentioned previously, all patients will receive this pharmacological treatment and cardiovascular risk factors recommendations (BMT), following standard clinical practice, immediately after admission and regardless of the randomization arm in which they are subsequently allocated.

On the fifth day after randomization, the study of the presence of MEs will be repeated, thus evaluating the impact of the treatment received in the acute phase (CEA/stent vs. BMT) on them. It is performed by continuous bilateral monitoring of the MCA with transcranial Doppler ultrasound and specific software for the detection of cerebral MEs, for at least 1 hour.

7.5.4. Follow-up

As mentioned in the Objectives section, one purpose of this study is to determine the recurrence of stroke according to the treatment administered in the acute phase (CEA/stent vs BMT) at one month, three months and one year post-MCP associated stroke.
Subsequently, the participants must attend 3 scheduled visits at 1, 3 and 12 months post-index stroke. What will be evaluated in each visit is specified in later sections.

The visit **one month** after the stroke has been established, since if there has been a recurrence in this period of time, it is expected that this is a reflection of the treatment carried out in the acute phase. In clinical trials with objectives similar to ours, the first month is considered the period with the highest risk of recurrence (while the plaque stabilises after treatment), as well as the period where most of the post-surgery complications occur or adverse effects of medical treatment appear.

Another visit has been scheduled at **3 months**, since it is the moment in which a faster recovery from the sequelae caused by the stroke is achieved. Thereafter, recovery is much slower. For this reason, both in clinical trials that study the degree of post-stroke disability using the mRS, and in daily clinical practice, a visit is scheduled at 3 months to study this objective. Therefore, depending on the degree of disability of the patient, we will be able to know if the intervention (CEA/stent vs. BMT) has clinical relevance or not.
Taking advantage of this visit, it will also be determined whether or not there have been recurrences of the stroke in this period of time.
In the case of patients undergoing CEA/stent, the risk of restenosis will also be assessed at this visit, since it is maximum up to 3 months post-intervention, but decreases after one year.

The visit **one year** after MCP-related stroke is scheduled to determine long-term recurrence. To this day, the long-term risk of MCP is unknown, and also how these plaques evolve, whether or not the plaque persists, whether it has been re-stenosed... It will help us to determine the progression or not of the carotid disease caused by MCP.
In addition, in the case of patients undergoing CEA/stent, the risk of restenosis will also be assessed. After this time, re-stenosis is rare.

7.5.5. Safety

The interventions proposed in this clinical trial are invasive, especially the CEA/stent procedure. However, serious complications derived from this surgery (disabling stroke and death) happen only in 0.03% of the patients (48), while the recurrence of stroke associated with MCP is up to 33.3% according to Ogata *et al.* (36).

Regarding postoperative complications, the "The Carotid Revascularization Endarterectomy versus Stenting Trial" (CREST, (64)) found no significant differences between **CEA** and **stenting**. This study also states that they have "similar short- and longer-term outcomes" (64) These complications are:

- Clots at the site of the intervention.
- Cerebral haemorrhage.
- Disabling stroke.
- TIA.
- Seizures.
- Myocardial infarction.
- Problems derived from general anaesthesia: allergic reactions, respiratory problems due to edema of the respiratory tract... etc.
- Allergy to contrast used in angiography during stent placement.
- Pain or discomfort in the neck and/or the catheter insertion site.
- Cervical bruise.
- Dysphagia.
- Infection at the incision or catheter insertion site.
- Hyperperfusion syndrome.
- Nerve damage, particularly to the hypoglossal, vagus, glossopharyngeal, trigeminal, and facial nerves.
- Re-stenosis.
- Death.

However, these procedures will be performed by expert surgeons and interventionists, so a low complication rate is expected. In addition, we will request participation in the study of the Vascular Surgery Service, for a greater commitment to patients.

To avoid iatrogenesis derived from CEA or stent placement in extremely high-risk patients, one criterion for exclusion from the study is having a severe neurological deficit after the index stroke (mRS ≥4).

Regarding the **BMT group**, the adverse effects derived from treatment with *ASA, ASA + Clopidogrel* and *Atorvastatin*, the 3 pillars of BMT, are listed below:

The adverse effects of ASA are (65):

- Allergy or hypersensitivity.
- Risk of bleeding during a minor surgery (e.g. tooth extraction).
- Risk of gastrointestinal bleeding (maelena, hematemesis, etc.) or ulcers/perforations, especially in:
    - Elderly.
    - Patients with a history of gastric ulcer (especially if they were complicated).
    - If alcohol is consumed concomitantly.
    - If taken together with other drugs that also increase the risk of bleeding, ulceration and gastrointestinal perforation (even in patients with no history of gastric pathology), such as: non-steroidal anti-inflammatory drugs, other antiplatelet agents, corticosteroids, antidepressants of the selective inhibitor type the reuptake of serotonin, anticoagulants… etc.
    - If it appears, treatment should be discontinued.
- Increased risk of persistent kidney damage, especially if combined with analgesics.
- Use with caution in patients with: hypersensitivity to other anti-inflammatories, asthma, urticaria, rhinitis, HBP, patients with a history of gastritis, gastroduodenal ulcer or gastrointestinal bleeding, women with metrorrhagia or menorrhagia, renal insufficiency, mild or moderate hepatic insufficiency or heart failure.

The adverse effects of ASA + Clopidogrel are (66):

- Risk of haemorrhage, the most frequent adverse effect: gastrointestinal haemorrhage, skin haematomas, epistaxis, haematuria, subconjunctival haemorrhage, intracranial haemorrhage, pulmonary or joint haemorrhage.
- In 1/10 people, diarrhoea, abdominal pain, dyspepsia or heartburn have been observed.

- Other less frequent side effects (1 in 100 people) are: headache, stomach ulcer, nausea and vomiting, nausea, constipation, itching, meteorism, dizziness and tingling sensation.
- Rare and very rare side effects are: vertigo, jaundice, fever, dyspnea, allergic/hypersensitivity reactions, stomatitis, hypotension, changes in the taste of food, tinnitus, etc.

Adverse effects of Atorvastatin are (67):

- Some frequent adverse effects are: inflammation of the upper respiratory tract, hyperglycemia, headache, nausea and vomiting, diarrhoea, alteration of transaminases (hepatitis)..., etc.
- Less frequent adverse effects are: changes in weight, dizziness, sensitivity changes, fatigue, severe allergic reaction, erythematous and bullous skin reaction, rhabdomyolysis (muscle pain, malaise, fever, nausea and vomiting, choluria, etc.), vision disturbances, cholestasis and tendon injuries.
- Other very rare side effects (affects 1/10,000 patients) are: haemorrhage, lupus-like syndrome, hearing loss or gynaecomastia.

If any of the serious adverse effects just mentioned appear, or the patient does not tolerate the treatment for other reasons, the medication will be changed to an equivalent drug.
Patients are cautioned that if they notice any of the above mentioned side effects, they should immediately contact their physician and investigators. For this, they will be provided with a contact telephone number.

Regarding the **privacy** of the patient, it will also be insured since, as mentioned, all the data of the participants will be anonymized. Each patient will receive a numerical ID code so that their privacy is guaranteed, as well as to avoid bias.

A summary scheme of the dynamics of "The PLACA VIL Trial" is shown below.

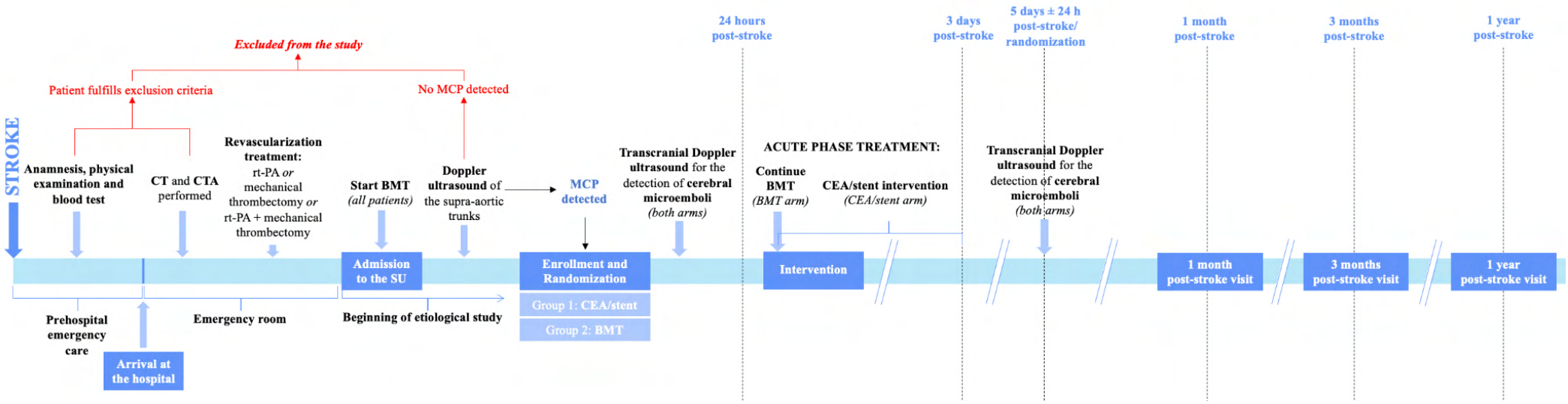

Figure 32. Dynamics of "The PLACA VIL Trial".

The process is shown from the moment a patient suffers an atherothrombotic stroke until he or she is enrolled into the trial, according to whether the subject meets all the inclusion criteria and none of the exclusion criteria. The two interventions (BMT vs. CEA/stent) are also shown. The intervention of the BMT will begin immediately after the randomization process, while the CEA/stent intervention will be performed within the first 3 days post-randomization. In addition, follow-up visits are shown.

Best Medical Treatment (BMT); Carotid Endarterectomy (CEA); Computed Tomography Angiography (CTA); Computerised Tomography (CT); Mobile Carotid Plaques (MCP); recombinant tissue Plasminogen Activator (rt-PA); Stroke Unit (SU).

7.6. Data collection

The information necessary for this work will be obtained from the computerised clinical history, scheduled clinical visits and complementary tests. The data obtained will be collected in a case report form (CRF, Annex 14) to later be stored in a database.

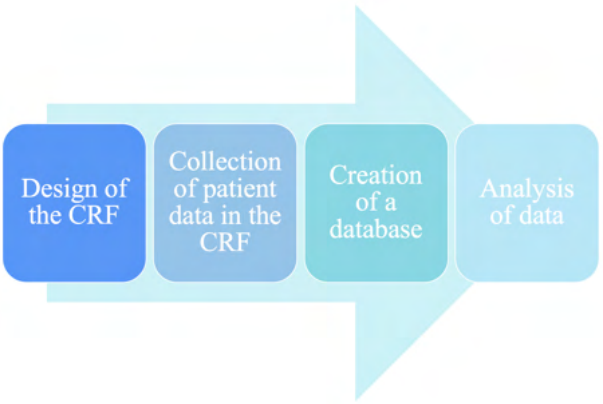

Figure 33. Summary of the data collection process.

Case report form (CRF)

The researchers who detect and follow up the patients will be in charge of filling out the CRFs with the anonymized patient data (with the ID). The ID corresponding to each patient will be available on a separate database.

During the first face-to-face meeting, a manual will be given to know how to correctly fill in the CRF, as well as to solve possible doubts when interpreting any variable. The head co-investigators will receive prior training on the data collection process, so that they can then relay this knowledge to the researchers at their centre.

Before starting the definitive collection, a pilot test will be carried out with a small number of patients to see the reliability of the CRF, the difficulty of collecting the data, of transferring them to the computerised database… etc. Difficulties encountered during this pilot test will be corrected.

In the following online meetings, the correct collection of data in the CFR will be supervised.

Throughout the clinical trial, the principal investigator will supervise and monitor the quality of the collected data. This process will be done frequently and periodically to detect errors and solve them as soon as possible. The final data will have to be purified before analysis.

- The following data will be obtained from the **clinical history**:
  - Patient's personal data, age and sex.
  - Presence of comorbidities: HBP, diabetes mellitus, dyslipidemia, smoking, intermittent claudication, previous mRS, NIHSS at admission, previous history of stroke and previous acute myocardial infarction.

  - Baseline medical treatment: antihypertensive, hypoglycaemic, lipid-lowering, antiplatelet or anticoagulant.
  - Previous carotid status (if available): presence or absence of plaque, area of stenosis, presence or absence of MCP, type of blood flow and flow velocity.

- Between the **time of admission and the following 72 hours**, the following information shall be obtained by specially trained neurologists of the participating centres (belonging to *SONES, RICORS-Ictus* and *Proyecto Ictus,* Annex 10):
  - Presence or not of cerebral ischaemia detected by neuroimaging at admission. This test will be repeated after 24 hours to monitor the evolution of the cerebral ischaemia and to determine possible hemorrhagic transformation.
  - Neurological examination, using NIHSS, caused by ischaemic stroke both acutely and throughout the patient's admission to the SU, especially in the first 72 hours (time recommended by guidelines to be admitted at a SU). In this way, early clinical recurrences (first 72 hours post-admission) can be detected and could be confirmed by neuroimaging.
  - mRS score derived from acute neurological focality both acutely and throughout the patient's admission to the SU, especially in the first 72 hours.
  - Constant monitoring throughout SU admission of heart rate, blood pressure, ECG, respiratory rate, oxygen saturation and urine volume.
  - Doppler ultrasonographic study of the supra-aortic trunks, as soon as possible within the first 24 hours after admission, to study the presence or absence of atherosclerotic plaque, area of carotid stenosis, presence or absence of MCP, type of blood flow, and flow velocity.
  - Transcranial ultrasound study, as soon as possible and within the first 24 hours after randomization, to study the presence or absence of cerebral MEs.

- On the **fifth post-randomization day**, the MEs study will be repeated using transcranial ultrasound. In this way, the effect of the intervention (CEA/stent vs. BMT) will be observed in the MEs with respect to the baseline values (measured in the first 24 hours post-admission).

- **Three visits are scheduled to follow up** each participant and will be carried out by the specially trained neurologists of the centres involved. They will be carried out

during months 1, 3 and 12. Short-term (during the 1 and 3-month visit) and long-term (12-month visit) stroke recurrence will be studied mainly.

In addition, the degree of disability caused by the stroke will be assessed using the mRS at the visit of the 3rd month. Furthermore, the following data will be obtained at each of these visits:

- Neurological symptoms due to the index stroke, using the NIHSS scale.
- Disability by mRS.
- Report whether in the inter-visit period a new stroke episode, TIA or death from a cerebrovascular event has occurred.
- Adverse events associated with CEA/stent.
- Ultrasonographic study of supra-aortic trunks to assess presence or absence of MCP and potential stenosis, in both arms.

7.7. Flow chart

Below is a flow chart of "The PLACA VIL Trial" with approximate figures of the patients flow, considering a 3% prevalence of MCP and a total of 8000 patients evaluated, which would correspond, approximately, to the participation of 13 of the 23 potential participating centres (assuming about 600 ischemic stroke patients per year in each centre).

