



FIRST LONG-TERM EVALUATION
OF THE RISK OF RECURRENCE AND
PROGNOSIS OF CRYPTOGENIC
STROKE IN PATIENTS WITH AND
WITHOUT PATENT FORAMEN
OVALE

FINAL DEGREE PROJECT

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1. ABBREVIATIONS

ASA: Atrial septum aneurism

CEIC: Ethical and Clinical Investigation Committee

CN: Chiari network

CODICIA: Comunicación Derecha-Izquierda estudio Cooperativo en el Ictus Agudo

CRF: Case report form

CS: Cryptogenic stroke

c-TCD: Contrast-enhanced transcranial Doppler

c-TEE: Contrast transesophageal echocardiography

c-TTE: Contrast-enhanced transthoracic echocardiography

EV: Eustachian valve

GC: General coordinator

HJT: Hospital Dr. Josep Trueta

m-RLSh: Massive right to left shunt

mRS: Modified Rankin Scale

NNT: Number needed to treat

Non-m-RLSh: Non-massive right to left shunt

PFO: Patent foramen ovale

RCT: Randomized clinical trials

RLSh: Right to left shunt

RoPE: Risk of Paradoxical Embolism

TIA: Transitory Ischemic Attack

SSS-TOAST: Trial of Org 10172 in Acute Stroke Treatment

VM: Valsalva maneuver

2. ABSTRACT

Background: Between 30% and 40% of ischemic strokes remain unclassified after an exhaustive etiologic study, being defined as cryptogenic strokes (CS). The presence of a patent foramen ovale (PFO) has been strongly associated with CS, especially in younger patients. The best treatment for PFO-related stroke has not been fully established. 6 randomized clinical trials (RCT) comparing PFO closure with medical treatment have been published but the obtained results were inconclusive, with short follow-up times (<6 years) and a narrow cost-benefit balance with high NNT. Furthermore, when PFO is considered as causal, patients have a better short-term prognosis (modified Rankin Scale) than in CS in general what increases even more the doubts about their management. No studies analyzing long-term PFO-related stroke recurrence risk and prognosis have been conducted. The cohort of the CODICIA study offers the opportunity to make a first long-term evaluation of this group of patients.

Objective: The aim of this study is to make an extension of the CODICIA study (2000-2005) (1), a prospective cohort that analyzed the short-term risk of CS recurrence in patients with and without PFO treated with medical therapy. Our objective is to analyze retrospectively the same sample with a mean follow-up time of approximately 15 years, obtaining long-term data about the risk of stroke recurrence and prognosis of these patients.

Design: The study will be a multicenter observational retrospective cohort. 16 hospitals will participate with the University Hospital Dr. Josep Trueta (HJT) as the coordinator center.

Participants: Patients previously included in the CODICIA study. People older than 18 years who suffered a CS (cerebral infarct or TIA) more than 10 years ago treated with medical therapy (antiplatelet/anticoagulation or both). All the analysis will be repeated in the group of patients younger than 55 years.

Methods: We will record any vascular event in case report forms (CRF). The data will be obtained mainly by phone contact and/or medical histories if available. Some data are already registered in the database of the original CODICIA study. For the statistical analysis we will use χ^2 test and Exact Fisher test for qualitative variables and t-Student or Mann-Whitney for quantitative variables. A confidence interval of 95% will be assumed and a $p < 0,05$ will be considered statistically significant. The association between the independent and dependent variables will be adjusted by means of logistic-regression analysis in order to avoid possible confounding factors.

Keywords: cryptogenic stroke, patent foramen ovale, right to left shunt

3. INTRODUCTION

3.1. Stroke overview

3.1.1. Definition and classification

The World Health Organization defines stroke as a clinical syndrome with a fast development of focal (sometimes global) neurologic signs and symptoms, lasting more than 24 hours or leading to death, due to a disturbance of the cerebral function that is caused by a vascular etiology (2).

It can be classified in (3):

- **Ischemic stroke (80-85%):** it is caused by a lack of blood supply (4,5):
 - **Global ischemia:** it affects to the whole encephalon, so the main affection is in frontier territories, the ones that belong to the terminal arterial irrigation (4).
 - **Focal ischemia:** it affects to a part of the encephalon, so its signs and symptoms will be the ones related to the specific affected part. In this group, we must distinguish transitory ischemic attack (TIA), defined as a cerebral or retinal ischemia, which symptoms last less than one hour, and without evidence of lesion in neuroimaging tests; and cerebral infarct, which symptoms persist more than 1 hour and/or neuroimaging tests show an affection that gives evidence of tissue necrosis (4).

- **Hemorrhagic stroke (15-20%):** it is caused by a rupture of an artery or a vein, producing a blood extravasation:
 - **Intracerebral hemorrhage:** the blood extravasation goes to the cerebral parenchyma.
 - **Subarachnoid hemorrhage:** the blood extravasation goes to the subarachnoid space (4,5).

3.1.2. Epidemiology and risk factors

Worldwide, stroke is a frequent disease. Its incidence varies across countries (6,7) and it is around 180-200 cases per 100.000 patient-years (8). It is growing because of the aging population (9). After myocardial infarction it is the second single most common cause of death, causing 6.7 million deaths each year (10). It is, also, the first cause of disability (5), and the second cause of dementia.

In Spain, stroke is also very prevalent, with high mortality, and the main cause of disability disease. It is the first mortality cause in women and the second one in men. However, the

improvement in detection and control of the risk factors, and in the diagnosis and treatment of its acute phase is decreasing the mortality. Stroke is, also in Spain, the first cause of disability (4).

Regarding at the problem with a socioeconomic perspective, between 3% and 4% of the health expenditure in high-income countries are caused by stroke (3).

Several variables have been identified as risk factors. They can be divided into modifiable, potentially modifiable and not modifiable. The ones that have been well documented are (11):

- **Modifiable:** hypertension, atrial fibrillation, hypercholesterolemia, smoking, asymptomatic carotid stenosis, obesity, sedentarism, sickle-cell disease, substitutive hormonal therapy.
- **Potentially modifiable:** diabetes.
- **Not modifiable:** age, sex (male increases slightly the risk only at old ages of life (12)), hereditary factors, race/ethnic group, sociocultural level.

The main risk factor in stroke is advanced age followed by hypertension (4,8). The association between risk factors increases the risk much more than the addition of each risk factor individually (13).

3.2. Ischemic stroke

3.2.1. Etiopathology

The most extended stroke etiological classification is the one developed for the Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST) (4,14). The distribution of the different ischemic stroke-subtypes can be observed in **Figure 1**. Their specific classification is described in **Annex 1**.

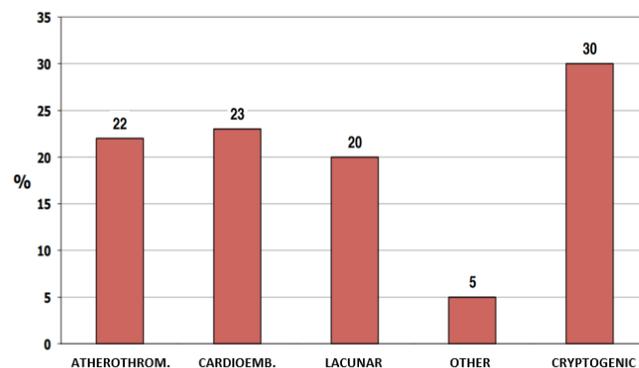


Figure 1. Distribution of ischemic stroke depending on its etiopathology (adapted from 15).

- **Atherothrombotic infarct**

The origin is an atheroma plaque in an artery, which can occlude progressively the vessel, break causing a thrombosis in situ (exceptional), or break and embolize to a distal artery of the brain stopping blood flow and causing the stroke.

- **Cardioembolic infarct**

It is caused by an embolism that comes from a cardiological source like atrial fibrillation or hypokinetic areas after an acute myocardial infarction.

- **Lacunar infarct**

Small infarct which diameter measures less than 1,5 cm in the territory of a cerebral perforating artery caused by lipohyalinosis, a wall thickening with a resultant reduction and occlusion of the luminal diameter.

- **Stroke of other determined etiology**

Include infrequent and specific causes of stroke. They can be systemic pathologies (connective tissue pathologies, infections, neoplasms, myeloproliferative syndromes, metabolic or coagulation disorders) or other diseases like: arterial dissections, fibromuscular dysplasia, aneurism, arteriovenous malformation, cerebral venous thrombosis, vasculitis, migraine, etc.

- **Stroke of undetermined etiology:**

This particular stroke subtype includes:

- Undetermined etiology due to an incomplete etiological study.
- Undetermined etiology due to the coexistence of two potential causes of stroke (e.g. severe carotid stenosis in a patient with atrial fibrillation).
- Cryptogenic stroke, that we describe below.

3.2.2. Etiological study

After acute phase management of a stroke, even if it has been a TIA, an etiological study must be performed to classify the stroke in one of the previous categories. Currently, the diagnosis of ischemic stroke etiology is determined from a combination of patient history, clinical assessment, cerebrovascular imaging, and cardiovascular evaluation (16).

3.2.3. Secondary prevention (11,17–19)

The importance of making an accurate etiological study with a precise classification of the subtype of ischemic stroke relies on the individualization of the best secondary prevention therapy. If an etiology can be determined, there exist some specific recommendations for each one of the different etiologies supported by strong levels of evidence (17). It will focus on an individualized control of the risk factors of stroke and recurrence of stroke to decrease the recurrence episodes.

A summary of these recommendations would consist in a control of the hyperglycemia and hypertension, and the addition of general primary prevention measures like avoiding obesity, stopping smoking, having a moderate intake of alcohol, making physical exercise and having a proper diet. These recommendations would be applicable for the secondary prevention of any stroke episode (11).