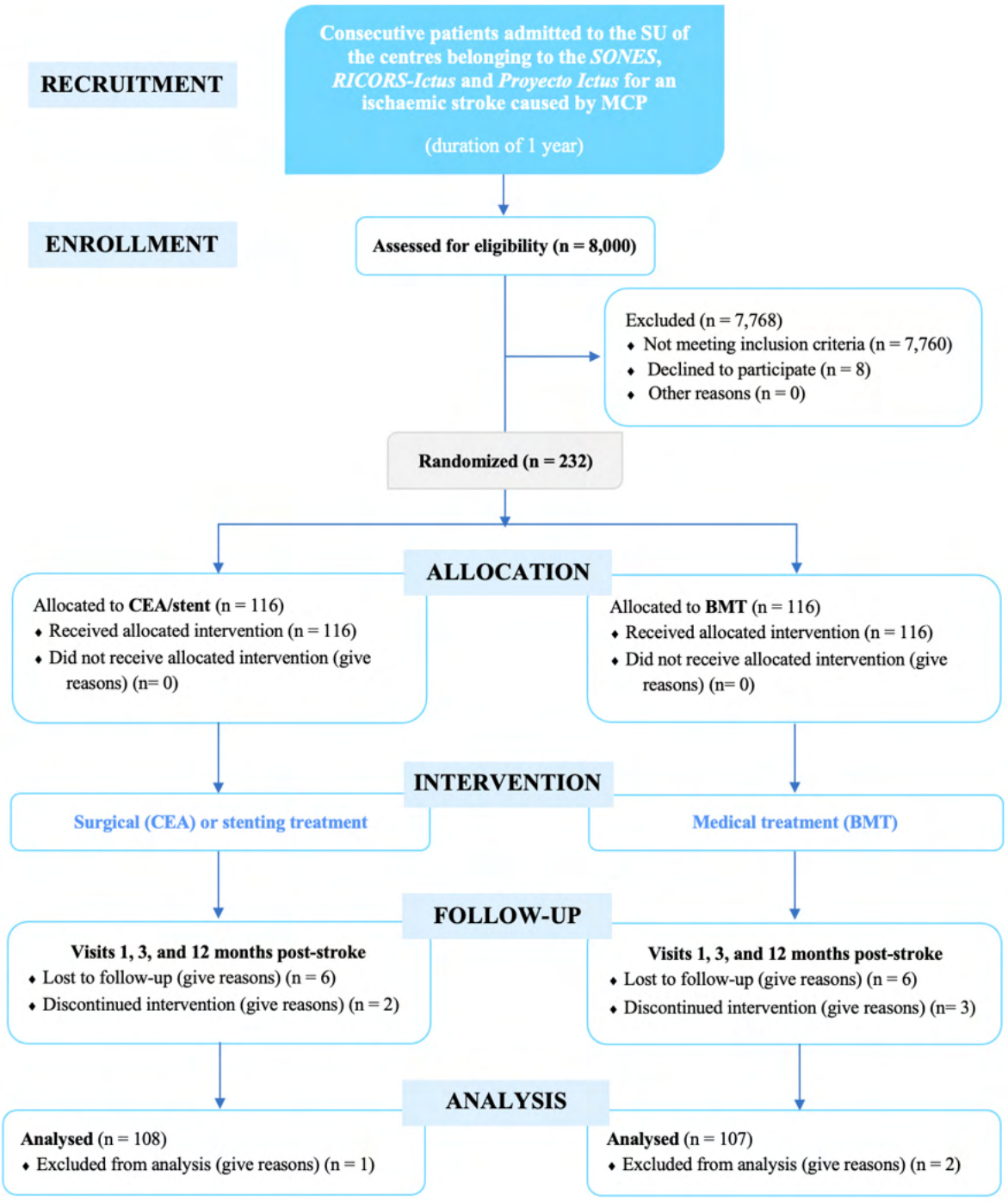

***Figure 34. Study flow diagram. Based on the CONSORT Flow Diagram** (68).*

Best medical treatment (BMT); Carotid endarterectomy (CEA); Mobile Carotid Plaque (MCP); Sociedad Española de Neurosonología (SONES); Stroke unit (SU).

8. STATISTICAL ANALYSIS

The statistical analysis will be performed using the Statistical Package for Social Sciences (SPSS) software version 28.1. It will be carried out by a statistician, who will not know the assignment to each of the groups of each patient.

We will set a p-value of $p<0.05$ as statistically significant, defining a 95% confidence interval for all analyses.

1) Descriptive statistics

The main dependent qualitative variable (*Early recurrence*) and the secondary dependent qualitative variables (*Recurrence at 1 month, Recurrence at 3 months*, *Long-term recurrence, Degree of dependency in activities of daily life* and the *Presence of cerebral MEs*) will be summarised using proportions.

We will stratify these descriptives by the intervention (CEA/stenting) and control (BMT) groups. Additional stratification will be done by the covariates. *Age* will be categorised in quartiles. *BMI* and *MCP subtype* will be summarised as proportions.

2) Bivariate analysis:

The difference in proportions of the dependent qualitative variables between those treated with CEA/stenting and those treated with BMT will be tested using the $\chi 2$ test. When the expected frequencies are less than 5%, Fisher's Exact Test will be used.

These analyses will be stratified according to covariates.

3) Multivariate analysis: independent covariates

Logistic regression will be used to assess the association between the independent and dependent variables, controlling for the covariates to avoid potential confounding factors.

9. ETHICAL AND LEGAL CONSIDERATIONS

The protocol for conducting this study will be submitted to the **CEIC** (Comité de Ética de Investigación Clínica) of the main centre, the HUDJT, and it will be optional for each one of the participating centres (hospitals belonging to *SONES, RICORS-Ictus* and *Proyecto Ictus,* Annex 10), to present it to their respectives CEICs. The objections made by the CEIC will be considered and introduced. This study can only start after receiving your approval.
Likewise, the authorisation of the Management Department of all participating medical centres is required to initiate this project. Furthermore, we will request the participation of the Vascular Surgery Department in order to guarantee its involvement in the surgical and interventional procedures of the clinical trial.

All patients included in this clinical trial must read, understand and sign an **informed consent form** (Annex 11 and 12) evaluated by the CEICs of the participating centres.

All persons belonging to the research team and management of each participating hospital must sign a **statement attesting to having read and approved the final protocol and agreeing to the national and international ethical aspects** of the clinical trial.

This study will follow the ethical requirements expressed in the **Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects** signed by the World Health Association in October 2013. It will also respect the **Principles of Biomedical Ethics from Beauchamp and Childress** from 1970 and reviewed in 2009 (Autonomy, Non-maleficence, Beneficence and Justice).

The clinical trial will be conducted under the following ethics laws and principles:

- **Clinical trial regulation:**
    - Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.
    - Ley 14/2007, de 3 de julio, de Investigación biomédica, por la que se regulan las investigaciones relacionadas con la salud humana que impliquen procedimientos invasivos.

- Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios.
- Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios.

- **Patient autonomy:**
  - Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.
  - Llei 16/2010, del 3 de juny, de modificació de la Llei 21/2009, del 29 de desembre, sobre els drets d'informació concernent la salut i l'autonomia del pacient, i la documentació clínica.

- **Privacy and confidentiality:** the following legal considerations will be met as all participating patients' data, including names, telephone numbers, addresses and medical history information will be anonymised, with each patient being given a code number. These codes and data will be stored in a database. Only researchers will have access to this information, solely for scientific purposes related to this study. No third parties will be allowed access to this information. The processing of personal data required in this study, the personal data cession of all the patients and their confidentiality and communication will:
  - Obey the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.
  - Repealing Directive 95/46/EC (General Data Protection Regulation)
  - Obey the Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales.
  - Obey Real Decreto 1720/2007, de 21 de diciembre por el que se aprueba el Reglamento de desarrollo de la Ley Orgánica 15/1999.

10. STRENGTHS AND LIMITATIONS OF THE STUDY

10.1. Strengths of the study

- The main objective of this study is to elucidate the best treatment for an entity with a suspected high morbidity and mortality rate, such as strokes caused by MCP, a particularly aggressive condition. It is, therefore, a **study of special scientific, health and social importance,** as it would allow a better management and prognosis of this type of patient.
- It is a completely **innovative study** as there is little literature on the subject. This is the first clinical trial for studying the treatment of MCP. No project with this objective or similar characteristics has been carried out worldwide.
- The design of the project is the one with **the best scientific evidence**, as a randomised clinical trial is planned.
- Although it is an open-label trial, the **data obtained** (both in the first 72 hours and at the follow-up visits at months 1, 3 and 12 post-stroke) are **objective**. It is difficult for the patient to over- or underestimate his or her NIHSS score, as it will be assessed by expert neurologists. The same applies to the degree of dependency (mRS scale), the occurrence of new stroke recurrences, treatment-related events or the outcome of imaging tests. Therefore, it is difficult for an attentional bias or Hawthorne effect to occur. In any case, mRS scale is planned to be conducted by a neurologist not involved in patient attention in the acute phase and randomization process.
- The fact that the clinical trial is **multicentre** allows it to embrace different regions and hospitals in Spain. Thus, patients with very diverse characteristics can be included, which **enriches the sample and strengthens the statistical results.**
- As the number of centres involved is high, the **time to complete the sample size will be short**. It is expected to take one year, so it could be carried out within the funding period established by the Convocatoria de Acción Estratégica de Salud 2024 of the Instituto de Salud Carlos III (Gobierno de España), if awarded.

10.1. Limitations of the study

- The consecutive sampling method is used to obtain the sample for this study. By using this sampling method, and **not random sampling**, the whole population is not represented. Therefore, sampling or selection bias can exist. However, the sample is

of a considerable size (206 patients), so even using this sampling method, we can still come close to representativeness.

- Since a surgical/interventional treatment is compared to a medical treatment, it is impossible for patients or researchers not to know which group they belong to. Therefore, the fact that **there is no masking (open-label trial)** may encourage the appearance of biases, such as observer bias. For this reason, as mentioned, the outcome assessment will be performed by a vascular neurologist not involved in the management of the patient in the acute phase and unaware of the patient's allocation to one arm or the other. He or she will be in charge of carrying out the follow-up visit at 1 month, 3 months (to assess the degree of disability) and the visit one year after the stroke, since the professional does not need to know if the patient has undergone surgical or medical treatment during the acute phase (although he or she could look it up in the patient's medical history).

  This is because, during these visits, the patient's score on the mRS will be evaluated, whether there has been a recurrence or not… etc., for which they do not need to know this background. In addition, the medical treatment in this phase will be the same in all patients: some will carry it like this from the beginning (BMT group, as acute phase and secondary prevention treatment) and the others (CEA/stent group) as secondary prevention treatment. In the same way, the statistician who will analyse the data will also be blinded.

- The fact that it is a multicentre clinical trial also has limitations, as **the participation of multiple hospitals increases variability**, even though all participating hospitals have a SU, and therefore, similar resources and capabilities. Inter-observer biases, information biases and detection biases (for example of MCP) may occur. Thus, an agreed and extensively detailed document on the characteristics of these plaques and how to diagnose them properly will be developed. In addition, theoretical and practical training on MCP diagnosis will be provided in each hospital to instruct the neurologists involved in the project.

  Similarly, there may also be collection bias. To avoid or minimise this, a detailed protocol will be drawn up to specify how to collect the data and explain each step of the study. To ensure the correct application of the protocol, a person responsible for each centre will be designated to supervise it. Meetings will be held every 6 months between the principal investigator and those responsible for each centre to ensure that the protocol is faithfully applied and that the study proceeds correctly.

Additionally, the images and videos of the atheromatous plaques will be sent for blind evaluation at the promoter centre, which will review and classify them without knowledge of the classification performed at the centre of origin, evaluating the kappa index between observers for each subtype of MCP.

- One arm of the study employs an interventional/surgical treatment, so there may also be **greater variability as it is performed by different surgeons**, with varying degrees of experience. However, both CEA and carotid stenting are procedures with well-established surgical protocols that have been practised for years. In addition, to overcome this inconvenience, training will be carried out for those physicians that will perform the surgeries/interventional procedures.
- It may be possible that some of the covariates studied modify the results of recurrence, degree of dependence or presence of MEs, acting as a confounding variable. Therefore, this **confusion bias** will be minimised using multivariate analysis.
- A long-term study is proposed, in which patients have to come for three follow-up visits. Given the severity profile of the participants, it is not expected that there will be a large **loss of patients**. It is estimated at 5%, a small percentage, although it must be taken into account.
- Both arms of the study involve invasive interventions: the application of drug therapy and surgery/stenting. Both strategies have **adverse effects and complications**, respectively. Therefore, patients must be warned of the possible harm derived from the intervention so that, if they perceive any, they must immediately go to the hospital.

11. WORK PLAN AND CHRONOGRAM

11.1. Participating Centres

As it has already been mentioned, the study will be carried out in some of the potential 23 centres belonging to the *SONES*, *RICORS-Ictus* and *Proyecto Ictus* networks. The centres belonging to each of the associations and, therefore, participating in this study, are specified in the Annex 10.

11.2. Research Team

- **Director, Coordinator and Principal Investigator:** Dr Joaquín Serena will be in charge of these three tasks. As director of the research, he will direct the execution of the project, ensure the correct application of the protocol and the correct storage of the data. As coordinator, he will be responsible for supervising the proper functioning of the rest of the participating centres. As principal investigator, he has been in charge of designing the current protocol, together with Yanire Altuzarra. In addition, he will participate in the discussion of the results, will prepare the final report of conclusions and its subsequent dissemination through the publication of the results.
- **Co-investigator Head:** for each of the potential 23 participating hospitals, one of the co-investigators will be appointed as "Head co-Investigator", to ensure compliance with the protocol at their centre and to facilitate coordination with the principal investigator.
- **Co-investigators:** include expert vascular neurologists, neurosonologists, and surgeons/interventionists from each participating centre in the clinical trial.
- **Health personnel:** necessary to carry out this clinical trial, such as nurses, vascular surgeons, radiologists… etc.
- **Statistical Analyst:** responsible for carrying out the statistical analysis of the study.

11.3. Stages

The process of creation, implementation, analysis and publication of the results will be carried out in 6 stages, which are detailed below. The total duration of the study will be 3 years.

Stage 0. Study design (November 2024)

- *Protocol development (already done)*: to carry out the clinical trial, the present protocol will be followed. To elaborate it, an exhaustive bibliographic search on MCP has been carried out in order to establish the main objectives, hypotheses and design the methodology.
  Led by: Dr Joaquín Serena and Yanire Altuzarra.

- *Participating hospitals contact (November 2024)*: during this period, the centres belonging to the *SONES*, *RICORS-Ictus* and *Proyecto Ictus* (Annex 10) networks with which there have already been previous collaborative projects with the Neurology Service of the HUDJT, will be contacted. After their approval to participate, the following stages of the study will continue.
  Led by: Dr Joaquín Serena.

Stage 1. Ethical evaluation (November 2024 - December 2024)

Once the protocol has been drafted, it will be submitted to the CEIC of the main research centre, the HUDJT of Girona, for approval. The length of this stage may vary depending on how long it takes for the CEIC to approve the study. In anticipation of the CEIC considering it to be an invasive clinical trial, it will be at this stage that liability insurance will also be taken out.

Led by: Dr Joaquín Serena and members of the CEIC.

Stage 2. Initial coordination (January 2025 - February 2025)

- *First meeting with the research team (January 2025 - February 2025)*
  During this time, a date will be set for the first face-to-face meeting between Dr Joaquín Serena and the head co-investigators of each centre. At this meeting, the different phases of the study, the timeline, the criteria for including and excluding patients in the study and the roles of each investigator will be reviewed. An email and/or telephone number will be provided for better coordination, as well. After this meeting, each head co-investigator will be asked to have a second meeting with all the co-investigators of his/her centre to provide them with the same information.