Then the recommendations vary between the stroke etiology. For atherothrombotic, lacunar, and undetermined etiology strokes high dose statins and antiplatelet therapy are recommended. In the other hand, cardioembolic strokes must be usually treated with an anticoagulation therapy, if the etiology is nonvalvular. If it is valvular, the recommendations depend on the specific etiology between antiplatelet and anticoagulation therapy (17).

3.3. Cryptogenic stroke

3.3.1. Concept and definition

As mentioned above, a stroke can be classified inside a group called “stroke of undetermined etiology”. There are three possible scenarios (20):

- A complete etiological study has not been performed.
- Conflicting causes are detected, so the stroke remains unclassified.
- A complete etiological study has been performed, but no specific cause has been detected, classifying the stroke into the category of “cryptogenic”.

Cryptogenic stroke (CS) is defined as a territorial brain infarction not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac, and serologic evaluation (14).

3.3.2. Epidemiology

According to SSS-TOAST classification criteria, the proportion of strokes and TIAs that remain unclassified after exhaustive investigation, so get into the definition of CS make up 30% to 40% of the total. This proportion is even higher in young patients (<55 years) (21).

3.3.3. Potential causes

There are three big groups of diseases that have been described as potential causes of CS:

- **Arterial diseases**

An atherosclerosis disease too mild to be classified into the category of an atherothrombotic stroke etiology could break or erupt causing a stroke via atheroembolism. These vulnerable plaques could not be detected by the usual techniques because they grow initially out of the artery, so the lumen is well-preserved. Other potential transitory or spontaneously reversible arterial causes could be vasculitis, arterial dissection, vasospasm/reversible vasoconstriction syndrome, and migraine-induced stroke (22,23).

- **Cardiac diseases**

There are cardiac diseases that can be potential cardioembolic sources that are transitory or have a spontaneous resolution. If the etiological study is performed after the time it has returned to normalcy it will not be detected classifying the stroke as cryptogenic. Some examples are paroxysmal atrial fibrillation and takotsubo syndrome (that is a vasospasm/reversible vasoconstriction syndrome). The presence of a patent foramen ovale, has been strongly associated, mainly because of the possibility of the production of paradoxical embolisms, as will be explained afterwards.

- **Blood diseases**

Gastrointestinal and lung cancer (specially adenocarcinoma) can secrete substances with procoagulant activity such as cysteine proteases, tissue factor, and sialic acid moieties of mucin resulting in the activation of factors X and VII (24). Also, aggressive antitumor therapy could increase the risk of thrombosis (25).

Something that must be understood, even more considering the objectives of this project, is that if in this context a patent foramen ovale (PFO) is detected, and it is thought that it is implicated in the etiology of the before named CS, it should be classified as PFO-related stroke instead of cryptogenic. It is reasonable taking into account that the evidence about how a secondary prevention treatment must be performed is different, so the management of the

patient too (26). The situations when we will consider that a PFO has a causative role in a CS context will be explained afterwards.

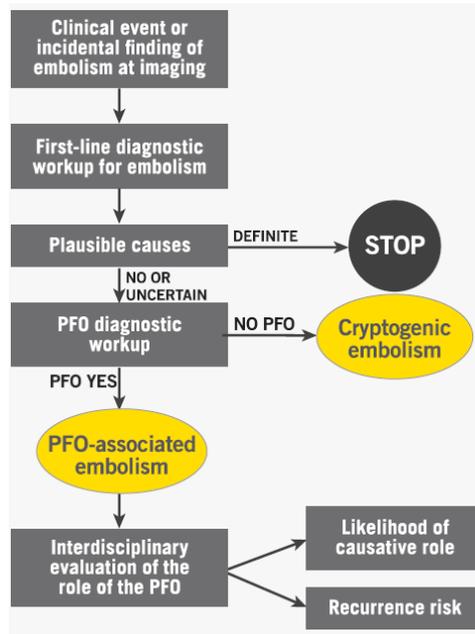


Figure 2. Summary of the diagnostic process of PFO-related stroke: since stroke condition is diagnosed and it is likely to have an embolic mechanism, until a PFO is detected and it is likely to have a causative role (26).

3.4. Patent foramen ovale

3.4.1. Basic concepts about cardiac cycle

Our cells need oxygen to survive and to perform their metabolism and functions. This oxygen is transported in oxygenated blood. The vessels that allow the pass of oxygen through their walls to nourish them are systemic capillaries. After that, the deoxygenated blood must be transported until an organ that oxygenates it again, repeating the cycle. These organs are lungs, since birth, and maternal placenta, during fetal life. Pulmonary capillaries are the ones that will take the oxygen from the pulmonary alveolus into the blood. Blood will be transported inside vessels (arteries and veins), and impulsed by the heart. The movement of it will depend on the presence of a pressure gradient, which means that blood will always move from a place with a higher pressure to a place with a lower pressure. That circuit is schematized in **figure 3**.

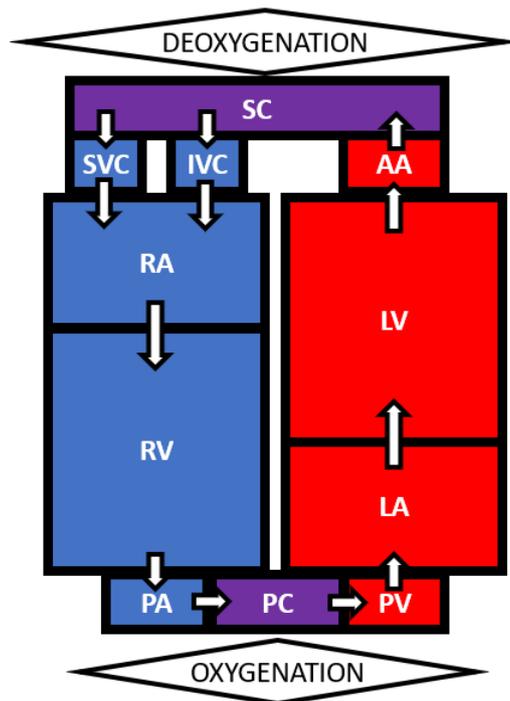


Figure 3. Cardiac cycle after birth. AA: aorta artery; LA: left atrium; LV: left ventricle; IVC: inferior vena cava; PC: pulmonary capillaries; PA: pulmonary artery; PV: pulmonary veins; RA: right atrium; RV: right ventricle; SVC: superior vena cava; SC: systemic capillaries. Red represents oxygenated blood, blue represents deoxygenated blood, purple represents the place where the transition (oxygenation or deoxygenation) is being performed.

The heart impulses the blood with the combination of two phases:

- **Ventricular systole:** LV and RV muscular fibers make a contraction, increasing their pressure, so increasing the differential pressure between them and the next artery in the circuit, and impulsing blood along AA and PA, respectively.
- **Ventricular diastole:** LV and RV muscular fibers make a relaxation, decreasing their pressure, and permitting the entrance of blood that comes from LA and RA, respectively, inside them.

3.4.2. Anatomy and physiology

During cardiovascular embryological development, there are two septa between the two atriums, septum primum and septum secundum, and two foramens, ostium primum and ostium secundum. These two foramens create a channel that communicates the two atriums through the two septums. This channel is called foramen ovale (27).

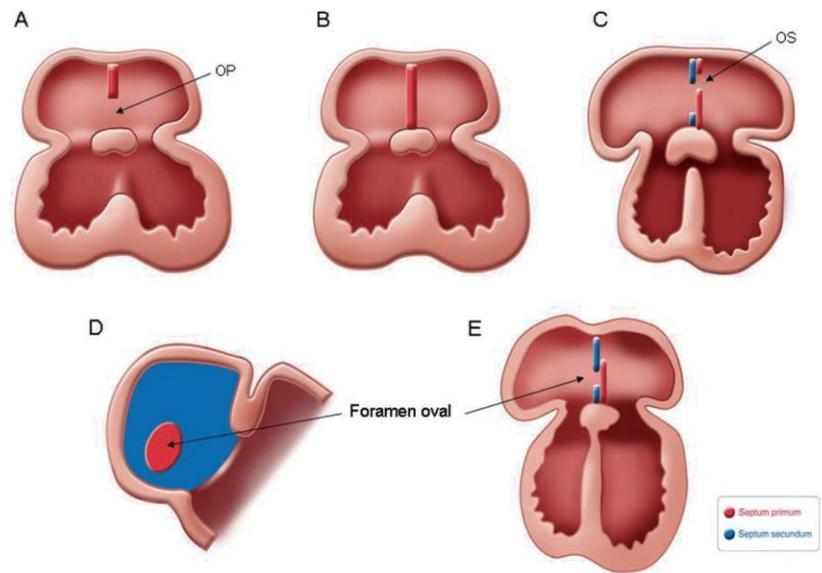


Figure 4. Embryological development of foramen ovale. The red stripes represent septum primum and the blue stripes represent septum secundum. OP is ostium (foramen) primum and OS is ostium (secundum). The development of the interatrial sept can be observed as well as the channel created by the two foramens, communicating the two atriums (27).

During fetal period, the foramen ovale is the normal pathway of blood from right to left cardiac cavities, avoiding the pulmonary bed and being oxygenated when it passes through the placenta (28). This right to left way of the blood is due to differential pressures between pulmonary circulation and systemic circulation of the fetus. The lungs are collapsed because of the presence of amniotic fluid, so pulmonary resistances and pressure are high. In the other hand, systemic pressure is low because of the low resistances of the placenta. These situations produce a pressure gradient that impulses blood from right atrium to left atrium in a physiological right to left shunt (RLSh).

Immediately after birth, the ejection of the amniotic fluid, the pulmonary expansion and the oxygenation produce a vasodilatation of pulmonary vessels, decreasing the pressure of right circulation. Furthermore, the occlusion of the umbilical cord and the loss of the placenta highly increase systemic resistances. This situation inverts the pressure gradient: the situation has changed from a state of gradient from right to left, to a pressure gradient from left to right. The new differential pressure compresses the two septa, septum primum and septum secundum, sealing functionally the foramen ovale (29). The permanent closure by the adhesion of the two septa typically occurs in the first three months. However, there is a large proportion of people whom foramen oval persists open, leading on a patent foramen ovale (28).

3.4.3. Definition and epidemiology

Patent foramen ovale (PFO) is, so, a channel that communicates the two atriums, which existence has been physiological during fetal life, but that has persisted because of an inadequate sealing after birth (28). Its size has been ranged from 1 mm to 19 mm (mean 4,9 mm). This size increases with age (30). That communication, in specific conditions, can produce a RLSH, a movement of blood from the right cardiac cavities to the left ones. In autopsy studies, PFO is found in 27% of normal hearts. This proportion is obtained with an overall view. However, it varies depending on age. In the first three decades of life the prevalence is 34%, decreasing to 24% between the 4th and the 8th decades, and reaching a 20% during the 9th and 10th decades (30) (Figure 6).

These proportions are obtained with autopsy studies in patients without cardiac disease, the ones that use what we could consider as a gold-standard test. If the used test to determine this prevalence is a contrast transesophageal echocardiography this proportion decreases until 10%-26%. In the other hand, if the used test is a contrast-enhanced transcranial Doppler (c-TCD), it is obtained a 25%-35%, much more closer to the one obtained in autopsy studies (28).

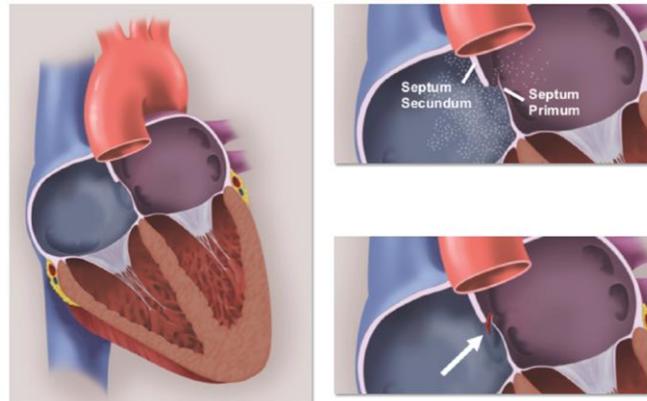


Figure 5. Normal appearing atrial septum (left). Agitated saline study demonstrating RLSH through the PFO (upper right) and blood clot passing through the PFO becoming a paradoxical embolism (lower right) (31).

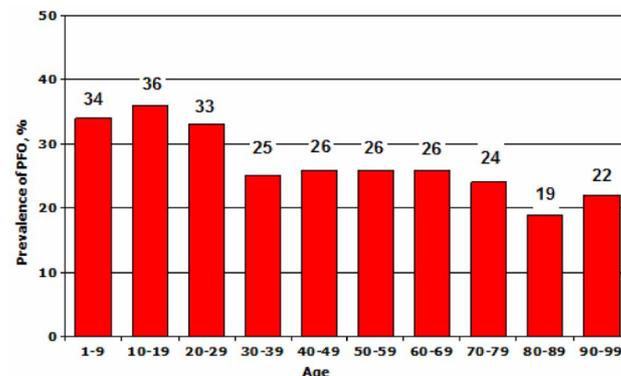


Figure 6. Prevalence of PFO in autopsy studies in subjects without heart disease (28).

3.4.4. Association between stroke and PFO

PFO is present in patients younger than 55 years with a CS in between 40-50% of the cases, if detected by echocardiography or c-TCD. It shows a strong association considering that the studies that performed this analysis only found a PFO in 10-15% of healthy subjects (32,33).

Author	Year	Unselected patients	Age range (mean)	N° of Patients with stroke	% PFO patients c-TEE c-TCD	RLSh quantification	% PFO in cryptogenic stroke	Controls n (% PFO)
Lechat et al. [2]	1988	No	<55 (36)	60	40* n.p.	No	54	100 (10)
Webster et al. [3]	1988	No	<44 (36.1)	40	50* n.p.	No	56	40 (15)
Pearson et al. [18]	1991	No	17-84 (59)	79	11.3 n.p.	No	11.3	No
Hausmann et al. [16]	1992	No	18-84 (52+/-10)	103	26.1 n.p.	No	31.6	116 (21.6)
de Belder et a. [17]	1992	No	16-84	104	21.1 n.p.	No	26	94 (3.2)
Cabanes et al. [6]	1993	No	<55 (40.2)	100	43 n.p.	No	56.3	50 (18)
Ranoux et al. [5]	1993	No	<55 (38.6)	68	47 n.p.	No	57	No
Schminke et al. [12]	1995	Yes	18-87 (57)	100	37 39	Yes	55	No
Molins et al. [10]	1996	No	< 45	58	19* 34.5	No	42.8	No
Di Tullio et al. [4]	1992	No	(61.4+/-15.7)	146	18* n.p.	No	42	No
Klötzsch et al. [8]	1994	No	(61.4+/-15.7)	111	45 46	No	77.5	No
Anzola et al. [11]	1995	No	18-75 (45+/-14)	72	52.5 47.5	No	n.d.	No
Job et al. [9]	1994	No	< 45	74	51.3 47.3	Yes	66	63 (43)
Jones et al. [13]	1994	Yes	(66±13)	220	16 n.p.	No	20	202 (15)
Petty et al. [14]	1997	No	(60±3)	116	32 n.p.	No	40	No
Homma et al. [20]	1994	No	n.d.	74	31 n.p.	Yes	44	No
Nighoghossian et al. [15]	1996	No	23-59 (47+/-8.9)	118	25.4 n.p.	No	34	No
Serena et al. [21]	1998	Yes	33-85 (64.8+/-12)	208	37.2† 33.5	Yes	56.6	100 (28.2)

Figure 7. Summary of observational studies that established the relevance of PFO/RLSh in CS, including prevalence of PFO by echocardiography and/or c-TCD and main characteristics of studies, in CS and healthy controls (28).

If the subject has a known cause of stroke, according to SSS-TOAST classification, the prevalence of PFO is around 20% and, if it is cryptogenic but there are risk factors of stroke (migraine, mitral valve prolapse, use of contraceptive agents) it grows until 40% (32).

This shows a clear association between CS and PFO in subjects under 55 years. Furthermore, this decreasing of the prevalence that can be observed as more identifiable is a stroke etiology is giving even more arguments to affirm that there are etiopathological mechanisms that lead PFO to be a potential cause of a stroke.

CS and the presence of PFO are also associated in patients older than 55 years. However, the association is weaker than in younger patients (26). This could be explained because of a lack of other stroke risk factors in younger patients, what could lead into a higher probability of an etiological role of the PFO in this group.

3.4.5. Potential mechanisms

- **Paradoxical embolism**

The most described potential way of a PFO to lead into a CS condition is paradoxical embolism (28).

An embolism is defined as a particle originated in one vessel that moves following the blood circulation towards another part of the body (34). If this embolism is a thrombus, it is called thromboembolism. With that definition, some vessel occlusive syndromes could be expected if we knew in what vessel has the thromboembolism been originated. Some examples are cardioembolic stroke (the embolic source is the heart so following the circulation a cerebral artery is occluded) or pulmonary thromboembolism (the origin is usually a deep venous thrombosis in the legs, so the thrombus travels along the veins until right cardiac cavities, and then makes an occlusion in the pulmonary circulation).

Considering what has just been said, if there was an unexpected communication between venous and systemic circulation, or between right and left cardiac cavities, a shunt inside them would be created, allowing the pass of potential thrombus through them and generating unexpected occlusive syndromes. This is, in fact, the definition of a paradoxical embolism, the one that is due to a pass of an embolus from the venous to the arterial circulation, producing systemic clinical manifestations (35).

Knowing that, it is reasonable to affirm that a venous thrombus could move through the PFO, from the right atrium to the left atrium, if a RLSH was generated, and then move from left atrium to left ventricle, to the systemic circulation, and finally, to cerebral arteries producing the stroke. This affirmation makes even more sense if we consider that an embolus of just 1mm is sufficient to occlude a large cortical arterial branch, and an embolus of 3 mm is sufficient to occlude the middle cerebral artery, and the mean size of the PFO is of 4,9mm (28).

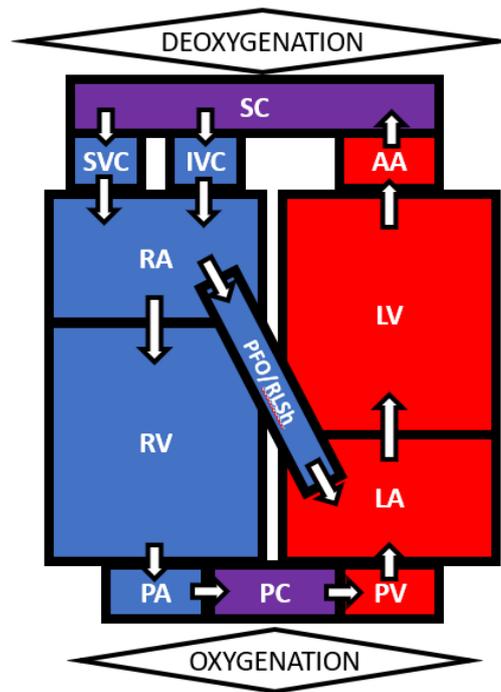


Figure 8. Cardiac cycle with the addition of the PFO, in a situation when a RLSH is happening. AA: aorta artery; LA: left atrium; LV: left ventricle; IVC: inferior vena cava; PC: pulmonary capillaries; PA: pulmonary artery; PV: pulmonary veins; RA: right atrium; RV: right ventricle; SVC: superior vena cava; SC: systemic capillaries. Red represents oxygenated blood, blue represents deoxygenated blood, purple represents the place where the transition (oxygenation or deoxygenation) is being performed.