- *Training (January 2025 - February 2025)*

  A first online meeting will be held with the whole team where theoretical training on the diagnosis of MCP will be provided. Images and videos of Doppler ultrasound scans of atheromatous plaques in the supra-aortic trunks will also be shown and sent as practical training. During this meeting, a consensual and detailed document will also be sent to the heads of each centre with the characteristics of these plaques and how to diagnose them properly, so that they can consult it if they have any doubts. The aim of all this training is to homogenise the process and reduce the differences in the results of each centre.

Led by: the whole team.

Stage 3. Recruitment and Data collection (March 2025 - February 2027)

- *Patient Recruitment (March 2025 - February 2026)*

  As mentioned above, a consecutive non-probabilistic sampling method of patients with ischaemic stroke associated with MCP admitted to the SU of the participating centres will be used. Each co-investigator at each centre will be responsible for including patients who meet the inclusion criteria and none of the exclusion criteria, after signing the informed consent form (Annex 12). Each participant will be randomised to one of the intervention groups of the clinical trial. The head co-investigators of each centre will supervise this process.

- *Intervention (March 2025 - February 2026)*

  During this period, surgeries (CEA/stent) will be performed in one arm of the study and BMT will be administered in the other arm.

  Online meetings will be held every 6 months between the principal investigator and the head co-investigators of each centre to ensure the faithful application of the protocol and the correct development of the study.

- *Follow-up (March 2025 - February 2027)*

  Patients being included in the study will be followed during the first 72 hours post-admission, as well as at subsequent follow-up visits at 1, 3 and 12 months post-index stroke. Therefore, this phase will last one year beyond the date when the last patient is added to the trial. These patients will be visited during the follow-up by

vascular neurologists not involved in the treatment of the patient in the acute phase and unaware of the allocation of the patient to one or the other arm.

- *Data registry (March 2025 - February 2027)*
  As the patients are added and followed up, the researchers will record the data of each variable to be studied in the CRFs to later enter them in a database shared among the 23 hospitals.

Led by: the whole team.

Stage 4. Statistical analysis and Data interpretation (March 2027 - July 2027)

- *Final statistical analysis (March 2027 - May 2027):*
  During this period, statistical analysis of the data will be carried out by a subcontracted statistician. He or she will be blinded for the study groups.
  Led by: statistical analyst.

- *Second meeting (May 2027):*
  After completing Stage 3 and the final statistical analysis, the second face-to-face meeting will be organised by Dr Joaquín Serena and the head co-investigators of each centre. The results of the study will be presented and discussed at this meeting.
  Led by: the whole team.

- *Data interpretation (June 2027 - July 2027):*
  Dr Joaquín Serena will carry out the interpretation of the results.
  Led by: Dr Joaquín Serena.

Stage 5. Results publication (August 2027 - October 2027)

In this period, the results will be written up after their correct interpretation, in order to publish them in a scientific journal.
The results will also be disseminated at the national congress of the SEN and at an international congress.
Led by: Dr Joaquín Serena.

11.4. Chronogram

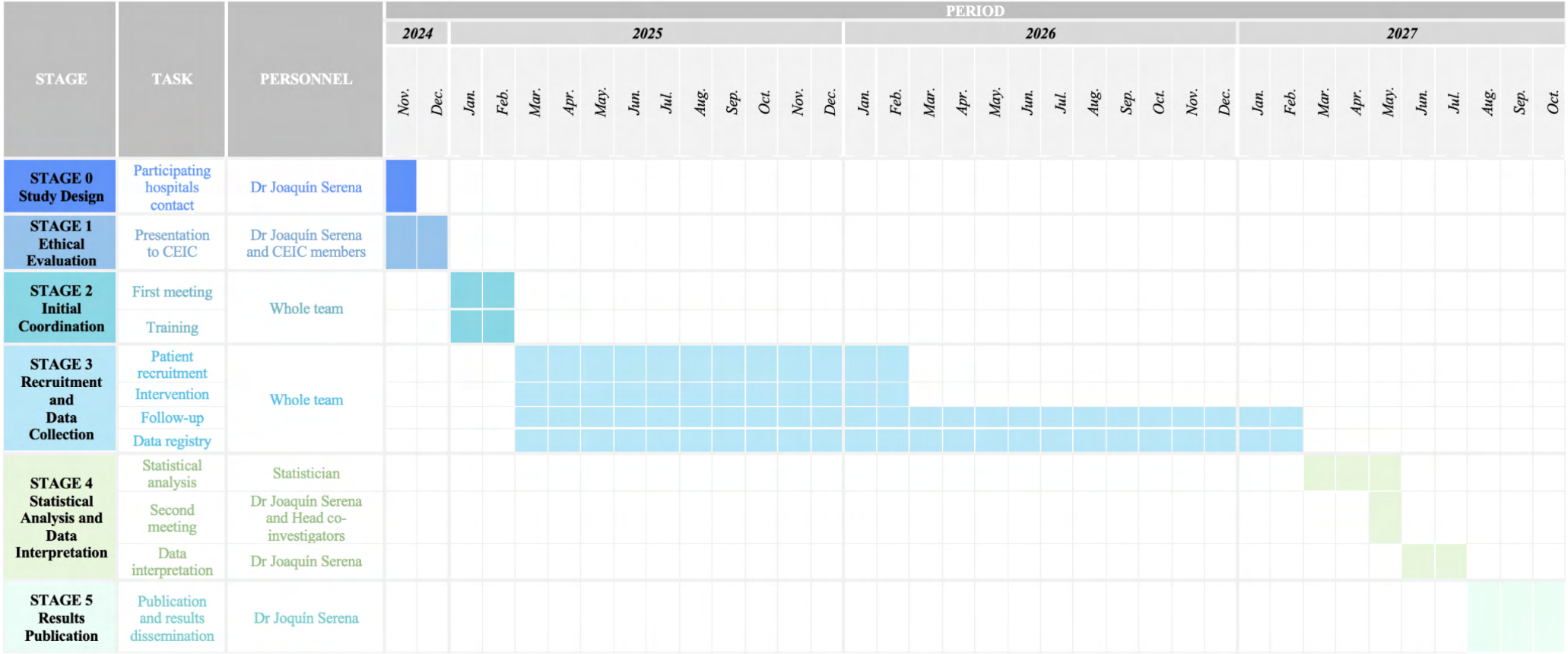

Figure 35. Chronogram of "The PLACA VIL Trial".

12. FEASIBILITY

This study is expected to be feasible because, despite being multicentre and, somewhat, more difficult to coordinate, all the centres and researchers involved have experience in this type of project. In addition, it is supported by three networks that promote collaborative research in neurology, such as *SONES, RICORS-Ictus* and *Proyecto Ictus.* Furthermore, all these centres have an SU and all the relevant resources for the type of patients included in this project.
As discussed later, the lead research team, belonging to the SU of the HUDJT, has extensive research experience. In addition, large-scale collaborative projects have already been carried out (even with more than 500 patients), among several of the participating centres.

The entire research team will be composed of expert vascular neurologists as well as leading neuro-sonologists with extensive research experience who are currently working in the centres participating in the study. There will also be the participation of the nursing staff from the SU of each centre, as well as the commitment of the Vascular Surgery Service and the Radiology Service to participate in the clinical trial.
Therefore, the only additional member to be recruited for our clinical trial is the statistical analyst who will perform the statistical analyses.

On the other hand, few extra visits and imaging tests are proposed in addition to those currently performed in routine clinical practice. All the participating centres have the resources to carry these visits and neuroimaging tests out.

We study severe patients, with many comorbidities and at high risk of recurrence. These characteristics within the participants make it unlikely that there will be large losses of subjects during the study process, as they will want to benefit from closer medical follow-up than usual. A loss rate of 5% is expected, which is quite acceptable, because in other clinical trials carried out by Dr. Joaquín Serena, the loss of patients was less than 3%.

13. BUDGET

In order to carry out this study, the following budget is planned:

13.1. Personnel expenses

The researchers (expert vascular neurologists) and other professionals who carry out the clinical trial will not receive extra remuneration for their involvement in the project, as this is part of their normal professional activity.
The selection of patients participating in the study who meet the inclusion criteria and none of the exclusion criteria will be carried out by the principal investigator of the clinical trial and the head co-investigators of each centre. Their cost will also not be included in this budget.
This is done in order to avoid any financial incentive to join the study.

The only extra cost in terms of personnel will be the hiring of an independent statistical analyst. This will require an estimated 80 hours of work, paid at €50/hour, and is expected to cost €4,000.

13.2. Liability insurance

Since one of the study arms will require a surgical intervention, the CEIC is likely to consider this project as an invasive clinical trial. Therefore, a liability insurance will be required to cover possible complications of the procedure. The estimated cost is €50,000, if the insurance per patient costs, approximately, €200.

13.3. Execution expenses

There are extra expenses derived from the need for additional material, such as:

- Printing costs: the printing of the protocol, detailed document of the MCP, informed consent form and information sheet, is estimated to cost €350 in total, taking into account that each side is printed at €0.05.
- The paper packs needed will cost approximately €78, since each package costs €5.2 and we estimate that we will use 15 packages.

13.4. Publication expenses

We will publish the results of this clinical trial in an international Open Access medical journal. We estimate that the edition, formatting, layout/graphic design, revision and final publication

will cost approximately €3,000. An additional cost for the revision of the translation of €500 will also be required.

13.5. Travel expenses

For the proper functioning of the study, a series of online meetings are planned every 6 months between the principal investigator and the heads of each centre. Their cost is not included in the budget.

However, a meeting of the principal investigator with the 23 head co-investigators of each centre will be organised at the beginning and end of the clinical trial at the HUDJT. In the first meeting the study will be organised and, in the last meeting, the discussion of the results obtained will take place in order to draw the appropriate conclusions.
Therefore, all the heads of the participating centres will have to travel to Girona. We estimate an average cost of €500 per person, including travel, accommodation and subsistence expenses, for the two stays. We estimate an approximate cost of €11,300.

The results of this clinical trial will be disseminated at two congresses, one national (SEN congress) and one international. Taking into account registration costs, transport, accommodation and diets, we expect around €2,000 between the two congresses.

The total budget to carry out "The PLACA VIL Trial" is €71,228. We will apply for the Convocatoria de Acción Estratégica de Salud 2024 of the Instituto de Salud Carlos III (Gobierno de España) to cover all costs of the trial. If more funds are needed, we will send the protocol to other calls for public and/or private funding.

Table 5. Approximate budget for the clinical trial.

EXPENSES	COST PER UNIT	NUMBER OF UNITS	SUBTOTAL
Personnel expenses			
Investigators	-	-	€0
Statistical analysis	€50/hour	80 hours	€4,000
Subcontracted services			
Liability insurance	≈ €200/patient	238	€50,000
Materials			
Printing costs	€0.05	7,000	€350
Paper costs	€5.2	15	€78
Dissemination and Publication			
Translation revision cost	€500	1	€500
Article publishing fees	€3,000	1	€3,000
Congresses	€1,000	2	€2,000
Travel expenses			
Meetings	€500	23	€11,300
		TOTAL	**€71,228**

14. EXPERIENCE OF THE RESEARCH TEAM

The research team includes experts in vascular neurology and neurosonology, as centres belonging to *SONES, RICORS-Ictus* and *Proyecto Ictus* (Annex 10) are participating.

Most of the vascular neurologists at the coordinating centre (HUDJT) are part of the research team, with Dr. Joaquín Serena as the team leader. They work together at the care level, but have also worked together on multiple occasions as a team on other research projects.

The neurovascular research group of the HUDJT has more than 20 years of experience in the field of cerebrovascular disease research. This background has allowed them to maintain relationships with other members of the vascular neurology research collaboration network initiated more than 10 years ago. This cooperation has led to multi-centre research projects, such as the one presented in this study.

As a result, it has gained national and international renown as a reference research group, due to its contributions in various clinical aspects of stroke as well as in the field of neuroimaging (especially neurological ultrasound) and other biological, molecular and inflammatory factors.

As mentioned, Dr. Joaquín Serena is the leader of the team, and is an expert in the field of cerebrovascular disease, especially in ultrasound and pathology of the carotid artery, a field considered a reference at national and international level. In addition, he is constantly involved in new research, attends congresses both as a speaker at conferences and lectures and as an attendee. He is a member of several societies and projects of great importance in the field of neurology. For example, he is a member of the SEN evaluation board for accreditation in Neurosonology, he was editor of the first book on neurosonology published in Spain, and also the most recent.
One of the societies to which he belongs, of which he was one of the founders, is the *Sociedad Española de Neurosonología (SONES)*, whose centres are participating in the present clinical trial.

SONES has been working for 25 years to promote the development of ultrasound technology used in neurology through the continuing education of neurologists in the field of neurosonography. All centres belonging to this society have several experts in this field.

Another network participating in this study is *RICORS-Ictus*, which has 34 research groups committed to generating knowledge on cerebrovascular disease and its communication. It was founded by the European Union and is funded by the Instituto de Salud Carlos III.
Its main objective is to create a cooperative research network on various aspects of stroke (detection, biomarkers of recovery, treatment, secondary prevention...) in Spain, as all the autonomous communities of Spain are represented in the network.

The *Proyecto Ictus* is an initiative of the *Grupo de Estudio de Enfermedades Cerebrovasculares of the Sociedad Española de Neurología* aimed at facilitating the development of collaborative clinical research in the field of stroke. It was created 24 years ago with the purpose of encouraging collaboration, participation and communication of research on stroke, as well as the creation of new projects and the promotion of new researchers.

15. IMPACT ON THE NATIONAL HEALTH SYSTEM

As mentioned in the *Introduction* section, stroke is the second leading cause of death worldwide in both sexes and the leading cause in women. Thanks to research, there are more and more stroke survivors. This leads to high rates of morbidity and disability (it is the leading cause of disability worldwide), resulting in social problems and significant consumption of health resources.

Among the different aetiologies of stroke, those caused by MCP are one of the most aggressive, as they are plaques that tend to produce a lower degree of carotid stenosis (36), so their potential to cause a stroke is underestimated. They are also plaques with a higher rate of ulcer formation (46), which makes them vulnerable atheroma plaques and, therefore, more malignant. In addition, they have a higher recurrence rate of new strokes (33). Thus, they are a subtype of patients with higher mortality, but where their impact is more noticeable is in the greater morbidity they cause and, consequently, increased health care costs.

The literature on MCP is diffuse, scarce and of low quality. The most important scientific, health and social issue is how to treat these aggressive plaques. The acute phase treatment of MCP remains totally unknown. This study will be the first published clinical trial on this topic when it is concluded. Hence, its likelihood to have a large clinical international influence is high.

As these are more aggressive plaques with a higher risk of recurrence, information regarding their diagnosis, but most importantly which treatment method is associated with a lower risk of early and medium to long-term recurrence, would improve the prognosis of patients with MCP-related strokes. In addition, the importance of determining the optimal treatment would have an impact on the National Health System by reducing stroke recurrence, hospital stay times, rehabilitation rates and times, physiotherapy, speech therapy, etc., and, hence, the costs involved.