Attending at the fact that a RLSH between the two atriums is mandatory for a thrombus to move across the PFO, the pressure inside the right atrium must increase to lead into a differential pressure that permits it. This situation happens when the subject makes an expiratory effort against a closed airway, what is known as Valsalva maneuver (VM) (36). Just immediately after the VM, the venous return increases, increasing also the flux of blood inside the right atrium and its pressure inside producing after that the RLSH.

Another possibility is the presence of a chronic pulmonary hypertension, so a chronic RLSH. However, it has been seen in usual clinical practice that in basal conditions (without a VM) the existence of a RLSH without the need of a pulmonary hypertension is possible. This can be explained because of a physiological inversion of the pressure gradient between the two atriums at the last phase of ventricular diastole. At this phase there can exist an auricular contraction that increases more the pressure in the right atrium than it does in the left one, producing the RLSH.

In addition, there are some structural alterations that have been associated to PFO that may explain, partially, its association with stroke:

- **Atrial septum aneurism (ASA):** excursion of the interatrial septum into either atrial cavity of >15 mm (37). The presence of PFO and its magnitude depend directly on its association with ASA. While ASA is present in only 1% in healthy population (38), it can be found in 30%-40% of massive right to left shunts (m-RLSh) (28).
- **Prothrombotic states:** although most studies have failed in finding an association, recently, factor V Leiden and prothrombin G20210A mutations have been found to have a higher prevalence in people with CS associated to PFO than in the healthy population (39).
- **Eustachian valve (EV):** it is a valve with a semicircular shape that faces anterior-inferior surface that joints inferior vena cava to the atrial septum (28). It is present in 48% of CS (in echocardiographic studies) and determines that the blood flow of the inferior cava goes directly to the interatrial septum and to the PFO if it is present. (40).
- **Chiari network (CN):** it consists in a large EV with a network-like appearance (28). It is associated with PFO in 83% of cases (41) and produces the same hemodynamic alteration that we have just commented.

The role of EV and CN could remain onto a higher pressure inside the right atrium during ventricular diastole, being able to produce the RLSh even without the presence of a pulmonary hypertension or a VM. This is because during diastole, the atriums make a contraction increasing their pressure inside. Applied in the right atrium, that generates a reflux from itself to superior and inferior vena cava. If there is something acting as an antireflux valve, like EV or CN, which hinder the movement from the right atrium to inferior vena cava, this pressure inside the right atrium will increase even more and, parallelly, also the probability of a RLSh.

- **Other potential mechanisms**

Other potential mechanisms have been proposed:

- Thrombus formation inside the PFO.
- Atrial fibrillation: subjects with PFO may have an altered atrial electrical substrate that leded into supraventricular arrhythmias (42).

3.4.6. Clinical suspicion and severity of PFO-related stroke

Inside a context where a stroke has been finally classified as cryptogenic, a paradoxical embolism, so the presence and role of a PFO in its physiopathology, should be suspected in the following situations (26,28):

- Simultaneous or previous existence of pulmonary emboli.
- Documentation of a venous source of embolism around the time of the stroke, like thrombophlebitis.
- Absence of evidence of a venous source, but recent major surgery, immobilization, or extended car or airplane journey.
- Electrocardiogram or echocardiography showing pulmonary hypertension.
- VM or straining activities around the time of the stroke.
- High RoPE Score punctuation (explained afterwards) (43).

Obstructive sleep apnea and inherited thrombophilia still need more research for its association with PFO-related stroke.

Neither the localization or type of cerebral infarct pattern in neuroimaging tests have been fully associated with PFO-related stroke. The infarcts that are usually considered as embolic are the cortical ones, but subcortical infarcts can also have an embolic origin (26). However, in patients with a m-RLSh, bilateral topography is more frequent as it is a smaller volume of the infarct. This could lead into the fact that patients with m-RLSh also have less severe stroke at admission and a better modified Rankin Scale (mRS) score at discharge, not having so many neurologic sequels than in other types of stroke (1).

3.4.7. Diagnosis of PFO

If there is a clinical suspicion of PFO-related stroke, it should be searched with diagnostic tests. These tests are all characterized by the use of contrasted echography. The differences remain on where is the echograph being applied.

The use of contrast will usually consist in a mixture of sterile saline solution and air agitated between two syringes and connected by a three-way stopcock. This mixture and agitation generate air micro-bubbles that can be detected by echography and/or c-TCD. After that, it is injected into the right antecubital vein (28).

All images will be obtained breathing normally and during a VM, what will be standardized by asking the subjects to blow into a manometer until 50 to 60 mmHg. VM will make the RLSH if a PFO is present. However, in case that RLSH exists even without its realization, making the VM will increase the magnitude of the RLSH.

There are three main tests that can detect a PFO:

- **Contrast-enhanced transthoracic echocardiography (c-TTE):**

The echograph is located on thoracic wall giving an image of the heart structure and cavities. For the detection of PFO, it is 88% sensitive and 82% specific (26).

Before examination with contrast, some other potential sources should also be evaluated like the size of the left atrium, presence of atrial spontaneous contrast and/or thrombus, atrial septum aneurysm or interatrial septum defects (28).

- **Contrast transesophageal echocardiography (c-TEE):**

The echograph is introduced inside the esophagus giving images about the anatomical structures around it, including the heart in its horizontal and longitudinal views. It is the diagnostic test of reference because it permits the direct visualization of the size of the PFO and the demonstration of other cardiac sources of embolism like the presence of septal aneurysm and atherosclerosis of the aortic arch (28).

It will be considered that there is a RLSH if the microbubbles of the injected contrast are detected in the left atrium. If they are detected within 3 cardiac cycles of their appearance in the right atrium, a PFO will be diagnosed. If they appear after 3 cardiac cycles, it will usually be attributed to an intrapulmonary shunt (28). Its sensitivity for the detection of PFO is 89%, probably because of an inability of some patients for performing an adequate VM (26).

Depending on the number of microbubbles detected in the left atrium, the PFO can be classified by its size (44):

- **Small:** <10 microbubbles
- **Moderate:** too many microbubbles to be counted but without being as echogenic as in the right atrium.
- **Severe:** in a part of the left atrium there is at least the same echogenic intensity as in the right atrium.

It has some rare complications like bleeding, aspiration or esophageal perforation. As other limitations, swallowing difficulties are common in patients with stroke, what hinders the realization of VM; and the need of sedation, that can be problematic in patients with stroke (26).

- **Contrast-enhanced transcranial Doppler (c-TCD):**

The echograph is placed on the temporal window, and images about cerebral arteries are obtained. In this case, while a monitorization of both middle cerebral arteries is being

performed, the contrast will be injected. First breathing normally. After that, in the last one or two seconds of a five to seven seconds VM(28).

The number of Doppler signals detected in the middle cerebral arteries will be directly proportional to the number of microbubbles there, so also to the magnitude of the RLSH. Its sensitivity is 94% and its specificity is 92% (26). This is because there are other possible causes of a RLSH apart from PFO, like an arteriovenous pulmonary fistula. However, there are specific profiles that permit differentiate these two entities with c-TCD (45).

In this case, the size classification is (44):

- **Normal:** 0 signals.
- **Small:** <10 signals.
- **Large:** >10 signals.
- **Shower:** >25 microbubbles.
- **Curtain:** uncountable microbubbles.

Large, shower and curtain patterns are considered as a m-RLSh (28).

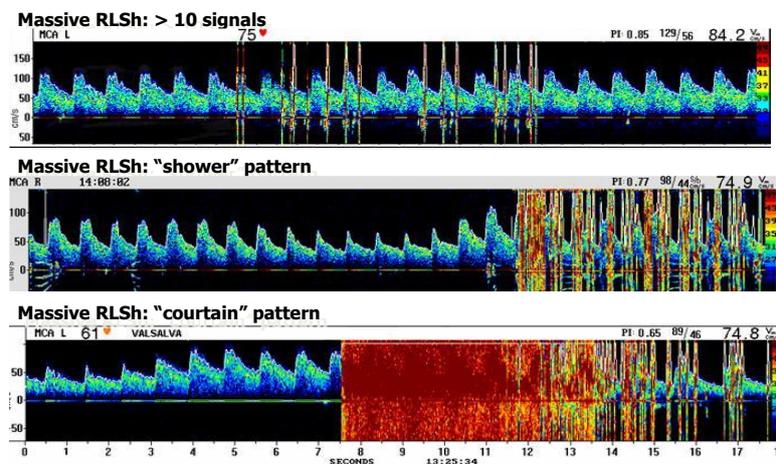


Figure 9. Main patterns of RLSH by c-TCD (28).

Again, an inability for performing an adequate VM may be a limitation for this diagnostic test.

The recommendations of the last *European position paper on the management of patients with patent foramen ovale* recommend the following algorithm for the diagnosis of PFO (26):

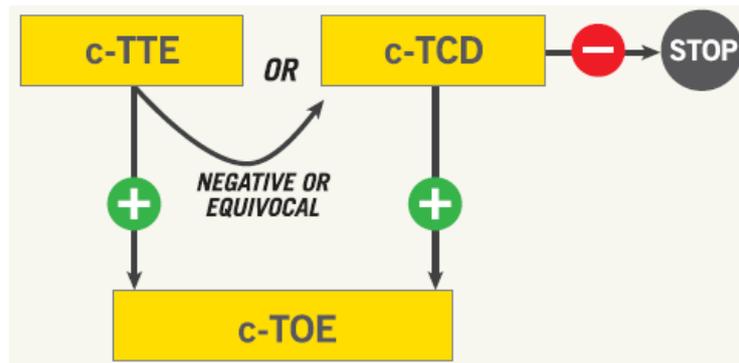


Figure 10. Algorithm for the diagnosis of PFO. + = detection of a RLSH and - = absence of detection of a RLSH (26).

3.4.8. Risk of recurrence of PFO-related stroke

The annual recurrence of stroke in this group of patients, treated with a medical secondary prevention treatment (antiplatelet or anticoagulation) varies from 0% to 5,8%. It is a low rate of recurrence if it is compared to the one belonging to TIA or stroke as a whole, which varies from 0% to 14%. This wide variability can be explained because of the heterogeneity of phenotypes how these subjects can be stratified (26).

A stroke recurrence could happen because of a PFO-related mechanism, like the one that can be suspected for the first stroke episode or, of course, due to a non-PFO mediated mechanism, like the general stroke risk factors that can affect to the general population who do not have a PFO.

Several variables have been studied as potential recurrence risk factors specifically for PFO-related stroke. The ones that have a statistically significant association, increasing the risk of recurrence are:

- Age older than 65 years (46).
- Size of the PFO by TEE and magnitude of the RLSH by c-TCD (47).
- Presence of an ASA associated to the PFO (48).
- Ischemic stroke as inclusion event, not TIA (1).
- Coagulation disorders (26).
- D-Dimer > 1000 at admission (49).
- Having a “high risk PFO” instead of a “low risk PFO” (47).
- Low RoPE Score punctuation (explained below) (43).

The terms “high risk PFO” and “low risk PFO” are concepts that were used by De Castro et Al. in the year 2000 (47) which difference was found to have a clinical relevance in terms of PFO-related stroke recurrence risk:

- **High risk PFO:** mobile atrial septum and RLSH at rest.
- **Low risk PFO:** the RLSH is present only with the performance of the VM.

Risk of Paradoxical Embolism (RoPE) Score:

RoPE study (2013) was a collaborative study which combined the results of all the cohort studies performed until then, generating a unified database with 3400 patients which analysis (pooled data analysis) allowed the generation of a score (RoPE Score). RoPE Score represents an attempt to assign a causal relationship probability to individual PFOs in the setting of stroke of unknown cause. It is the only tool that exists nowadays to determine if the presence of a PFO in a patient with CS is stroke-related or incidental. Furthermore, it also calculates the probability of stroke recurrence after 2 years (43).

RoPE Score may be useful guiding management decisions. However, no large external validation studies have been performed, and internal validation studies have rated its quality of evidence as moderate at best. For that reason, it should always be used in conjunction with other parameters (26).

Risk factors (0 to 5 points)		POINT SCORE	Cryptogenic Stroke (N=3023)			
No hypertension	(1)		Probability of stroke related PFO	Stroke recurrence risk after 2 years		
No diabetes	(1)					
No previous stroke/TIA	(1)					
No smoking	(1)					
Cortical infarct	(1)					
Age (0 to 5 points)					0-3	20%
<30 years	(5)				4	12%
30 to 39 years	(4)				5	7%
40 to 49 years	(3)				6	8%
50 to 59 years	(2)	7			6%	
60 to 69 years	(1)	8	6%			
>70 years	(0)	9-10	2%			
			88%			

*Note: 95% CI for PFO prevalence and attributable fraction based on normal approximation to the binomial distribution.

Figure 11. RoPE Score. It also shows the probability of a PFO of being stroke-related and the risk of stroke recurrence after two years matched to each RoPE Score punctuation (adapted from 43).

3.4.9. Secondary prevention treatments

At the moment, there is a general agreement of not making any primary prevention treatment against the risk of having a first stroke episode in patients with a PFO (28). However, it is not the case when a stroke episode has happened, and a secondary prevention treatment must be performed.

As mentioned above, all strokes should undergo a secondary prevention treatment, and there are specific recommendations supported by strong levels of evidence for each etiology, even for CS in general. These recommendations can not be made for PFO-related stroke, as there is not enough evidence of what is the best option for preventing recurrences (17,26). Three main treatment lines are being used (26):

- **Antiplatelet therapy:** with acetylsalicylic acid
- **Anticoagulation therapy:** with antivitamin K (acenocoumarol)
- **PFO occlusion**

Until recently (2017), non-randomized studies performed in order to determinate the best option showed heterogeneous and non-conclusive results. Recent meta-analyses suggest a superiority of anticoagulation over antiplatelet in terms of prevention of stroke recurrence with a very low-quality evidence. However, patients treated with anticoagulation also have much more risk of bleeding complications (both extracranial and intracranial hemorrhages) than the ones treated with antiplatelet. For that reason, the low potential benefit of anticoagulation over antiplatelet could not be enough favorable considering a decreasing of the risk-benefit balance (26). No data exist about the risk-benefit of direct oral anticoagulants. If they were studied maybe the situation could change decreasing the risk and being more recommendable.

PFO occlusion is based on the elimination of the conduit for a paradoxical embolism (50). A device is introduced percutaneously and moved along vessels until the heart, where the PFO is occluded. After that, antiplatelet and antibiotic prophylaxis treatment for endocarditis should be given to the patient in order to prevent possible complications (26). Primary technical success reaches proportions near to 100% (51,52), and a complete closure is obtained in one year in between 93-96% of the patients (53). Unfortunately, there exist complications. The incidence of serious periprocedural ones is around 2,5% (54). The most frequent one is device thrombosis, followed by device embolism and, anecdotally, atrial wall erosions. The need for cardiac surgery and long-term mortality are less than one in 1.000. Minor complications happen in between 1-1,7% of times. After the procedure, atrial fibrillation is the most frequent undesirable event (26).

In 2012, 3 randomized clinical trials (RCT) that compared PFO closure with medical treatment alone were carried out (55–57). Two of them used AMPLATZER™ PFO Occluder; the other one used STARFlex® Septal Closure System, which is no longer manufactured. Their results did not show a superiority of PFO occlusion against medical treatment in the prevention of stroke recurrence episodes. In 2017, 3 more RCT were performed, with the difference that they demonstrated a superiority of PFO closure with statistical significance in patients with a high risk PFO. However, numbers needed to treat (NNT) were very high (31,58,59). All of them had short follow-up mean times (<6 years). For that reason, the following conclusions that can be obtained must be interpreted as short term secondary prevention information:

- AMPLATZER™ device has lower rates of stroke recurrences and lower rates of complications (including major bleeding, atrial fibrillation and vascular complications) than STARFlex® device.
- There is a nonsignificant trend toward reduced combined adverse events (ischemic cerebral infarct and TIA) with closure if patients treated with both devices are included in the analysis.
- If only AMPLATZER™ device treated patients are analyzed, PFO closure has lower rates of recurrences than medical therapy alone with statistical significance.
- NNT for preventing one recurrence episode, or one death, with closure are very high.
- Several complications, like vascular sequelae or atrial fibrillation are found in higher proportions in the closure group than in the medical therapy alone group.
- Attending at the high cost of one procedure (around 8700\$ (60)) and the high NNT, a lot of money must be spent in order to prevent only one recurrence episode.

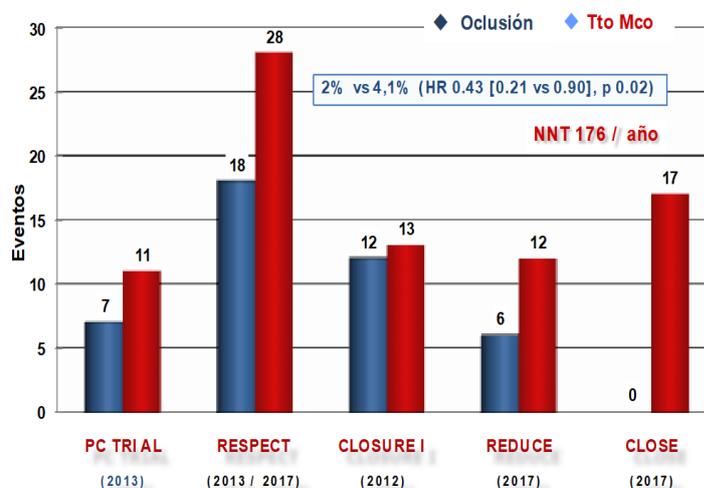


Figure 12. Summary of main results (stroke recurrences) of RCT comparing PFO closure (red) with best medical treatment (blue) (adapted from 31,55–59).

In this situation, it is recommended to start the management with an accurate evaluation of:

- The probability that the PFO has a relevant role in the observed clinical picture (RoPE Score)
- The likelihood that the observed clinical event will recur (high risk markers of stroke recurrence).

If after a clinical, anatomical and imaging evaluation both are high the percutaneous closure must be proposed to the patient, who should be proactive in the decision (26).

In conclusion, although there are some provisional recommendations based in short-term evidence about what is the best option for these patients, long-term studies are needed in order to have more accurate information about the true risk of recurrence of PFO-related stroke and establish the best treatment options in each case.