16. FUTURE DIRECTIONS

Mobile carotid plaques (MCP) conform a largely unknown entity in all aspects. In the case of the present clinical trial, the optimal treatment for these plaques with malignant behaviour is being studied, but there are many other areas that can be investigated or expanded, such as:

- Study of the prevalence of MCP in the population of consecutive stroke patients. The literature data on this subject is very poor, mostly based on case series or studies with very few patients. There is no project to date that has studied this point in depth or with precision.
- Study of the prevalence of the different subtypes of MCP according to the criteria defined in the *Introduction* section. The same phenomenon occurs as mentioned in the previous point.
- It would also be interesting to study each subtype of MCP separately to find out, for example, which of them is associated with a higher risk of recurrence. There is data in this regard (33), but no conclusions can be extrapolated to the population since the sample size is very small. Therefore, quality studies are needed to investigate this point.
- The creation of a website for this study would be a good option that would help disseminate information about MCP, promote their correct diagnosis and be an easily accessible source of knowledge. A repository of videos and still images of Doppler ultrasound MCP could be published on the website, with periodic centralised re-evaluation. Special emphasis would be placed on the diagnostic criteria of MCP and their malignant features such as the "Jellyfish" or "Snake fang" sign.
- Given the low prevalence of MCP or their under-diagnosis, it would be interesting to set up an online registry (in collaboration with the *Universitat de Girona*, for example) with data collection on patients with MCP (anonymised), classic vascular risk factors, classification of the subtypes of MCP, treatment prescribed in the acute phase and evolution at 3 months (score on the mRS and recurrences). As an online registry, vascular neurologists from all over the world would be able to enter their patients' data. This would favour the expansion of knowledge about MCP, their better characterisation and, therefore, a radical change in the prognosis of these patients.

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ANNEXES

1. CHA_2DS_2-VASC Score

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age > 75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease*	1
Age 65–74	1
Sex **c**ategory (ie, female sex)	1
Maximum score	9

Note: *Prior myocardial infarction; peripheral artery disease; aortic plaque.
Abbreviations: LV, left ventricular; TIA, transient ischemic attack.

2. SSS-TOAST Classification Criteria

Table 1. CCS Classification of Ischemic Stroke Etiology

Stroke Mechanism	Level of Confidence	Criteria
Large artery atherosclerosis	Evident	1. Either occlusive or stenotic (≥50% diameter reduction or <50% diameter reduction with plaque ulceration or thrombosis) vascular disease judged to be caused by atherosclerosis in the clinically relevant extracranial or intracranial arteries
		2. The absence of acute infarction in vascular territories other than the stenotic or occluded artery
	Probable	1. History of ≥1 transient monocular blindness (TMB), TIA, or stroke from the territory of index artery affected by atherosclerosis within the last month
		2. Evidence of near-occlusive stenosis or nonchronic complete occlusion judged to be caused by atherosclerosis in the clinically relevant extracranial or intracranial arteries (except for the vertebral arteries)
		3. The presence of ipsilateral and unilateral internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery
	Possible	1. The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis (<50%) in the absence of any detectable plaque ulceration or thrombosis in a clinically relevant extracranial or intracranial artery and history of ≥2 TMB, TIA, or stroke from the territory of index artery affected by atherosclerosis, at least 1 event within the last month
		2. Evidence for evident large artery atherosclerosis in the absence of complete diagnostic investigation for other mechanisms
Cardio-aortic embolism	Evident	1. The presence of a high-risk cardiac source of cerebral embolism (see Table 3)
	Probable	1. Evidence of systemic embolism
		2. The presence of multiple acute infarctions that have occurred closely related in time within both right and left anterior or both anterior and posterior circulations in the absence of occlusion or near-occlusive stenosis of all relevant vessels. Other diseases that can cause multifocal ischemic brain injury such as vasculitides, vasculopathies, and haemostatic or hemodynamic disturbances must not be present
	Possible	1. The presence of a cardiac condition with low or uncertain primary risk of cerebral embolism (see Table 3)
		2. Evidence for evident cardio-aortic embolism in the absence of complete diagnostic investigation for other mechanisms
Small artery occlusion	Evident	1. Imaging evidence of a single and clinically relevant acute infarction <20 mm in greatest diameter within the territory of basal or brainstem penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, etc)
	Probable	1. The presence of stereotypic lacunar transient ischemic attacks within the past week
		2. The presence of a classical lacunar syndrome
	Possible	1. Presenting with a classical lacunar syndrome in the absence of imaging that is sensitive enough to detect small infarctions
		2. Evidence for evident small artery occlusion in the absence of complete diagnostic investigation for other mechanisms
Other causes	Evident	1. The presence of a specific disease process that involves clinically appropriate brain arteries
	Probable	1. A specific disease process that has occurred in clear and close temporal or spatial relationship to the onset of brain infarction such as arterial dissection, cardiac or arterial surgery, and cardiovascular interventions
	Possible	1. Evidence for an evident other cause in the absence of complete diagnostic investigation for mechanisms listed above
Undetermined causes	Unknown	
	Cryptogenic embolism:	1. Angiographic evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal looking intracranial arteries
		2. Imaging evidence of complete recanalization of previously occluded artery
		3. The presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels
	Other cryptogenic:	1. Those not fulfilling the criteria for cryptogenic embolism
	Incomplete evaluation:	1. The absence of diagnostic tests that, under the examiner's judgment, their presence would have been essential to uncover the underlying etiology
	Unclassified	1. The presence of >1 evident mechanism in which there is either probable evidence for each, or no probable evidence to be able to establish a single cause

Table 3. Cardioaortic Sources of Cerebral Embolism

Sources with high primary risk of stroke
Left atrial thrombus
Left ventricular thrombus
Atrial fibrillation
Paroxysmal atrial fibrillation
Sick sinus syndrome
Atrial flutter
Recent myocardial infarction
Rheumatic mitral or aortic valve disease
Bioprosthetic and mechanical heart valves
Chronic myocardial infarction together with low ejection fraction <28%
Symptomatic congestive heart failure with ejection fraction <30%
Nonischemic dilated cardiomyopathy
Nonbacterial thrombotic endocarditis
Infective endocarditis
Papillary fibroelastoma
Left atrial myxoma
Sources with low or uncertain primary risk of stroke
Mitral annular calcification
Patent foramen ovale
Atrial septal aneurysm
Atrial septal aneurysm and patent foramen ovale
Left ventricular aneurysm without thrombus
Isolated left atrial smoke
Complex atheroma in the ascending aorta or proximal arch
Other (third-degree atrioventricular block, pre-excitation syndromes, etc)

The high- and low-risk sources are separated using an arbitrary 2% annual or 1-time primary stroke risk threshold.

3. Modified Rankin Scale, Spanish version

0. Asintomático
1. Sin discapacidad significativa
Presenta algunos síntomas y signos pero sin limitaciones para realizar sus actividades habituales y su trabajo. Preguntas: ¿Tiene el paciente dificultad para leer o escribir, para hablar o encontrar la palabra correcta, tiene problemas con la estabilidad o de coordinación, molestias visuales, adormecimiento (cara, brazos, piernas, manos, pies), pérdida de movilidad (cara, brazos, piernas, manos, pies), dificultad para tragar saliva u otros síntomas después de sufrir el ictus?
2. Discapacidad leve
Presenta limitaciones en sus actividades habituales y laborales previas, pero es independiente para las actividades básicas de la vida diaria (ABVD). Preguntas: ¿Ha habido algún cambio en la capacidad del paciente para sus actividades habituales o trabajo o cuidado comparado con su situación previa al ictus? ¿Ha habido algún cambio en la capacidad del paciente para participar en actividades sociales o de ocio? ¿Tiene el paciente problemas con sus relaciones personales con otros o se ha aislado socialmente?
3. Discapacidad moderada
Necesita ayuda para algunas actividades instrumentales pero no para las actividades básicas de la vida diaria. Camina sin ayuda de otra persona. Necesita de cuidador al menos dos veces por semana. Preguntas ¿Precisa de ayuda para preparar la comida, cuidado del hogar, manejo del dinero, realizar compras o uso de transporte público?
4. Discapacidad moderadamente grave
Incapaz de atender satisfactoriamente sus necesidades, precisando ayuda para caminar y para actividades básicas. Necesita de cuidador al menos una vez al día, pero no de forma continuada. Puede quedar solo en casa durante algunas horas. Preguntas: ¿Necesita ayuda para comer, usar el baño, higiene diaria o caminar? ¿Podría quedar solo algunas horas al día?
5. Discapacidad grave
Necesita atención constante. Encamado. Incontinente. No puede quedar solo.
6. Éxitus

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ENSAYO IMPACT-24

FORMULARIO DE ESCALA DE RANKIN MODIFICADA | ID DEL PACIENTE: ☐ CÓD. SITIO CÓD. PACIENTE

Nombre del evaluador/a: _____ Fecha de la evaluación (DD/MM/AAAA): ____ / ____ / _____

Fase del estudio: ☐ Día 7 ☐ Día 30 ☐ Día 90 ☐ 1 año

La información se ha obtenido de (seleccione todas las opciones correspondientes): ☐ Paciente ☐ Familia ☐ Otro, especifique: _____

5	**EN CAMA**	
	¿La persona está en cama? El/la paciente no puede caminar, ni siquiera con la ayuda de otra persona. Si es transladado a una silla de ruedas, no es capaz de moverla por sí mismo/a adecuadamente. Generalmente requiere un cuidado casi constante - casi todo el tiempo debe haber alguien disponible.	☐ Sí (ERm = 5) ☐ No

Nota: si requiere traslado cama-silla y no mueve la silla por si mismo adecuadamente (video) → 5

Si su respuesta ha sido Sí, ¿quién se encarga del cuidado del/la paciente? _____

4	**ASISTENCIA PARA CAMINAR**	
	¿Es esencial la asistencia de otra persona para caminar? Requerir la asistencia de otra persona significa necesitar que haya otra persona constantemente presente al caminar, para brindar ayuda física o supervisión. → supervisión cte para caminar =4 • Si el/la paciente necesita asistencia para sentarse en y levantarse de una **silla de ruedas**, pero, una vez en la misma, puede trasladarse por sí mismo/a de forma adecuada → responda SÍ → no puede girar esquinas =4 • Si el/la paciente NO necesita asistencia para sentarse en y levantarse de una **silla de ruedas** → responda NO • Si el/la paciente utiliza **aparatos de asistencia** para caminar, pero no necesita la ayuda de otra persona; o si el/la paciente camina **cuando se le solicita que lo haga** durante la evaluación → responda NO (<4)	☐ Sí (ERm = 4) ☐ No

Nota: si requiere traslado cama-silla pero es autómomo en silla (demostrar en video) → 4
Si autopropulsa silla "mecánica": 4; si no: 5

Si su respuesta ha sido Sí, describa el **tipo de asistencia** que el/la paciente necesita **para caminar**:

_____

3	**ASISTENCIA PARA EL DESEMPEÑO DE TAREAS PERSONALES**	
	Asistencia incluye asistencia física, instrucciones orales o supervisión de otra persona. Cuestión principal: **Si fuera estrictamente necesario, ¿el/la paciente podría vivir solo, durante una semana?** **Nota:** insistir en si puede vivir solo 1 semana.	
3.1	**¿ Es estrictamente necesaria la asistencia para preparar una comida sencilla?** Por ejemplo: si el/la paciente puede prepararse el desayuno o un entremés → responda NO	☐ Sí (ERm = 3) ☐ No
3.2	**¿ Es estrictamente necesaria la asistencia para realizar a diario los quehaceres domésticos básicos?** Por ejemplo: si el/la paciente puede encontrar y guardar la ropa, limpiar la mesa después de las comidas→ responda NO	☐ Sí (ERm = 3) ☐ No
3.3	**¿ Es estrictamente necesaria la asistencia para encargarse de los gastos de la casa?**	☐ Sí (ERm = 3) ☐ No
3.4	**¿ Es estrictamente necesaria la asistencia para realizar desplazamientos locales?** Por ejemplo: si el/la paciente puede conducir o utilizar el transporte público; o llamar un taxi y darle instrucciones al conductor → responda NO	☐ Sí (ERm = 3) ☐ No
3.5	**¿ Es estrictamente necesaria la asistencia para realizar compras en establecimientos cercanos?** Por ejemplo: si el/la paciente puede comprar aunque sea un único artículo → responda	☐ Sí (ERm = 3)

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ENSAYO IMPACT-24

FORMULARIO DE ESCALA DE RANKIN MODIFICADA	ID DEL PACIENTE: ☐ CÓD. SITIO CÓD. PACIENTE

	NO	☐ No

Si su respuesta ha sido Sí a cualquiera de las preguntas anteriores, describa las actividades para las que el/la paciente recibe ayuda y quién se la brinda.

_____

2	TAREAS Y ACTIVIDADES DE RUTINA	
2.1	**Trabajo:** **¿Ha reducido el nuevo accidente cerebrovascular (en comparación con el estado previo al accidente cerebrovascular) de forma sustancial la capacidad de la persona para trabajar** (o, para un estudiante, la capacidad de estudiar)**?** Por ejemplo: cambios de tiempo completo a tiempo parcial, cambios en el nivel de responsabilidad, o ya no es capaz de trabajar.	☐ Sí (ERm = 2) ☐ No
2.2	**Responsabilidades familiares:** **¿Ha reducido el nuevo accidente cerebrovascular (en comparación con el estado previo al accidente cerebrovascular) de forma sustancial la capacidad de la persona para hacerse cargo de la familia en casa?**	☐ Sí (ERm = 2) ☐ No
2.3	**Actividades sociales y de ocio:** **¿Ha reducido el nuevo accidente cerebrovascular (en comparación con el estado previo al accidente cerebrovascular) la frecuencia de las actividades habituales de la persona durante su tiempo libre a menos de la mitad?** Actividades sociales y de ocio incluyen aficiones e intereses, actividades dentro o fuera de casa. Actividades fuera de casa: ir a tomar un café, a un bar, restaurante, club, iglesia, cine, visitar amigos, dar paseos. Actividades dentro de casa: aquellas que implican una participación "activa" como tejer, coser, pintar, jugar, leer, realizar mejoras en el hogar.	☐ Sí (ERm = 2) ☐ No

Si su respuesta ha sido Sí a cualquiera de los puntos anteriores (2.1 - 2.3), describa el cambio que se ha producido entre el estado previo y posterior al accidente cerebrovascular:

_____

1	SÍMTOMAS COMO CONSECUENCIA DEL ACCIDENTE CEREBROVASCULAR	
	¿Presenta el/la paciente algún síntoma como resultado del nuevo accidente cerebrovascular? Por ejemplo, problemas a la hora de: leer/escribir, hablar, mantener el equilibrio o coordinar movimientos, ver, tragar; o: entumecimiento, debilidad, pérdida de movilidad u otros síntomas	☐ Sí (ERm = 1) ☐ No (ERm = 0)

Si su respuesta ha sido Sí, registre los síntomas a continuación. Confirme que los mismos **están relacionados con el nuevo accidente cerebrovascular** y no existían antes de la admisión al estudio:

_____

La puntuación final ERm debe ser la más alta que figura en la primera pregunta a la que haya respondido "Sí"

Puntuación ERm: _____ Firma del evaluador/a: _____

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4. National Institute Health Stroke Score (NIHSS), Spanish version

NIH Stroke Scale
(Escala de ictus del National Institute of Health)

Normas generales:
Puntuar siempre la primera respuesta después de una orden.
Puntuar aunque existan secuelas previas.