3.5. CODICIA study

CODICIA (Comunicación Derecha-Izquierda estudio Cooperativo en el Ictus Agudo) study is a Spanish multicenter study that analyzed the short-term risk of CS recurrence in patients with and without PFO treated with medical therapy. It was developed between 2000 and 2005 and published online on the 25th of September 2008 (1).

486 patients (47,1% <55 years) with CS were included and followed during a mean time of 729 ± 410,8 days (around 2 years). It included patients without RLSH through PFO (38,9%), with a non-massive RLSH (non-m-RLSh) (19,9%) and with a m-RLSh (41,2%). The prevalence of both types of RLSH was higher in younger patients than in the whole group. Patients with a m-RLSh had a less severe stroke at admission and a better mRS score at discharge. The following results were obtained:

	Whole group (n=486)	Younger group (<55 years) (n=229)
Total stroke recurrence	5,8%	3,4%
Without RLSH	6,3%	4,5%
With a non-m-RLSh	6,2%	2,3%
With a m-RLSh	5,0%	3,4%

Table 1. Results of the CODICIA study. Representation of the proportions of recurred patients stratified by RLSH magnitude and age (adapted from (1)).

The aim of this study is to make an extension of the CODICIA study. Our objective is to analyze retrospectively the same sample with a mean follow-up time of approximately 15 years, obtaining long-term data about the risk of stroke recurrence and prognosis of these patients.

4. JUSTIFICATION

Stroke is a devastating disease for patients and their families, one of the most important causes of mortality and the most frequent cause of disability worldwide and in Spain. From 30% to 40% of them are cryptogenic. However, there is a strong association of CS with the presence of a PFO, especially in young patients.

Although there exist some well-established recommendations about how to make an appropriate secondary prevention treatment for ischemic stroke in general, even for CS in general, the best treatment option in CS associated to PFO is not well established. Recent RCT suggest that PFO closure is the best option in selected high-risk patients, with a mean follow up of 4,8 years (31,58,59), a narrow cost-benefit balance and a high NNT.

No studies analyzing long-term PFO-related stroke recurrence risk have been conducted. The cohort of the CODICIA study offers an opportunity to obtain relevant long-term recurrence data in patients suffering CS with/without PFO treated with medical therapy after a mean follow-up of 15 years, which would be important to clarify the most appropriate treatment in the particular group of patients with CS associated to PFO. Furthermore, an evaluation of long-term impact on the quality of life (mRS) of PFO-related stroke could help even more in that decision.

5. HYPOTHESIS

Based on the revised bibliography and the daily clinical experience obtained by neurovascular expert neurologists, our **main hypothesis** is:

1. Long-term risk of recurrence in patients with CS associated to PFO and treated with medical therapy is low, similar to the short-term risk of recurrence observed in the original CODICIA study. These recurrences represent mainly cerebral infarcts, in a higher proportion than TIA.

Our **secondary hypothesis** are:

2. Long-term risk of recurrence of CS treated with medical therapy is lower in patients with PFO than in CS without PFO. RLSH magnitude through PFO increases this risk of recurrence.
3. Long-term prognosis (mRS) of patients who had a CS treated with medical therapy is better in patients with RLSH/PFO than in patients without RLSH/PFO.

6. OBJECTIVES

In order to confirm our hypothesis, our **main objective** is:

1. To determinate the long-term risk of stroke recurrence in patients with CS with/without PFO treated with medical therapy and the proportions of TIA and cerebral infarcts in these recurrences.

Our **secondary objectives** are:

2. To analyze how the presence and magnitude of a RLSH through PFO affects to the long-term risk of stroke recurrence in patients with CS treated with medical therapy.
3. To determinate the influence of the presence and magnitude of a RLSH through PFO in the long-term prognosis of CS treated with medical therapy in terms of quality of life and mortality (mRS).

7. SUBJECTS AND METHODS

7.1. Study design

The study will be a multicenter observational retrospective cohort. 16 hospitals will participate (**Annex 2**) with the University Hospital Dr. Josep Trueta (HJT) as the coordinator center.

7.2. Study population

Patients previously included in the CODICIA study (1) between 2000 and 2005. The global population of this study is people older than 18 years who suffered a CS (cerebral infarct or TIA) more than 10 years ago, treated with medical therapy (antiplatelet/anticoagulation or both) since the index stroke. All the patients included in the sample, in order to represent this population, will accomplish this definition and, additionally, all the analysis will be repeated in the group of patients younger than 55 years.

7.3. Subjects selection

7.3.1. Inclusion criteria

- Age > 18 years.
- To have suffered an ischemic stroke or TIA between March 2000 and October 2005.
- To have the diagnosis of CS according to the SSS-TOAST criteria after an exhaustive etiological study.
- To have been included in the original CODICIA study, which had the previous criteria as its own inclusion criteria.
- To have a follow-up time of ≥ 10 years after the first stroke episode.
- A follow-up time of ≤ 10 years will be accepted only if the patient has died, directly or indirectly, due to a stroke recurrence.

7.3.2. Exclusion criteria

- Patients who have been treated with PFO occlusion devices to prevent recurrent stroke.
- Patients who did not receive any medical treatment (antiplatelet/anticoagulation).
- Patients who do not give informed consent.
- Non-localized patients.

7.4. Sampling

7.4.1. Sample size

In a bilateral sample with a significance level (α) of 5% and a statistical power of 80% and foreseeing a moderate risk and a 20% of losses we will need 235 patients. The computations were carried out with the Prof. Marc Sáez's software based on based on the pwr package of the free statistical environment R (version 3.5.1).

7.4.2. Sample collection

We will try to contact with the patients using the contact data that we have in the original CODICIA data bank (names, surnames, telephone contact and address). Each hospital will be responsible of the contact of its own patients. For the patients who can not be directly contacted, their information will be obtained from their current computerized medical history. Case report form (CRF) have been designed for the collection of the needed data (**Annex 3**). Each hospital will fill the CRF related to their own patients.

All the collected CRF will be revised by the same investigator who will determine attending at the mentioned criteria what patients will be included in the definitive sample and analyzed. The parts of the CRF that contains the relevant information about the inclusion/exclusion of a patient are:

- **Follow-up time:** calculated by the difference of the date of contact (the date of the telephonic interview or the date when we find the last veracious information disponible in the medical history) with the index stroke episode.
- **Death and cause of the death:** to link it or not with a stroke recurrence.
- **Received treatment:** to know if PFO closure has been performed or if they did not receive any medical treatment.

In order to link the cause of the death of a patient with ≤ 10 years of follow-up with a stroke recurrence or not and, consequently, including him/her in the sample, a committee of 3 neurovascular experts will be formed to discuss and arrive to a consensus.

7.5. Variables

7.5.1. Main objective

Stroke recurrence: it is a dichotomous nominal qualitative variable. It will be expressed by **yes** (presence of recurrence) or **not** (absence of recurrence). Any vascular event will be recorded in the CRF by phone contact or medical history.

Type of stroke recurrence: dichotomous categorial qualitative variable. It will be expressed by **cerebral infarct, TIA, or systemic emboli** (exceptional).

7.5.2. Secondary objectives

- **Independent variable:**

RLSh magnitude: ordinal qualitative variable. It was already determined and quantified at rest and during VM in the original CODICIA study by c-TCD according to the specific procedure mentioned in the introduction (see **3.4.7. Diagnosis of PFO**). It will be expressed by:

- **No RLSH:** no microbubbles detected by c-TCD
- **Non-massive RLSH:** <25 microbubbles detected by c-TCD
- **Massive RLSH:** shower or curtain pattern detected by c-TCD

- **Dependent variables:**

Stroke recurrence: dichotomous nominal qualitative variable. Expressed by **yes** or **not**. Any vascular event will be recorded in the CRF by phone contact or medical history.

Quality of life: it is a discrete quantitative variable. It is measured with the degrees of mRS (0 to 6). We will categorize it as an ordinal qualitative variable expressed by **independent** (0-2) and **dependent/dead** (3-6). We will use a structured interview document as a guide for the assignation of the punctuations of the Scale to each patient (**Annex 5**).

7.5.3. Co-variables

- **General stroke risk factors:**

Age: it is a continuous quantitative variable. It will be measured in years (at the moment of the first stroke episode). The patients will be categorized in two groups, so we will treat it as an ordinal qualitative variable. It will be expressed by **≤55 years** or **>55 years**.

Sex: dichotomous nominal qualitative variable. **Male** or **Female**.

Arterial hypertension: dichotomous nominal qualitative variable. It will be expressed by **yes** or **not**. It is defined as a systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or history of medical treatment of hypertension.

Atrial fibrillation: dichotomous nominal qualitative variable. It will be expressed by **yes** or **not**. It is defined a supraventricular arrhythmia, with a narrow QRS (<120 ms), absence of P waves and, usually, presence of f waves. It will be considered as present whether if it is paroxysmal (<7 days) or persistent (>7 days).

Diabetes mellitus: dichotomous nominal qualitative variable. It will be expressed by **yes** or **not**. It is defined as a HbA1c > 6,5%, a fasting serum glucose of >126 mg/dL, a serum glucose >200 mg/dL after 2 hours of a glucose oral tolerance test, a glucose >200 mg/dL in any moment of the day in patients with classical symptoms of hyperglycemia or acute complication of hyperglycemia, or the use of a hypoglycemic agent.

Dyslipidemia: dichotomous nominal qualitative variable. It will be expressed by **yes** or **not**. It is defined as a total cholesterol \geq 200 mg/dL, a triglyceride level \geq 150 mg/dL, a low-density lipoprotein \geq 130 mg/dL, or the use of a lipid-lowering agent.

Obesity: dichotomous nominal qualitative variable. It will be expressed by **yes** or **not**. It is defined as a body mass index >30 kg/m².

Smoking: dichotomous nominal qualitative variable. It will be expressed by **smoker** or **non-smoker** (those who have never smoked).

- **Cryptogenic stroke risk factors:**

History of neoplasia: categorial qualitative variable. It will be expressed by **procoagulant neoplasia** (gastrointestinal or lung cancer), **other neoplasia**, or **no history of neoplasia**.

- **PFO-related risk factors of recurrence:**

Presence of ASA: dichotomous nominal qualitative variable. It will be expressed by **yes** or **not**. It is defined as an excursion of >15mm of the atrial septum detected by echocardiography.

Inclusion event: dichotomous categorial qualitative variable. It will be expressed by **cerebral infarct** or **TIA**.

Secondary prevention treatment: categorial qualitative variable. It will be expressed by **antiplatelet**, **anticoagulation** or **antiplatelet and anticoagulation** together.

Probability of causal PFO: it is a discrete quantitative variable. It is measured with the RoPE Score. We will categorize it as an ordinal qualitative variable expressed by **zero probability** (0-3), **low probability** (4-5), **moderate probability** (6-7) and **high probability** (8-10).

7.6. Data collection

Information will be recorded directly from the patient or relatives or from medical histories if available and registered in the CRF. We will record any vascular event with particular attention to ischemic stroke recurrence and etiopathogenic subtype of recurrence (cerebral infarct, TIA, systemic emboli (exceptional)). The following data will be collected using this procedure (see **annex 3**):

- Identification of the patient (and sex), correlating him/her with his identification in the original CODICIA study.
- Presence/absence of stroke recurrence.
- Date of the stroke recurrence.
- Type of stroke recurrence.
- Presence/absence of comorbidities: arterial hypertension, atrial fibrillation, diabetes mellitus, dyslipidemia, smoking, obesity, neoplasia.
- The received treatment.
- If the patient has died and the cause of the death.
- The actual mRS score.

The rest of the needed data will be collected with a revision of the database of the original CODICIA study:

- Age at the moment of the first stroke episode.
- Presence/absence of RLSH through PFO.
- Magnitude of RLSH.
- Presence/ absence of ASA.
- Inclusion event (Cerebral infarct or TIA).
- Infarct location (if it is cortical or non-cortical) and previous stroke/TIA (before the inclusion event in CODICIA study): they are needed for the calculation of the RoPE Score.

8. STATISTICAL ANALYSIS

The statistical analysis will be performed by the statistical analyst. The data will be computed and managed using Statistical Package for Social Sciences version 25.

- **Descriptive statistics:**

We will express all the qualitative variables by percentages \pm confidence interval (95%) and the quantitative variables by mean \pm standard deviation or median and quartiles. All the descriptions will be stratified by RLSH magnitude.

- **Simple inference:**

In order to compare the proportions between RLSH magnitude and the other qualitative variables we will use χ^2 test and Exact Fisher Test when the expected frequencies are $<5\%$. For its comparison with quantitative variables we will use t-Student or Mann-Whitney tests as appropriate. A p value $<0,05$ will be considered statistically significant.

- **Multivariate analysis:**

The association between the independent and dependent variables will be adjusted by means of logistic-regression analysis in order to avoid possible confounding factors. All the co-variables with statistical significance in the bivariate analysis will be included in the multivariate analysis.

In addition, we will stratify all the analysis by age groups, expressing the results attributed to the whole sample also to patients younger than 55 years.

9. ETHICAL AND LEGAL ASPECTS

All the patients included in CODICIA study signed a written informed consent that included the permission of telephoning them during their follow-up, initially expected for 3 to 5 years. When we contact the patients by telephone a new oral informed consent (**Annex 4**) will be asked to the patient before the new data collection. Non-localized subject's data collection will be obtained from medical histories without the need of an informed consent, but this represents an ethical consideration that must be submitted to be eventually approved by the Ethical and Clinical Investigation Committee (CEIC).

Each person of the research team and each hospital direction must sign a statement attesting to having read and approved the final protocol and agree with the national and international ethical aspects of research.

This protocol will be presented to the CEIC of the HJT. The objections performed by the CEIC will be considered and introduced.

This study will be conducted according to the requirements expressed in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects* signed by the World Health Association in October 2013, and to *ministerial order SAS/3470/2009* defined in the current legislation in Spain related with the conduct of observational studies.

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, and repealing Directive 95/46/EC (General Data Protection Regulation)* and the *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales*.

Patients data including names, surnames, telephones, addresses and clinical history information will remain anonymous after their introduction and processing into a database which will also be handled according to the mentioned Law and exclusively used for the development of the study. The data access will only be available for the research team. The access to this information for a third person will not be allowed.

10. STUDY LIMITATIONS

This study has several limitations that must be bore in mind:

- **Study design:**

As an observational study, without a randomization of the subjects in the different categories of the independent variable, it is possible that there are some confounding factors that we have not included as co-variables.

- **Inclusion/exclusion criteria:**

Including patients with ≤ 10 years of follow up only if they have died due to a stroke recurrence could overrate slightly the risk of recurrence, causing a selection bias.

- **Collaborating hospitals:**

The possibility that some of the hospitals do not collaborate exists, with a potential decrease of the number of included patients in the sample. However, the reference neurovascular experts of most of the hospitals have been contacted and agree with the procedure of the current protocol (see **Annex 2**), what decreases the impact of this limitation.

- **Localization of the patients:**

When CODICIA study was conducted, communication systems and computerized medical histories were not so evolved as nowadays. It is possible that we can not localize some of the patients included in CODICIA study and, consequently, it will not be possible to include these patients in the current protocol.

At present time, we have several contact data of the patients included in CODICIA study at the moment of its conduction. For that reason, if the first phone contact fails, other contact efforts can be tried (a greater number of phone calls, written letters, etc.). Data of non-contacted patients will be obtained from medical histories taking advantage of their computerization in the last years.

As this is probably the most relevant limitation of this project, we have made a feasibility analysis trying to localize the patients of HJT and H. General de Albacete, as will be explained afterwards (see **13. Feasibility**).

- **Insufficient sample:**

Although we will probably have an enough sample size to represent our whole population, it is not the case of the particular group of patients younger than 55 years. We need 235 patients to obtain a statistical power of 80% and the maximum obtainable <55 years patients (without considering losses) at the included hospitals is 226. This represents a limitation of this study decreasing the statistical power in this age group.

- **Investigator variability:**

As a multicenter study with one reference person per center, there will be an investigator variability in the evaluation of the variables included in this study. For that reason, we highlight the importance of the evaluation of the variables by vascular expert neurologists certified in the mRS evaluation in order to decrease it.

- **Evaluation of the variables:**

It is possible that some of the variables of the CRF sometimes can not be filled completely or that they get filled without a perfect precision. This can happen because the patient does not remember correctly some of the collected data (memory bias) or a lack of information in medical histories.

11. WORK PLAN AND CHRONOGRAM

11.1. Research team personnel

The research team will be composed by the general coordinator (GC) of the study, the 15 additional neurologists of reference at each hospital and 1 statistical analyst.

11.2. Study stages

The study will be performed during 5 stages after the study design. Including the study design, the execution of the study and the publication and dissemination of the results it will last 2 years and 6 months.

- **Stage 0. Study design (7 months)**

Activity 1. First meeting (June 2018)

The decision of the performance of the current protocol is taken in June 2018 by Dr. Joaquín Serena (GC) and Miguel Ferrer.

Activity 2. Study protocol development (November 2018 – January 2019)

The current protocol has been developed from November 2018 to January 2019. After a delimitation of the objectives, a bibliographic research has been performed about the general information and importance of stroke, more specifically CS, and even more specifically PFO, RLSH, and PFO-related stroke. After that, we have made the redaction of the different parts of this protocol, which has been finalized in January 2019.

- **Stage 1. Coordination (1 month)**

Activity 3. Presentation and approval by the CEIC (February 2019)

The current protocol will be presented to the CEIC of HJT.

Activity 4. Determination of the collaborating professionals in the study (February 2019)

The GC will contact the contact person at any participating center by the emails present in **Annex 2**. All the hospitals who agree with this collaboration will receive a copy of the current protocol. One investigator / reference person per hospital will be determined, who will be neurovascular experts.

- **Stage 2. Data collection (8 months)**

Activity 5. CRF filling (March 2019 – September 2019)

Each hospital reference person will fill the CRF related with its own patients.

Activity 6. Determination of the sample (October 2019)

The GC of the study will make a revision of the filled CRF classifying each patient according to inclusion and exclusion criteria as “included” or “excluded”. The included patients will represent the definitive sample.

The committee of 3 neurovascular experts will be formed by the GC and 2 other collaborators of the study (reference persons of the hospitals) for the discussion of dead patients with ≤ 10 years of follow-up.

- **Stage 3. Computerization and data analysis (3 months)**

Activity 7. Computerization of the data (November 2019 – December 2019)

The statistical analyst will create a common database, associating each patient with his/her identification in the original CODICIA study. All the patients will be listed encoded with a number, in order to avoid confidentiality problems, and all the data from the CRF will be computerized and matched to each specific patient.

The statistical group will revise the databases of the original CODICIA study adding its variables to the new database and matching them to each specific patient

Activity 8. Statistical analysis (December 2019 – January 2020)

The statistical analyst will analyze the data and obtain the results of the study.

- **Stage 4. Interpretation and discussion of the results (1 month)**

Activity 9. Meeting of the whole team (February 2020)

A meeting at HJT will be organized, inviting all the collaborators of the study. There, the results will be evaluated and debated.