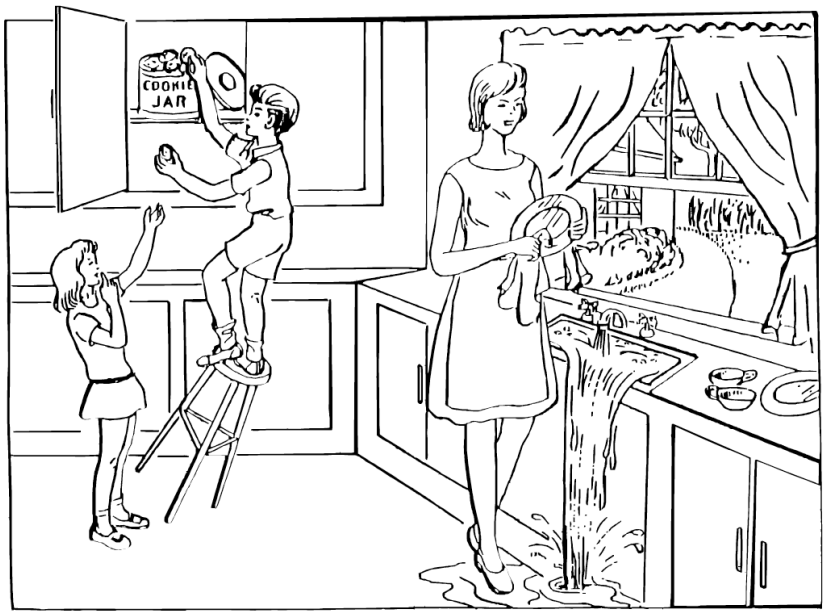
1a. Nivel de consciencia	0 = Alerta, respuestas normales. 1 = No alerta pero responde a mínimos estímulos verbales para obedecer o responder. 2 = No alerta. Requiriere estímulos repetidos o dolorosos para realizar movimientos (no estereotipados o reflejos). 3 = Sólo respuestas reflejas o falta total de respuestas.
1b. Nivel de consciencia-Preguntas orales Preguntar: ¿En que mes vivimos? y ¿ Que edad tiene? Puntuar sólo la primera respuesta. (Aproximaciones o rectificaciones deben puntuarse como incorrecto, no ayudar ni dar pistas) Si el paciente no puede emitir sonidos y no está afásico (Intubado, mudo, muy disártrico-anártrico, barrera idiomática), puntuar "1". Si el paciente está afásico o estuporoso, puntuar "2".	0 = Ambas respuestas son correctas. 1 = Una respuesta correcta. 2 = Ninguna respuesta correcta.
1c. Nivel de consciencia-Órdenes motoras Ordenar : "Cierre los ojos" "Ahora abra los ojos" y con el lado no parético "Cierre la mano haciendo un puño y luego abra la mano." Si no hay respuesta, hacer el gesto para que el paciente imite y posteriormente puntuar. Sólo puntuar la primera acción. Si existe algún impedimento físico para realizar estas órdenes, escoger otra orden motora simple.	0 = Ambas órdenes son correctas. 1 = Una orden correcta. 2 = Ninguna orden correcta.

2. Mirada conjugada Sólo valorar la mirada horizontal de manera voluntaria o con los reflejos oculo-cefálicos (no permitido los test calóricos) Si el paciente tiene la mirada desviada pero esta se corrige de manera voluntaria, por contacto visual o de manera refleja, puntuar "1". Si el paciente tiene una paresia periférica de un nervio oculomotor (III, IV o VI), puntuar "1".	0 = Normal. 1 = Paresia parcial de la mirada. Ausencia de paresia total o desviación forzada. 2 = Paresia total o desviación forzada de la mirada conjugada.
3. Visual Explorar los campos visuales por confrontación, cuadrantes superiores e inferiores. Si ceguera unilateral, explorar sólo el ojo no ciego. Si ceguera bilateral de cualquier causa, puntuar "3". Si sólo existe extinción visual, puntuar "1".	0 = No alteración visual. 1 = Hemianopsia parcial. 2 = Hemianopsia completa. 3 = Ceguera total.
4. Paresia facial. Ordenar enseñar los dientes, sonreír o hacer mímica para que el paciente lo imite. Si el paciente está afásico o poco reactivo dar un estímulo doloroso para observar la mueca.	0 = Movimiento normal y simétrico. 1 = Borramiento del surco nasogeniano o mínima asimetría al sonreír. 2 = Parálisis total o casi total de la zona inferior de la hemicara. 3 = Parálisis completa con ausencia de movimiento en la zona superior e inferior de la hemicara o bilateral.
5. Paresia del brazo Explorar el lado no parético en primer lugar. Ordenar levantar y extender el brazo. No valorar la fuerza de la mano. Si el paciente está en decúbito, la posición del brazo extendido es a 45º. Si el paciente está sentado, la posición del brazo extendido es de 90º. En segundo lugar se explora el lado parético.	**Lado derecho** 0 = Mantiene la posición durante 10 segundos. 1 = Claudicación en menos de 10 segundos, aunque la extremidad no llega a contactar con la cama. 2 = Puede levantar la extremidad pero esta contacta con la cama en menos de 10 segundos. 3 = Existe movimiento de la extremidad pero no la levanta contra gravedad o cae inmediatamente. 4 = Ausencia total de movimiento. 9 = Extremidad amputada a nivel proximal o inmovilizada. No sumar en la puntuación global.
	Lado izquierdo 0 = Mantiene la posición durante 10 segundos. 1 = Claudicación en menos de 10 segundos, aunque la extremidad no llega a contactar con la cama. 2 = Puede levantar la extremidad pero esta contacta con la cama en menos de 10 segundos. 3 = Existe movimiento de la extremidad pero no la levanta contra gravedad o cae inmediatamente. 4 = Ausencia total de movimiento. 9 = Extremidad amputada a nivel proximal o inmovilizada. No sumar en la puntuación global.

6. Paresia de la pierna Ordenar levantar la pierna extendida y mantenerla a 30º. Explorar la pierna no parética en primer lugar y posteriormente explorar el lado parético.	**Lado derecho** 0 = Mantiene la posición durante 5 segundos. 1 = Claudicación en menos de 5 segundos, aunque la extremidad no llega a contactar con la cama. 2 = Puede levantar la extremidad pero esta contacta con la cama en menos de 5 segundos. 3 = Existe movimiento de la extremidad pero no la levanta contra gravedad o cae inmediatamente. 4 = Ausencia total de movimiento. 9 = Extremidad amputada a nivel proximal o inmovilizada. No sumar en la puntuación global.
	Lado izquierdo 0 = Mantiene la posición durante 5 segundos. 1 = Claudicación en menos de 5 segundos, aunque la extremidad no llega a contactar con la cama. 2 = Puede levantar la extremidad pero esta contacta con la cama en menos de 5 segundos. 3 = Existe movimiento de la extremidad pero no la levanta contra gravedad o cae inmediatamente. 4 = Ausencia total de movimiento. 9 = Extremidad amputada a nivel proximal o inmovilizada. No sumar en la puntuación global.
7. Dismetría Explorar dedo-nariz y talón-rodilla con los ojos abiertos. En caso de existir un déficit motor que impida valorar la dismetría, puntuar como ausente "0."	0 = Ausente. 1 = Presente en una extremidad. 2 = Presente en 2 extremidades. Si presente, detallar (pero no sumar en la puntuación global) Brazo derecho a = Si; b = No; 9 = Extremidad amputada a nivel proximal o inmovilizada. Brazo izquierdo a = Si; b = No; 9 = Extremidad amputada a nivel proximal o inmovilizada. Pierna derecha a = Si; b = No; 9 = Extremidad amputada a nivel proximal o inmovilizada. Pierna izquierda a = Si; b = No; 9 = Extremidad amputada a nivel proximal o inmovilizada.
8. Sensibilidad Con aguja, o ver la retirada ante estímulo doloroso en el paciente obnubilado. Explorar cara, brazos, tronco, abdomen y piernas (no tener en cuenta manos o pies). Sólo valorar hipoestesia relacionada con el Ictus (no hipoestesia por neuropatía, etc). Si alteración bilateral o en coma, puntuar "2".	0 = Normal. 1 = Leve o moderada hipoestesia (posible anestesia algésica pero el paciente nota que se le toca). 2 = Anestesia severa o total (no nota que se le toca).

9. Lenguaje En la evaluación del lenguaje se tiene en cuenta las respuesta a los ítem previos realizados hasta el momento (grado de compresión y expresión). Solicitar que describa lo que sucede en el dibujo, denominar las figuras dibujadas, leer la lista de palabras y frases. Si intubación traqueal o mudo, hacer escribir. Si en coma, puntuar "3".	0 = Normal, no afasia. 1 = Afasia leve o moderada. 2 = Afasia severa (imposible entenderse con el interlocutor). 3 = Mudo con comprensión nula.
10. Disartria. A pesar de la afasia, valorar sólo la articulación. Si afasia=3 (mudo), valorar como Disartria=0	0 = Normal. 1 = Leve o moderada, puede ser entendido aunque con dificultad. 2 = Severa, ininteligible o mudo/anártrico (con independencia de la presencia de afasia). 9 = Intubado u otras barreras físicas. No sumar en la puntuación global.
11. Extinción-Negligencia-inatención. Ya explorada la extinción visual y la extinción sensitiva. Valorar la anosognosia (falta de reconocimiento de la presencia del déficit) o negligencia visoespacial (con la lectura de palabras largas o durante la descripción del dibujo). En pacientes en coma, puntuar "2."	0 = Sin alteraciones. 1 = Inatención o extinción en una de las modalidades visual, tactil, espacial o corporal. 2 = Hemi-inatención o negligencia severa, o a más de una modalidad. No reconoce su propia mano (asomatognosia) o sólo reconoce una parte del espacio.
A. Fuerza motora distal (habitualmente no se incluye en la puntuación global) Levantar el brazo del paciente e indicarle que extienda la mano al máximo. Si no colabora, extenderle pasivamente los dedos. Sólo un intento.	**Mano derecha** 0 = Normal sin flexión de los dedos en 5 segundos. 1 = Alguna extensión aunque no completa y menos de 5 segundos de duración. 2 = No extensión voluntaria en 5 segundos. **Mano izquierda** 0 = Normal sin flexión de los dedos en 5 segundos. 1 = Alguna extensión aunque no completa y menos de 5 segundos de duración. 2 = No extensión voluntaria durante 5 segundos.

Puntuación global: excluir las puntuaciones "9" y la fuerza motora distal.



MAMA

TIC-TAC

CINCO-CINCO

GRACIAS

MERMELADA

FUTBOLISTA

EXCAVADORA

Ya lo veo.

Baja a la calle

Volví del trabajo a casa.

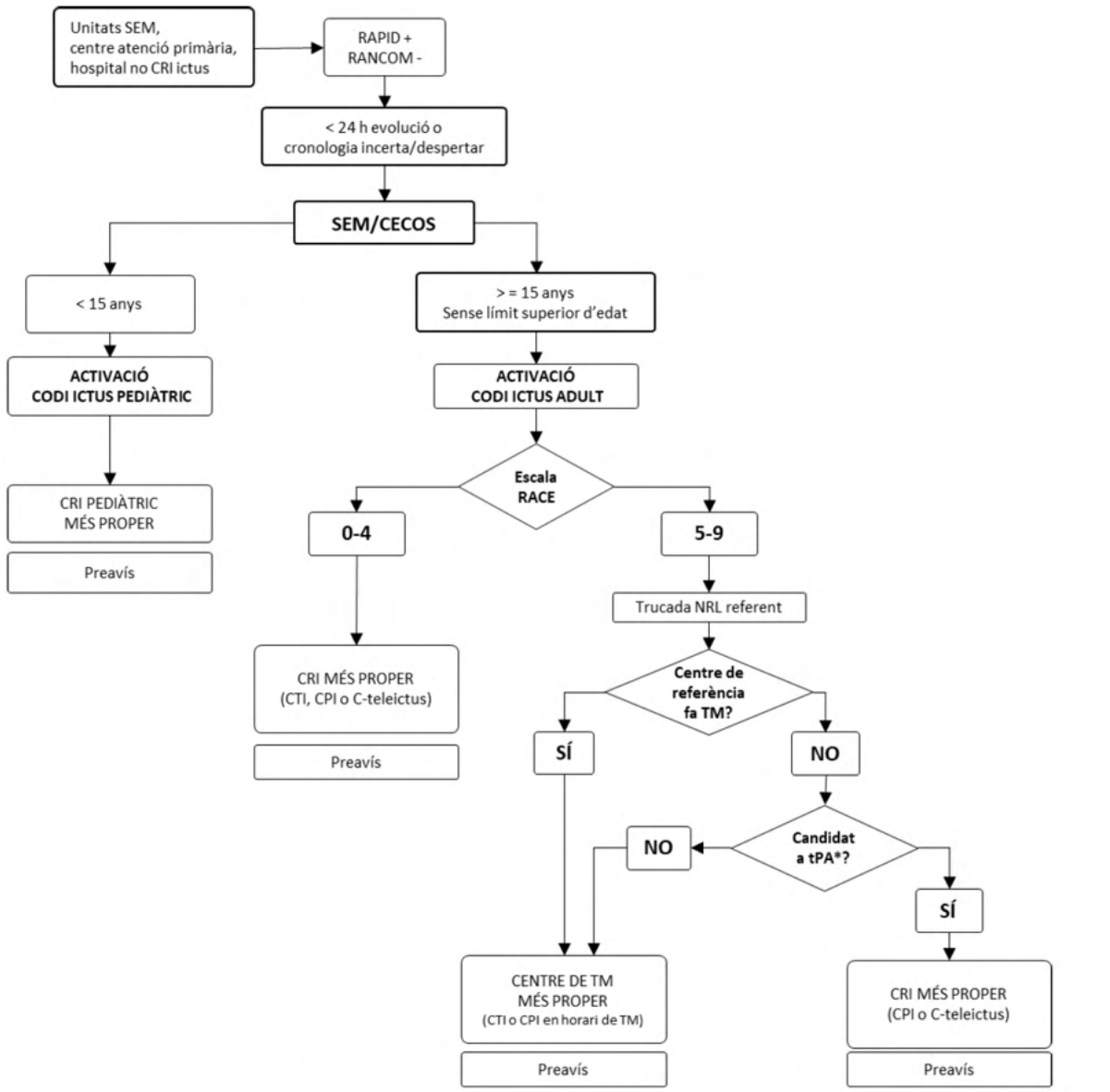
Está junto a la mesa del comedor.

Anoche oyeron al ministro hablar por la radio.

5. RAPID tool for the detection of a stroke, Catalan version

6. RANCOM tool for rapid and estimated determination of the patient's previous functionality, Catalan version

7. Decision algorithm, on suspicion of an acute stroke, for the activation of the Stroke Code in Catalonia, Catalan version



CRI: centre de referència ictus; CTI: centre terciari ictus; C-teleictus: centre teleictus; TM: trombectomia mecànica
*Candidat a tPA: 1) Temps estimat d'arribada al CRI < 4 hores des de l'inici dels símptomes o última hora vist asimptomàtic; 2) No anticoagulació; 3) No intervencions quirúrgiques en els darrers 15 dies; 4) No antecedents d'hemorràgia cerebral.

8. Class of Recommendations and Level of Evidence

CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) **(Generally, LOE A or B use only)**	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

9. Histopathological diagnostic criteria for vulnerable plaques.

Main criteria:

- Inflammatory activation in plaque (monocyte/macrophage or with T lymphocyte infiltration).
- Thin fibrous cap (thickness < 65 μm).
- Large lipid core (>40% of the plaque area).
- Vascular endothelial cell ablation with platelet aggregation on the surface.
- Fissures or damaged plaques.
- Severe luminal stenosis (>90%).

Secondary criteria:

- Intraplaque haemorrhage (IPH).
- Endothelial dysfunction.
- Superficial nodules or calcifications.
- Yellow plaques.
- Positive remodelling of vascular walls.

10. Hospital centres belonging to the SONES, RICORS-Stroke and Stroke Project networks

	Hospital	Co-investigator of reference
Catalonia	Hospital Universitario Doctor Josep Trueta (Girona)	Dr. Joaquín Serena
	Hospital Universitario Vall d'Hebron (Barcelona)	Dr. Carlos Molina
	Hospital de la Santa Creu i Sant Pau (Barcelona)	Dr. Joan Martí
	Hospital Universitario de Bellvitge (L'Hospitalet de Llobregat)	Dr. Pere Cardona
	Hospital Universitario Germans Trias i Pujol (Badalona)	Dra. Mónica Millán
	Hospital Universitario Joan XXIII (Tarragona)	Dr. Alan Flores
	Hospital Universitario Arnau de Vilanova (Lleida)	Dr. Francisco Purroy
Community of Madrid	Hospital Universitario La Paz (Madrid)	Dr. Exuperio Díez-Tejedor
	Hospital Universitario Ramón y Cajal (Madrid)	Dr. Jaime Masjuan
	Hospital Universitario de La Princesa (Madrid)	Dr. José Vivancos
	Hospital Universitario Puerta de Hierro (Majadahonda)	Dr. Carlos Jiménez
Basque Country	Hospital Universitario de Cruces (Barakaldo)	Dr. Alain Luna
	Hospital Universitario de Donostia	Dra. Ana de Arce
Galicia	Hospital Universitario de A Coruña (CHUAC)	Dra. Mar Castellanos
	Hospital Clínico Universitario de Santiago de Compostela (CHUS)	Dr. Manuel Rodríguez
Aragon	Hospital Clínico Universitario Lozano Blesa (Saragossa)	Dr. Carlos Tejero
	Hospital Universitario Miguel Servet (Saragossa)	Dr. Javier Martá
Asturias	Hospital Universitario Central de Asturias (Oviedo)	Dr. Sergio Calleja
Foral Community of Navarre	Hospital Universitario de Navarra (HUN)	Dr. Pablo Irimia
Castile-La Mancha	Hospital General Universitario de Albacete	Dr. Tomás Segura
Castile and Leon	Hospital Clínico Universitario de Valladolid (HCUV)	Dr. Juan Arenillas
Andalusia	Hospital Universitario Virgen del Rocío (Seville)	Dr. Francisco Moniche
Valencian Community	Hospital Universitario y Politécnico La Fe (Valencia)	Dr. Jose Tembl

11. Information sheet, Spanish version

Hoja de información para el paciente

Promotor: Instituto de Salud Carlos III, C/ Sinesio Delgado, nº 4, CP 28029 – Madrid, España.

Título del estudio: ENSAYO CLÍNICO MULTICÉNTRICO ALEATORIZADO SOBRE LA RECURRENCIA PRECOZ DE ICTUS ASOCIADO A PLACAS CAROTÍDEAS MÓVILES SEGÚN TRATAMIENTO EN FASE AGUDA (The PLACA VIL trial)

Investigador: Nombre: Dr. Joaquín Serena

Centro n.º: ES06. H. U. de Girona Dr. Trueta

Dirección: Avinguda de França, S/N

Ciudad/Código postal: Girona, 17007

Teléfono 24 horas: _____

Estimado/a Sr./Sra.:

Este documento va dirigido al paciente. Si el paciente se encuentra en situación de incapacidad temporal para poder otorgar el consentimiento, el familiar/un progenitor/el tutor legal deberá leer este documento. Si usted es un familiar/un progenitor/el tutor legal, a medida que vaya leyendo la información, deberá ponerse en el lugar de su familiar para decidir si permite que su familiar participe en este estudio. Por consiguiente, en el resto del formulario, la palabra "usted" se refiere a su "familiar".

Usted ha sufrido un accidente cerebrovascular isquémico agudo causado por la una placa de ateroma móvil en la carótida. Por ello le invitamos a que participe en un estudio de investigación clínica patrocinado por el Instituto de Salud Carlos III, sobre el tratamiento óptimo para la prevención de recurrencias de ictus ocasionados por dichas placas móviles. El promotor es la empresa que paga y organiza el estudio clínico.

El objetivo de este documento es proporcionarle la información sobre el estudio para ayudarle a decidir si desea participar en este estudio de investigación clínica. Nuestra intención es que usted reciba la información correcta y suficiente para que pueda decidir si acepta o no participar en este estudio. Lea con atención este documento y antes de decidir si desea participar, coméntelo con quien quiera, como por ejemplo, amigos, familiares o incluso con otros profesionales sanitarios. Si no está seguro de si ha entendido toda la información, no dude en hacer la preguntas necesarias al médico del estudio.

El nombre del médico del estudio (también llamado investigador) responsable de esta investigación clínica en este hospital y colegiado en el colegio de médicos, aparece en la primera página de este documento.

Su decisión de participar en este estudio es voluntaria. También cuenta con total libertad para abandonar el estudio en cualquier momento. Tanto si desea participar en este estudio como si no, la calidad de la asistencia médica que recibe no se verá afectada. Si decide no participar o si desea abandonar el estudio en cualquier momento, no perderá ninguna de las prestaciones sanitarias a las que tiene derecho. Si retira su consentimiento, los resultados de las muestras obtenidos antes de la retirada permanecerán en posesión del promotor del estudio

En el caso de que usted lo solicite, se le podrá facilitar información acerca de los resultado del estudio, en caso de que participe en él.

No percibirá ninguna recompensa económica o de otro tipo por las muestras y datos proporcionados y éstas no tendrán valor comercial.

1 TRATAMIENTO DEL ESTUDIO

Se le ha pedido que participe en un estudio de investigación clínica en el que se investiga cual es el tratamiento óptimo en fase aguda de la placa de ateroma móvil que le ha ocasionado el ictus, si el tratamiento quirúrgico o el tratamiento farmacológico. El tratamiento adecuado de dicha placa tiene como propósito disminuir el riesgo de que vuelva a padecer un nuevo ictus ocasionado por dicha placa móvil en la carótida.

Para ello, los pacientes que entren en este estudio serán distribuidos al azar en dos grupos: un grupo se someterá a cirugía para extraer la placa móvil carotídea, mientras que el en otro grupo de pacientes se administrará tratamiento farmacológico para disgregar dicha placa móvil.

El tratamiento farmacológico que se dará a ese subgrupo de pacientes es el tratamiento convencional recomendado por todas las guías de práctica clínica internacionales. Estos fármacos se consideran, en este grupo de pacientes, tratamiento de fase aguda y tratamiento de prevención secundaria de un nuevo ictus aterotrombótico.

El otro grupo de pacientes se someterá a una cirugía como tratamiento de fase aguda. Sin embargo, también recibirá dicho tratamiento farmacológico, pero en este caso tras la cirugía, únicamente como tratamiento de prevención secundaria.

Por lo tanto, pertenezca al grupo que pertenezca, siempre recibirá tratamiento preventivo de un nuevo ictus, tal y como recomiendan los principales organismos referentes en ictus.

Para el tratamiento quirúrgico de la placa móvil, pueden emplearse dos procedimientos equiparables entre sí en cuanto a eficacia y tasa de complicaciones se refiere. Estos son la Endarterectomía Carotídea o la Angioplastia Carotídea con colocación de un Stent.

Según los últimos datos, se estima que la recurrencia de ictus asociado a placas carotídeas móviles es de hasta el 33,3%. Sin embargo, las complicaciones graves derivadas de ambos procedimiento quirúrgicos solo en el 0,03% de los pacientes.

Por tanto, basándonos en estos datos, creemos que es seguro y ético someter a un subgrupo de pacientes a un procedimiento invasivo, como es una cirugía, ya que sus riesgos son mucho menores al riesgo inherente de las placas móviles.

2 OBJETIVO DE ESTE ESTUDIO CLÍNICO

El objetivo principal de este estudio clínico es determinar el riesgo de recurrencia temprana de ictus según el tratamiento recibido de fase aguda adjudicado (tratamiento quirúrgico o tratamiento farmacológico). Se ha visto que un potente predictor de recurrencia de nuevos ictus es la presencia y número de microémbolos cerebrales, por lo que también serán estudiados.
También se pretende estudiar el riesgo de recurrencia del ictus al mes, tres meses y un año del primer ictus que padeció a causa de estas placas móviles, según el tratamiento administrado en la fase aguda (tratamiento quirúrgico o tratamiento farmacológico).
Otro propósito de este estudio es establecer el grado de independencia que ha logrado alcanzar en los 3 meses posteriores al ictus, según el tratamiento administrado en la fase aguda (tratamiento quirúrgico o tratamiento farmacológico).

Para poder detectar estos posibles nuevos ictus, el médico le controlará muy de cerca. Será monitorizado y se le realizará una tomografía axial computerizada (TAC) del cerebro (una TAC es una técnica radiológica que utiliza una combinación de radiografía y un ordenador para obtener imágenes detalladas del interior del cuerpo que aportan información sobre los órganos, los huesos y la conformación de los tejidos) en caso de sospecha de nuevo ictus.

En este primer estudio en pacientes participarán un total de 206 pacientes en 23 hospitales de toda España.

1. 103 pacientes será incluidos en el grupo cuyo tratamiento de fase aguda es la cirugía (ya sea Endarterectomía Carotídea [CEA] o Angioplastia Carotídea con colocación de un Stent).
2. 103 pacientes será incluidos en el grupo cuyo tratamiento de fase aguda es el tratamiento farmacológico (que consta de tratamiento antiplaquetario, tratamiento con fármacos hipolipemiantes que disminuyen el colesterol y control de otros factores cardiovasculares)

Usted será aleatoriamente introducido en uno de estos dos grupos. Los dos grupos recibirán el mismo nivel de atención sanitaria por parte del médico.

Después de cada intervención, un equipo de expertos cualificados y con experiencia en neurología y ecografía, no vinculados al promotor, realizarán su seguimiento mediante 3 consultas distribuidas en los meses 1, 3 y 12 post-ictus.

3 PROCEDIMIENTOS DEL TRATAMIENTO

Si acepta participar en este estudio, se le comenzará a administrar en ese preciso instante un tratamiento farmacológico como tratamiento de fase aguda de las placas carotídeas móviles si pertenece a dicho grupo, o bien se someterá a tratamiento quirúrgico (CEA o Angioplastia Carotídea con colocación de un Stent) en los 3 días posteriores si pertenece al grupo tratado con cirugía.

En cuanto al tratamiento quirúrgico, en la mayoría de los pacientes de nuestro estudio, el método elegido será la colocación de stent, aunque también se permite la CEA si hay centros que prefieren uno u otro, o no pueden realizar la colocación de stent. Esto es así ya que ambos procedimientos son similares. Además, el stent es un método menos invasivo, más rápido y que no requiere anestesia general. Sin embargo, la elección del tratamiento para cada paciente debe ser individualizada.

La CEA consiste en la extirpación quirúrgica de la placa de ateroma móvil y parte de la pared de la , la capa carótida estenosada. Además, se puede implantar una vena o un injerto protésico para aumentar aún más la luz carotídea.

La CEA se puede realizar mediante dos técnicas quirúrgicas. Se escogerá entre una u otra a criterio del cirujano y según las características del paciente:

- Método clásico/convencional:

  Se realiza una incisión a lo largo de la cara medial del músculo esternocleidomastoideo (zona lateral del cuello) hasta llegar a las arterias carótidas. El flujo de la arteria carótida interna se dentendrá temporalmente para así poder abrirla longitudinalmente y llegar hasta la placa de ateroma. A continuación la placa se extraerá y se suturará la carótida y la incisión quirúrgica.

- Método de eversión:

  En este caso, la incisión en la carótida interna será oblicua, en la base de la bifurcación de la arteria carótida común. A continuación, se extrae la laca y se sutura la herida.

La Angioplastia Carotídea con colocación de un Stent es un procedimiento mínimamente invasivo. Para ello, se debe acceder a la arteria carótida a través de un catéter que se puede introducir a través de un acceso femoral, braquial/radial o carotídeo. Se realiza una angiografía intraoperatoria (prueba radiológica que permite visualizar los vasos de su cuerpo) para visualizar el trayecto del catéter. Este catéter llega hasta la placa carotídea donde se infla un globo (angioplastia) para abrir la luz del vaso y seguidamente colocar un stent (malla metálica tubular) para disminuir la posibilidad de que la arteria se estreche nuevamente.

En cuanto al grupo de pacientes cuyo tratamiento en fase aguda sea el tratamiento médico, se administrará el tratamiento del ictus aterotrombótico actualmente recomendado por la mayoría de las guías de práctica clínica. Este consiste en:

- Tratamiento antiplaquetario:
  - Ácido acetilsalicílico (AAS) 100 mg/día.
  - En ictus minor o ataque isquémico transitorio, el tratamiento antiplaquetario consiste en doble antiagregación plaquetaria, AAS 100 mg/día + Clopidogrel 75 mg/día, durante 21 días. Pasados los 21 días, se sigue la pauta habitual de AAS 100 mg/día.
- Tratamiento hipolipemiante con estatinas de alta potencia: Atorvastatina 80 mg/día.
- Control estricto de los factores de riesgo cardiovasculares clásicos:
  - Tratamiento antihipertensivo si la presión sistólica es ≥ 140 mmHg y/o la presión diastólica es ≥ 90 mmHg.
  - Tratamiento hipoglucemiante si el paciente es diabético.
  - Bajar de peso si hay sobrepeso u obesidad.
  - Dieta mediterránea (saludable, rica en potasio, baja en sal [<1,5 g/día] y grasas saturadas)
  - Aumentar la actividad física (ejercicio aeróbico de intensidad moderada durante 40 minutos 4 días a la semana o 150 minutos a la semana)
  - Deja de fumar.
  - Consumo moderado de alcohol.

4 ALTERNATIVAS MÉDICAS

El médico del estudio puede tratarle con el tratamiento farmacológico mencionado o mediante las cirugías recién expuestas ya que, por el momento no existen otros tratamientos aprobados que puedan ofrecerse a pacientes con su enfermedad.

Si lo desea puede comentarlo con el médico del estudio quien le dará más información al respecto. Si decide no participar en el estudio, el médico del estudio continuará con su tratamiento de referencia.

5 PROCEDIMIENTOS DEL ESTUDIO

Este estudio se realizará en varias partes y varias visitas de la siguiente manera:

- Un periodo de selección cuando sea admitido en la unidad de accidentes cerebrovasculares.
- Un periodo de administración del tratamiento en fase aguda, durante los 3 días posteriores su la inclusión en el estudio.
- Un periodo de seguimiento que incluye 4 evaluaciones posteriores al tratamiento: a las 72 horas, a los 1, 3 y 12 meses después del ictus.

A continuación se incluye una descripción detallada de los procedimientos y las pruebas realizadas durante los periodos de selección, tratamiento y seguimiento.

Selección para entrar en el estudio	- Obtención del consentimiento informado. Examen clínico que incluye lo siguiente: - Datos personales del paciente, edad y sexo. - Historia médica y medicación habitual del paciente. - Analítica de sangre. - Medición de las constantes vitales y evaluación del estado de salud general. - mRS previo. - Escala NIHSS. - ECG. - TAC (repetido también a las 24h) y angio-TAC. - Confirmación de criterios de selección.
Aleatorización en uno de los grupos de tratamiento de fase aguda	- Realización de una ecografía Doppler transcraneal para detección de microémbolos cerebrales a todos los pacientes. - Inicio de la administración del tratamiento farmacológico en el grupo de pacientes que hayan sido incluidos al azar en ese grupo.
Primeras 72 horas de ingreso	- Monitorización estrecha clínica (mediante la escala NIHSS) para detectar posibles recurrencias de ictus. - Se realizará un nuevo TAC si se sospecha un nuevo ictus. - Monitorización constante en la Unidad de Ictus de la frecuencia cardiaca, presión arterial, ECG, frecuencia respiratoria, saturación de oxígeno y volumen de orina. - En este periodo de tiempo, los pacientes incluidos en el grupo de cirugía se someterán a la CEA o bien a la colocación de un stent.
5º día tras la aleatorización	- Realización de una ecografía Doppler transcraneal para detección de microémbolos cerebrales a todos los pacientes.
Visitas en los meses 1, 3 y 12 post-ictus	- Determinación del grado de afectación cerebral residual a causa del ictus mediante la escala NIHSS. - Determinación del grado de discapacidad con la escala mRS. - Informar si en el periodo entre visitas se ha producido un nuevo episodio de ictus, AIT o muerte por evento cerebrovascular. - Determinar si ha habido eventos adversos asociados con la CEA o el stent. - Estudio ecográfico de troncos supraaórticos para valorar presencia o ausencia de MCP y potencial estenosis, en ambos brazos.

Usted podrá recibir el alta hospitalaria antes de la visita del día 30 y se le citará para que acuda al centro a las visitas de los meses 1, 3 y 12. Durante estas visitas, el médico del estudio le preguntará sobre los posibles cambios observados en su estado de salud desde la visita anterior, y también sobre los tratamientos actuales.

6 RIESGOS

6.1. Riesgos y efectos secundarios relacionados con los procedimientos del estudio

- **Muestras de sangre**: puede experimentar efectos secundarios de los análisis de sangre, como aparición de moratones, hemorragias leves o infección local (raras veces) en el lugar donde se ha realizado la extracción. El personal médico le preguntará si ha sufrido alguno de estos efectos secundarios.

- **Electrocardiograma**: Es una prueba indolora que detecta la actividad eléctrica del latido del corazón y se representa mediante un gráfico. Puede experimentar alguna molestia cuando le retiren los electrodos de la piel del pecho, los brazos y las piernas después de la prueba.

- **TAC:** La tomografía axial computerizada combina una serie de imágenes con radiografía tomadas desde diferentes ángulos alrededor del cuerpo y utiliza un procesamiento informático para crear imágenes transversales (cortes) de los huesos, vasos sanguíneos y tejidos blandos del cuerpo. Las imágenes de la TAC proporcionan información más detallada que la radiografía. Durante la TAC usted estará expuesto por un periodo breve de tiempo a la radiación ionizante. La cantidad de radiación es superior a la que estaría expuesto durante un radiografía normal ya que la TAC recoge información más detallada.

- **Ecografía Doppler**: es una prueba indolora y no invasiva que permite visualizar, en este caso, el estado de las arterias que irrigan su cerebro. Puede experimentar alguna molestia derivada de la presión que ejerce el ecógrafo sobre su cuello o cabeza.

- **Angiografía:** (solo para los pacientes con posibilidad de someterse a la colocación de un stent) un potente campo magnético, radiación ionizante y un ordenador producen imágenes detalladas de las arterias principales del cuerpo.
  Se puede administrar contraste a través de un pequeño catéter intravenoso (i.v.) colocado en una vena del brazo. Si el examen se realiza con contraste inyectado, pueden producirse reacciones alérgicas.

  El médico responsable de realizar estas pruebas le proporcionará toda la información y los procedimientos de preparación para estas pruebas.

6.2. Riesgos y efectos secundarios posiblemente relacionados con el tratamiento

Las intervenciones propuestas en este ensayo clínico son invasivas, especialmente el procedimiento CEA o colocación de un stent. Sin embargo, las complicaciones graves derivadas de esta cirugía (ictus incapacitante y muerte) ocurren solo en el 0,03% de los pacientes, mientras que la recurrencia del ictus asociado a placas carotídeas móviles es de hasta el 33,3%.

En cuanto a las complicaciones postoperatorias, no han encontrado diferencias significativas entre la CEA y la colocación de stent. Ambos tienen resultados similares a corto y largo plazo. Estas complicaciones son:

- Coágulos en el sitio de la intervención.
- Hemorragia cerebral.
- Accidente cerebrovascular incapacitante.
- Ataque isquémico transitorio.
- Convulsiones.
- Infarto de miocardio.
- Problemas derivados de la anestesia general: reacciones alérgicas, problemas respiratorios por edema de las vías respiratorias... etc.

- Dolor o malestar en el cuello y/o en el sitio de inserción del catéter.
- Contusión cervical.
- Disfagia.
- Infección en el sitio de incisión o inserción del catéter.
- Síndrome de hiperperfusión.
- Daño a los nervios, particularmente a los nervios hipogloso, vago, glosofaríngeo, trigémino y facial.
- Re-estenosis.
- Muerte.

Sin embargo, estos procedimientos serán realizados por cirujanos e intervencionistas expertos, por lo que se espera una baja tasa de complicaciones.

En cuanto al grupo que se someta a tratamiento farmacológico, los efectos adversos derivados del tratamiento con AAS, AAS + Clopidogrel y Atorvastatina, los 3 pilares más importante del tratamiento farmacológico de este ensayo clínico, se enumeran a continuación:

Los efectos adversos del AAS son:

- Alergia o hipersensibilidad.
- Riesgo de sangrado durante una cirugía menor (por ejemplo, extracción dental).
- Riesgo de sangrado gastrointestinal (melena, hematemesis, etc.) o úlceras/perforaciones, especialmente en:
  - Ancianos.
  - Pacientes con antecedentes de úlcera gástrica (especialmente si fueron complicadas).
  - Si se consume alcohol concomitantemente.
  - Si se toma junto con otros medicamentos que también aumentan el riesgo de hemorragia, ulceración y perforación gastrointestinal (incluso en pacientes sin antecedentes de patología gástrica), tales como: antiinflamatorios no esteroideos, otros antiagregantes plaquetarios, corticoides, antidepresivos del tipo inhibidor selectivo de la recaptación de serotonina, anticoagulantes… etc.

  Si aparece, se debe suspender el tratamiento.
- Mayor riesgo de daño renal persistente, especialmente si se combina con analgésicos.
- Se deben usar con precaución en pacientes con: hipersensibilidad a otros antiinflamatorios, asma, urticaria, rinitis, hipertensión arterial, pacientes con antecedentes de gastritis, úlcera gastroduodenal o sangrado gastrointestinal, mujeres con metrorragia o menorragia, insuficiencia renal, insuficiencia hepática leve o moderada o insuficiencia cardiaca.

Los efectos adversos de AAS + Clopidogrel son:

- Riesgo de hemorragia, el efecto adverso más frecuente: hemorragia gastrointestinal, hematomas cutáneos, epistaxis, hematuria, hemorragia subconjuntival, hemorragia intracraneal, hemorragia pulmonar o articular.
- En 1 de cada 10 personas se ha observado: diarrea, dolor abdominal, dispepsia o acidez estomacal.
- Otros efectos secundarios menos frecuentes (1 de cada 100 personas) son: dolor de cabeza, úlcera de estómago, náuseas y vómitos, náuseas, estreñimiento, picor, meteorismo, mareos y sensación de hormigueo.

- Los efectos adversos raros y muy raros son: vértigo, ictericia, fiebre, disnea, reacciones alérgicas/de hipersensibilidad, estomatitis, hipotensión, cambios en el sabor de los alimentos, tinnitus, etc.

Los efectos adversos de la atorvastatina son:

- Algunos efectos adversos frecuentes son: inflamación de las vías respiratorias altas, hiperglucemia, dolor de cabeza, náuseas y vómitos, diarrea, alteración de las transaminasas (hepatitis)...
- Efectos adversos menos frecuentes son: cambios de peso, mareos, cambios de sensibilidad, fatiga, reacción alérgica grave, reacción cutánea eritematosa y ampollosa, rabdomiólisis (dolor muscular, malestar general, fiebre, náuseas y vómitos, coluria, etc.), alteraciones de la visión, colestasis. y lesiones de tendones.
- Otros efectos adversos muy raros (afectan a 1/10.000 pacientes) son: hemorragia, síndrome lupus-like, pérdida de audición o ginecomastia.

7 BENEFICIOS PREVISTOS

Debido a que ambos tratamiento van dirigidos a eliminar la placa carotídea móviles, el riesgo de padecer un nuevo ictus ocasionado por dichas placas, el cual es muy alto, se reducirá considerablemente. Esto mejorará su pronóstico a largo plazo.

No obstante, es posible que no se beneficie directamente pero su participación podría beneficiar a futuros pacientes gracias a la valiosa información obtenida relacionada con el tratamiento del accidente cerebrovascular isquémico agudo.

8 INTERRUPCIÓN DEL ESTUDIO

Puede retirarse del estudio en cualquier momento y sin que esto tenga consecuencias en el tratamiento de referencia que recibe.

El médico del estudio también puede detener su participación en el estudio si lo considera necesario en las siguientes situaciones:

- Si la continuación con el tratamiento del estudio puede ser perjudicial para usted.
- Si precisa de un tratamiento que no está permitido según el protocolo del estudio.
- Si su seguridad está en peligro por no seguir las instrucciones del médico del estudio o del personal médico.

Si decide que ya no desea participar en el estudio, se le pedirá que acuda a una visita de seguimiento. La información recopilada durante su permanencia en el estudio y en esta visita de seguimiento todavía se podrá utilizar a menos que usted indique lo contrario.

Su decisión de dejar de participar en el estudio no se utilizará en su contra ni tendrá consecuencias en el tratamiento de referencia que recibe.

El promotor o las autoridades sanitarias también tienen derecho a finalizar de forma prematura el estudio en cualquier momento, si procede. En este caso, el investigador continuará con su seguimiento y usted recibirá los tratamientos disponibles. Usted también tendrá la posibilidad de participar en otra investigación clínica.

9 MUJERES EN EDAD DE PROCREAR

No se dispone de información suficiente sobre este tipo de intervenciones en mujeres embarazadas. Por ello, y este es el caso, en la mayoría de los estudios clínicos, no permiten participar a mujeres embarazas o en periodo de lactancia.

Si acepta participar en este estudio y si es una mujer en edad de procrear, el médico del estudio le realizará una prueba de embarazo en orina o suero (GCH) antes de que inicie su participación en el estudio. Si la prueba resulta negativa, el médico del estudio le pedirá que no planifique quedarse embarazada durante al menos 2 meses después de recibir su correspondiente tratamiento de fase aguda. En la visita de seguimiento del día 90 se le realizará una prueba de embarazo en orina o suero (GCH).

Entre los métodos anticonceptivos que pueden considerarse muy eficaces se incluyen los siguientes:

- dispositivo intrauterino;
- sistema de liberación hormonal intrauterino;
- oclusión tubárica bilateral;
- pareja vasectomizada;
- abstinencia sexual;

Las mujeres esterilizadas quirúrgicamente o posmenopáusicas durante más de 12 meses no se consideran mujeres en edad de procrear.

La combinación de condón masculino con capuchón, diafragma o esponjas con espermicidas (métodos de doble barrera) también se considera aceptable, pero no es muy eficaz.

Si en los 3 meses posteriores a la administración de cualquiera de los 2 tratamiento de fase aguda, cree que está embarazada o si tiene retrasos en el periodo, debe informar de inmediato al médico del estudio.

10 COSTES POSIBLES

No se le pagará ni recibirá ninguna compensación económica por participar en este estudio. Los costes adicionales causados por el estudio los cubrirá el promotor del estudio (Instituto de Salud Carlos III).

El tratamiento del estudio se le suministrará de forma gratuita y no tendrá que pagar las visitas al centro ni las pruebas que le realicen durante el estudio.

11 SEGURO

De conformidad con las directrices de las Buenas prácticas clínica y con las leyes nacionales vigentes en cada país participante, el promotor ha contratado un seguro de responsabilidad civil que cubre cualquier lesión que pueda resultar de su participación en esta investigación clínica.

Puede solicitar al médico del estudio la información relativa a las condiciones del seguro y las garantías.

Le informamos que es posible que su participación en este ensayo clínico pueda modificar las condiciones generales y particulares (cobertura) de sus pólizas de seguros (vida, salud, accidente, etc.). Por ello, le recomendamos que se ponga en contacto con su aseguradora para determinar si la participación en este estudio afectará a su actual póliza de seguro.

12 DERECHOS Y OBLIGACIONES

Su participación en este estudio es voluntaria y cuenta con total libertad para decidir si quiere participar o no. Tanto si desea participar en este estudio como si no, no cambiará la calidad de la asistencia médica que recibe ni los tratamientos a los que tiene derecho recibir.

Si decide participar en el estudio después de haber leído la información y de haberlo comentado con el médico del estudio, se le pedirá que firme el formulario de consentimiento al final de este documento. Podrá retirar el consentimiento y dejar de participar en el estudio en cualquier momento sin que tenga que justificarlo y sin consecuencias para usted ni para su asistencia médica. Si se da a conocer nueva información importante durante el estudio que pudiera afectar a su estado de salud o a su decisión de continuar participando en el estudio, será informado.

Durante el estudio o al final del estudio, tiene el derecho de acceder directamente o a través del médico del estudio a cualquier información relacionada con su salud. El médico del estudio puede proporcionarle los resultados de las pruebas iniciales así como la información sobre su salud recopilados durante su participación en el estudio.

Al final del estudio, y después del análisis de los datos del estudio de todos los pacientes, puede solicitar al médico del estudio que le proporcione los resultados del estudio.

Si acepta participar en este estudio, tendrá que hacer lo siguiente:

- Acudir a las citas. Si no puede acudir a una cita, póngase en contacto con el médico del estudio o con el personal médico lo antes posible para volver a programar la cita.
- Informar al médico del estudio o al personal médico de cualquier posible efecto secundario, de las visitas a otros médicos o de las hospitalizaciones.
- Durante su participación en el estudio, no participe en ninguna otra investigación sin la aprobación del médico del estudio.
- Si cambia de opinión sobre la participación en el estudio, notifíqueselo al médico del estudio o su personal.

13 INFORMACIÓN PARA EL MÉDICO DE CABECERA

Para su propia seguridad, se informará por escrito al médico de cabecera sobre su participación en este estudio, a menos que usted indique lo contrario. Aprobaciones reglamentarias

14 AUTORIZACIÓN DEL ESTUDIO

Este estudio ha sido evaluado y autorizado por las autoridades sanitarias nacionales, así como por los correspondientes comités éticos de investigación clínica. La misión de los comités éticos de investigación clínica es proteger a las personas que participan en una investigación clínica. El comité ético de investigación clínica garantiza que se respeten su derechos como paciente participante en una

investigación clínica, que la relación riesgo/beneficio todavía es favorable para los participantes y que el estudio es ético y pertinente desde el punto de vista científico. No debe considerar la aprobación por parte del comité ético de investigación clínica como un incentivo para participar en este estudio.

15 CONFIDENCIALIDAD/PROTECCIÓN DE LOS PACIENTESAUTORIZACIÓN DEL ESTUDIO

Sus datos personales recopilados durante la investigación clínica se tratarán de modo que los resultados de la investigación se analicen para cumplir el objetivo del estudio. De conformidad con las normativas vigentes, el promotor procesará los datos de forma legal, justa y transparente.

Tanto el Centro como el Promotor son responsables respectivamente de sus datos del estudio y su archivo en el hospital y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio estarán identificados mediante un código, de manera que no se incluya información que pueda identificarle, y sólo su médico del estudio/colaboradores podrá relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica. Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor, únicamente podrán acceder para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información)

El médico del estudio recopilará información sobre sus datos demográficos (incluido su origen étnico) e información sobre su salud. El archivo del estudio se mantendrá estrictamente confidencial de conformidad con el Reglamento (UE) 2016/679 del Parlamento europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD) en lo sucesivo denominado "Normativa vigente".

Sus datos personales codificados se pueden transferir a otros países o una organización internacional (i) en la que la Comisión europea ha adoptado una decisión adecuada reconociendo que garantizan un nivel adecuado de protección (ii) o en la que el promotor haya establecido las garantías adecuadas que le permitan tener derechos ejecutorios y efectivos de recurso jurídico. Los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las autoridades de protección de datos.
De conformidad con la Normativa vigente relativas al procesamiento de datos personales el promotor es el controlador responsable de procesar los datos recopilados en el transcurso del estudio. Usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio o al/a la Delegado/a de Protección de Datos del hospital del centro/institución. Le recordamos que los datos no se pueden eliminar, aunque deje de participar en el ensayo para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.

Sus datos se utilizarán de forma anónima para evaluar este estudio, pero también para evaluar otros estudios futuros. Sus datos pueden ser útiles para responder a cuestiones de eficacia y seguridad sobre el producto

probado, para solicitar una autorización comercial o para una publicación sobre el producto del estudio. No obstante, su nombre no se mencionará nunca en el informe del estudio ni en las publicaciones.

El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 25 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si usted hubiera otorgado su consentimiento para ello y si así lo permite la ley y requisitos éticos aplicables.

La provisión de sus datos personales se basa en el consentimiento que se obtendrá cuando usted firme este formulario. Si no indica lo contrario, sus datos personales se utilizarán para realizar más investigaciones científicas sobre su enfermedad (siempre de conformidad con las leyes y normativas vigentes).

Al firmar el formulario de consentimiento, acepta que sus datos del estudio codificados se utilizarán para los objetivos descritos en este documento de información y que sus datos se enviarán a los centros y a las autoridades sanitarias anteriormente mencionados.

Si tiene alguna pregunta sobre el manejo de sus datos en este estudio, póngase primero en contacto con su Investigador. Si es necesario, esta persona puede enviar su solicitud a las personas responsables de la protección de datos en la sede del Promotor o en el hospital en el que se realiza el ensayo clínico.

Datos de contacto del Responsable de Protección de Datos: placaviltrial@data.com

16 INFORMACIÓN ADICIONAL

Le instamos a que formule todas las preguntas que desee en cualquier momento durante el estudio. Si tiene preguntas relacionadas con la investigación clínica, sus procedimientos, sus riesgos y beneficios o sobre otros tratamientos, póngase en contacto con el médico del estudio responsable del estudio (consulte los datos de contacto en la primera página).

Una descripción de este ensayo clínico estará disponible en http://reec.aemps.es como exige la ley española.

12. Written informed consent, Spanish version

FORMULARIO DE CONSENTIMIENTO INFORMADO

PARA EL PACIENTE

Título del estudio: ENSAYO CLÍNICO MULTICÉNTRICO ALEATORIZADO SOBRE LA RECURRENCIA PRECOZ DE ICTUS ASOCIADO A PLACAS CAROTÍDEAS MÓVILES SEGÚN TRATAMIENTO EN FASE AGUDA (The PLACA VIL trial)

Sponsor: Instituto de Salud Carlos III, C/ Sinesio Delgado, nº 4, CP 28029 – Madrid, España.

Paciente: *(nombre)*..... *(fecha de nacimiento)* |__|__| |__|__| |__|__|
Día Mes Año

Investigador: Nombre: Dr. Joaquín Serena

Centro n.º: ES06. H. U. de Girona Dr. Trueta

Dirección: Avinguda de França, S/N

Ciudad/Código postal: Girona, 17007

Teléfono 24 horas: _____

Confirmo que se me ha informado acerca del estudio y que he recibido una copia de la "Información para el paciente" (versión 1 con fecha 25/01/2023).

He sido informado acerca de los objetivos, los procedimientos, los posibles riesgos y los beneficios del estudio. He tenido tiempo suficiente para leer la hoja de información para el paciente y hacer preguntas sobre los detalles adicionales acerca del estudio. He recibido respuestas a todas mis preguntas.

Entiendo que el médico del estudio me facilitará de forma oportuna cualquier nueva información significativa que aparezca en cualquier momento, durante o después de mi participación en este estudio que pueda afectar a mi salud o bienestar.

Entiendo que mi participación es voluntaria y que puedo retirarme del estudio en cualquier momento sin dar ninguna razón, y sin que esto afecte a mi atención médica.

Me comprometo a seguir las instrucciones del médico del estudio, así como a informarle de inmediato si considero que he sufrido un problema o síntoma imprevisto.
Consiento libremente a participar en este estudio, tal como se describe en el documento de información para el paciente.

Mi consentimiento no exime de sus responsabilidades a los organizadores de la investigación y mantengo todos mis derechos garantizados por la ley.

Entiendo asimismo que recibiré una copia firmada y fechada de este formulario deconsentimiento.

Entiendo que puedo terminar mi participación en el estudio en cualquier momento. Tengo derecho a pedir que se eliminen mis datos recopilados, en cuyo caso deberé informar por escrito al médico del estudio comunicándole mi decisión.

Doy mi autorización para el tratamiento informatizado de mis datos personales según lo dispuesto en el Reglamento general de protección de datos (UE 2016/679) del 25 de mayo del 2018 y en las leyes nacionales.

Sección para el paciente ***El paciente debe completar todos los datos.***
Basándome en la información anterior, acepto voluntariamente participar en este estudio de investigación, tal como se describe en la hoja de información para el paciente que he recibido. Nombre y apellidos del paciente: _____ Firma del paciente: Fecha de la firma_____ **O** Confirmo el consentimiento otorgado por mis familiares y confirmo que acepto voluntariamente continuar participando en este estudio de investigación, tal como se describe en la hoja de información para el paciente que he recibido. Nombre y apellidos del paciente: _____ Firma del paciente: Fecha de la firma:

Sección para el investigador
El médico del estudio debe completar todos los datos.

Declaro que he explicado la información relacionada con esta investigación clínica al paciente y que le he proporcionado una copia del documento de información para el paciente y del formulario de consentimiento firmado y fechado. Acepto responder todas las preguntas que puedan surgir en el futuro y declaro no haber influido en el paciente a la hora de tomar su decisión.

Nombre del investigador que ha entregado el consentimiento al paciente:

_____

Firma del investigador: Fecha de la firma_____

Hecho en 2 ejemplares originales: una copia original para el paciente y otra para el centro.

13. Application for Withdrawal of Consent to Study, Spanish version

FORMULARIO DE REVOCACION DEL CONSENTIMIENTO

Yo, _____ (nombre y apellidos), con DNI/NIF _____, revoco el consentimiento informado previamente firmado para participar en el estudio *"The PLACA VIL Trial"*.

Firma de revocación:

En _____, a _____ de _____ del año_____.

14. Case Report Form, Spanish version

Ensayo Clínico PLACA VIL (PLAca CArotídea móVIL)

Investigador: _____

Centro: _____

DATOS DE IDENTIFICACIÓN

Número de Identificación (ID): _____

DATOS GENERALES
Fecha nacimiento: ____/____/_____

Sexo (☐Varón / ☐Mujer)

ANTECEDENTES Y ENF. CONCOMITANTES

Índice de Masa Corporal

☐ Bajo-Normopeso (<25 kg/m²)

☐ Sobrepeso (25-30 kg/m²)

☐ Obeso (≥30 kg/m²)

Tabaquismo

☐ No

☐ Sí

Hipertensión arterial

☐ No

☐ Sí

Diabetes mellitus

☐ No

☐ Sí

Dislipemia

☐ No

☐ Sí

Claudicación Intermitente

☐ No

☐ Sí

Infarto de Miocardio previo

☐ No

☐ Sí

Ictus previo

☐ No

☐ Sí

Puntuación mRS previa

☐ ≤ 2

☐ > 2

Tratamiento previo de base

☐ Antiagregantes

☐ Anticoagulantes

☐ Estatinas

☐ Antihipertensivos

☐ Antidiabéticos (orales o insulina)

☐ Otros tratamientos

☐ Ninguno

☐ Desconocido

Estado carotídeo previo

☐ Estenosis carotídea conocida

- ☐ Área de estenosis: _____ %
- ☐ Velocidad del flujo sanguíneo carotídeo: _____
- ☐ Tipo de flujo: _____

☐ Placa Carotídea Móvil → Subtipo: _____

☐ Normal

DATOS SOBRE EL ICTUS ACTUAL

Fecha de inicio ___ / ___ / ___
Hora de inicio ___:___h

Ictus al despertar: ☐ No ☐ Sí

Inicio conocido de los síntomas: ☐ No ☐ Sí

Activación Código Ictus

☐ No

☐ Sí

Duración de los síntomas

☐ < 1 hora

☐ 1 - 24 horas

☐ >24 horas

Tratamiento Revascularizador en fase aguda:

☐ Fibrinolisis sistémica (rt-PA).

☐ Trombectomía mecánica

EXAMEN FISICO NEUROLOGICO AL INGRESO

Puntuación total NIHSS al ingreso: _____

NEUROIMAGEN / P. COMPLEMENTARIAS

NEURO-RADIOLOGÍA (Examen definitivo)
(Si se han realizado varias exploraciones, registrar la que muestre la máxima lesión, o en su caso, la transformación hemorrágica del infarto).

☐ TC-C simple

☐ RM-C multimodal

☐ TC multimodal

Resultado del examen definitivo

☐ Normal

☐ Patológico

- ☐ Infarto territorial
- ☐ Infarto lacunar
- ☐ Infarto de territorio frontera
- ☐ Hemorragia intraparenquimatosa
- ☐ Hemorragia intraventricular
- ☐ Hemorragia subaracnoidea

ESTUDIO VASCULAR

Estudio vascular

- ☐ Ultrasonografía
- ☐ Angio-RM
- ☐ Angio-TC

Neurosonología urgente (<24 h)

- ☐ Estudio TSA
- ☐ Estudio intracraneal

Estudio vascular transcraneal:

- ☐ Estenosis intracraneal sintomática.
- ☐ Estenosis intracraneal asintomática.
- ☐ Oclusión arteria intracraneal
- ☐ Microangiopatía
- ☐ Microémbolos
  - ☐ No
  - ☐ Sí → Número: _____
- ☐ Normal

Estudio vascular carotídeo:

- ☐ Normal
- ☐ Patológico
  - ☐ Carótida homolateral
    - ☐ Estenosis < 50%
    - ☐ Estenosis 50-69%
    - ☐ Estenosis 70-99%
    - ☐ Oclusión
    - ☐ Placa móvil
      - ☐ Tipo Jellyfish
      - ☐ Tipo Streaming-band
      - ☐ Tipo Trombo Carotídeo Flotante
      - ☐ Tipo Úlcera Fluctuante
      - ☐ Tipo Snake fang
  - ☐ Carótida contralateral
    - ☐ Estenosis < 50%
    - ☐ Estenosis 50-69%
    - ☐ Estenosis 70-99%
    - ☐ Oclusión

DIAGNÓSTICO ETIOLÓGICO

- ☐ Aterotrombótico o Aterosclerosis de gran vaso
  - ☐ Probable - Estenosis > 50%
  - ☐ Posible - Estenosis ≤ 50%
- ☐ Cardioembólico
  - ☐ Probable
  - ☐ Posible
- ☐ Lacunar o enfermedad de pequeño vaso
- ☐ Otras causas infrecuentes
  - ☐ Disección
  - ☐ Otras
- ☐ Indeterminado
- ☐ Criptogénico
  - ☐ Por dos causas coexistentes
  - ☐ Por estudio insuficiente

VISITAS DE SEGUIMIENTO

VISITA 1ER MES POST-ICTUS

Puntuación total NIHSS: _____

Recurrencia de ictus en este periodo de tiempo

- ☐ Sí
- ☐ No

Estudio vascular carotídeo:

- ☐ Normal
- ☐ Patológico
  - ☐ Carótida homolateral
    - ☐ Estenosis < 50%
    - ☐ Estenosis 50-69%
    - ☐ Estenosis 70-99%
    - ☐ Oclusión
    - ☐ Placa móvil
      - ☐ Tipo Jellyfish
      - ☐ Tipo Streaming-band
      - ☐ Tipo Trombo Carotídeo Flotante
      - ☐ Tipo Úlcera Fluctuante
      - ☐ Tipo Snake fang
  - ☐ Carótida contralateral
    - ☐ Estenosis < 50%
    - ☐ Estenosis 50-69%
    - ☐ Estenosis 70-99%
    - ☐ Oclusión

VISITA 3ER MES POST-ICTUS

Puntuación total NIHSS: _____

Puntuación mRS post-ictus

- ☐ ≤ 2
- ☐ > 2

Recurrencia de ictus en este periodo de tiempo

- ☐ Sí
- ☐ No

Estudio vascular carotídeo:

- ☐ Normal
- ☐ Patológico
  - ☐ Carótida homolateral
    - ☐ Estenosis < 50%
    - ☐ Estenosis 50-69%
    - ☐ Estenosis 70-99%
    - ☐ Oclusión
    - ☐ Placa móvil
      - ☐ Tipo Jellyfish
      - ☐ Tipo Streaming-band
      - ☐ Tipo Trombo Carotídeo Flotante
      - ☐ Tipo Úlcera Fluctuante
      - ☐ Tipo Snake fang
  - ☐ Carótida contralateral
    - ☐ Estenosis < 50%
    - ☐ Estenosis 50-69%
    - ☐ Estenosis 70-99%
    - ☐ Oclusión

VISITA 1ER AÑO POST-ICTUS

Puntuación total NIHSS: _____

Recurrencia de ictus en este periodo de tiempo

- ☐ Sí
- ☐ No

Estudio vascular carotídeo:

- ☐ Normal
- ☐ Patológico
  - ☐ Carótida homolateral
    - ☐ Estenosis < 50%
    - ☐ Estenosis 50-69%
    - ☐ Estenosis 70-99%
    - ☐ Oclusión
    - ☐ Placa móvil
      - ☐ Tipo Jellyfish
      - ☐ Tipo Streaming-band
      - ☐ Tipo Trombo Carotídeo Flotante
      - ☐ Tipo Úlcera Fluctuante
      - ☐ Tipo Snake fang
  - ☐ Carótida contralateral
    - ☐ Estenosis < 50%
    - ☐ Estenosis 50-69%
    - ☐ Estenosis 70-99%
    - ☐ Oclusión