- **Stage 5. Redaction, publication and dissemination of the research findings (10 months)**

Activity 10. Study writing (March 2020 – May 2020)

The GC will make a redaction of the study with an accurate interpretation of the results and a discussion including the debated aspects during the meeting in February 2020.

12.BUDGET

We would like to apply for the following expenses as a budget for the performance of this study:

- **Personnel expenses**

All the CRF filling and the selection of the included patients in the sample according to the inclusion and exclusion criteria will be performed by the GC of the study and the rest of reference vascular neurology experts. Their cost will not be included in this budget.

The only personnel extra expense will consist in hiring the statistical analyst. We have estimated that approximately 90 hours of work will be needed for the creation of the database, computerization of the collected data, their match with the database of the original CODICIA study and the statistical analysis. We will pay 50€/h so we calculate a cost of 4500€.

- **Execution expenses**

Articles and literature material for the bibliography research have not represented any extra cost. Printing the CRF and paper packs are the only material expense that will be required. Their cost will not be included in this budget.

- **Publication expenses**

We will publish the study as a journal article. We estimate that the revision, edition, formatting layout, graphic design and preparation of the digital metadata will cost approximately 2.000€.

- **Travel expenses**

A meeting of the whole team will be organized at HJT in order to make the discussion and obtain the appropriate conclusions of the results of the study. Apart from the GC, the rest of 15 reference collaborators of each hospital will have to travel to Girona. We estimate a mean expense of 250€ per person including travel costs, accommodation and diets. We calculate a cost of approximately 3750€.

We will disseminate the results of our study in one national congress and one international congress. We estimate an expense of approximately 1000€ per congress including the inscription, travel costs, accommodation and diets. We calculate a cost of approximately 2000€.

TYPE OF COST	UNIT COST	HOURS/UNITS	TOTAL
PERSONNEL EXPENSES			
Statistical analyst	50 €	90 hours	4.500 €
PUBLICATION EXPENSES			
Article publication (revision, edition, formatting layout, graphic design and preparation of the digital metadata)			2.000 €
TRAVEL EXPENSES			
Meeting for the discussion of the results (travels, accommodation, diets)	250 €	15 neurovascular experts	3.750 €
Congresses (inscriptions, travels, accommodation, diets)	1.000 €	2 congresses	2.000 €
TOTAL			12.250 €

13. FEASIBILITY

Although we expect a lower loss of patients in the follow-up of the initial CODICIA cohort, we will carry out this study accepting 20% as the maximum limit of acceptable losses (limit admitted in some of the RCT in this field). In order to foresee if this study could be feasible, we have performed a feasibility analysis including the patients of HJT and H. General de Albacete.

We have asked the oral informed consent to the patients as if the interview was part of the complete study and the performance of this feasibility analysis has been consulted to the CEIC.

- HJT: we were able to contact 84 of the 94 tried patients (89,4%)
- H. General de Albacete: they were able to contact 30/33 patients (90,9%)

114/127 (89,8%) of the patients were contacted, what shows the potential feasibility of the performance of this study if these proportions keep so high after the contact efforts performed by the rest of the hospitals.

We obtained the following results with a follow-up of 15,7 (\pm 1,5) years:

	Recurrences	mRankin Scale (0-1)
RLSh +	0,65% - 1,59%/year	60,4% – 66,7%
RLSh -	2,15% - 2,55%/year	14,3% - 18,1%

Table 2. Results of the feasibility analysis. Representation of the proportions of recurred patients and patients with a mRS score between 0 and 1 stratified by the presence or absence of a RLSH through PFO.

Unless with this small sample we can not obtain firm conclusions, the low number of losses and the congruence of these results with our hypothesis (the presence of PFO as a predictor of a better outcome) encourage us to the performance of this study.

Additionally, as mentioned above, most of the hospitals have already been contacted and agree with their collaboration in the study, which increases even more the feasibility in the recruiting of the needed sample (see **Annex 2**).

For the execution of this study we dispose at the hospitals of the needed data and materials: the contact data and medical histories of the patients, telephones, computers, printers and paper packs. The statistical analyst will be hired externally.

14. EXPERIENCE OF THE RESEARCH TEAM

The research team includes experts in vascular neurology. Most of them participated in the original CODICIA study, so worked at least once together as a research team with the HJT as the coordinator center, and Dr. Joaquín Serena as the leader of the team.

The neurovascular research team of the HJT has more than 15 years of research experience in cerebrovascular diseases area, maintaining relations with other members of a scientific collaboration network started more than 10 years ago. It has consolidated a prestigious name nationally and internationally as a research group due to several contributions in the stroke field (both ischemic and hemorrhagic) in areas like neuroimaging (and particularly neurologic ultrasonography), molecular markers, biologic factors, clinical aspects and inflammatory response.

Dr. Joaquín Serena, the GC of this project, is expert in cerebrovascular diseases, especially in the field of ultrasonography and carotid pathology, an area where is considered a referent at a national and international level. He participated in several studies about PFO and its relationship with CS, such as CODICIA study. It is also important to mention that he constantly participates in new studies, attends to congresses and meetings and gives conferences and speeches at many centers.

15.IMPACT

Stroke is a prevalent disease, with a high mortality and the main cause of disability in Spain. This supposes a high expense of medical resources (hospitalizations, doctors, nurses, physiotherapists, etc.). In fact, it must be remembered that between 3% and 4% of the health expenditure in high-income countries are caused by stroke. CS represents from 30% to 40% of the stroke episodes, which has a strong association with PFO, especially in younger patients, whom acquired disability generates even more indirect costs to the society.

The secondary prevention treatment to perform when a CS episode is due to a PFO has not been fully established. The new published RCT (2017) show a short-term superiority of PFO closure with very high NNT, what supposes a very high expense in order to avoid one recurrence if we consider that one intervention costs around 8700\$. Our preliminary results reinforce the hypothesis that patients with PFO have a very favorable prognosis, even the few cases with recurrences. This should redefine the benefit of closing the PFO, which is expensive and is not free from risks.

Having a first piece of information of long-term risk of recurrence and prognosis of PFO-related stroke could help to clarify the best option orientating, provisionally, the management of these patients until new long-term RCT are conducted. The importance of performing an accurate treatment would have an impact in the national health care system by a decrease of the stroke recurrences and its costs, and the avoidance of unnecessary (and expensive) PFO closure interventions.

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17. ANNEXES

17.1. Annex 1. SSS-TOAST classification criteria

Atherothrombotic infarct	Cardioembolic infarct	Lacunar Infarct	Stroke of other undetermined etiology	Stroke of undetermined etiology
<p>Probable:</p> <p>Evidence in ultrasonographic or arteriographic studies of:</p> <p>Stenosis of >50% of an extracranial or large intracranial artery.</p> <p>Possible:</p> <p>Evidence of stenosis <50% when there are more than two other vascular risk factors:</p> <ul style="list-style-type: none"> - >50 years - Arterial hypertension - Diabetes mellitus - Smoking - Hypercholesterolemia <p>Absence of other etiologies</p>	<p>Identification of one of the following cardiac embolic sources:</p> <ul style="list-style-type: none"> - Thrombus - Intracardiac tumor - Rheumatic mitral stenosis - Mitral or aortic prosthesis - Endocarditis - Atrial fibrillation - Sine node disease - Left ventricular aneurism - Akinesia after an acute myocardial infarction - Acute myocardial infarction in the last 3 months - Presence of a global cardiac hypokinesia or dyskinesia. <p>Absence of other etiologies</p>	<p>Small infarct which diameter measures < 1,5 cm.</p> <p>In the territory of a cerebral perforating artery.</p> <p>Usually causes a lacunar syndrome:</p> <ul style="list-style-type: none"> - Pure motor hemiparesis - Pure sensory stroke - Sensorimotor stroke - Ataxic hemiparesis - Dysarthria-clumsy hand syndrome <p>Presence of hypertension or other vascular risk factors</p> <p>Absence of other etiologies.</p>	<p>Atherothrombotic, cardioembolic, and lacunar etiologies have been discarded.</p> <p>Another less frequent cause has been identified.</p> <p>They can be systemic pathologies:</p> <ul style="list-style-type: none"> - Connective tissue pathologies - Infections - Neoplasms - Myeloproliferative syndromes - Metabolic or coagulation disorders <p>Other diseases:</p> <ul style="list-style-type: none"> - Arterial dissections - Fibromuscular dysplasia - Aneurism - Arteriovenous malformation - Cerebral venous thrombosis - Vasculitis - Migraine, etc. 	<p>Incomplete study:</p> <p>An incomplete etiological study has been performed.</p> <p>Two causes:</p> <p>Coexistence of two potential causes of stroke.</p> <p>Cryptogenic stroke:</p> <p>No cause has been found after an exhaustive evaluation (CS).</p>

Table 3. SSS-TOAST classification criteria (4).

17.2. Annex 2. List of potential collaborating hospitals

HOSPITAL	REFERENCE PERSON	EMAIL	N (500)	N (<55y) (227)
H. Josep Trueta Girona	Dr. Joaquín Serena	jserena.girona.ics@gencat.cat	155	55
H. de la Santa Creu i Sant Pau Barcelona	Dr. Joan Martí	jmarti@santpau.cat	71	26
H. Vall d'Hebron Barcelona	Dr. Álvarez Sabín	alsa@hg.vhebron.es	59	31
H. Virgen del Rocío Sevilla	Dr. Francisco Moniche	pmoniche@gmail.com	45	20
H. Ramón y Cajal Madrid	Dr. Jaime Masjuan	jmasjuan.hrc@salud.madrid.org	34	14
H. General de Albacete Albacete	Dr. Oscar Ayo Dr. Tomás Segura	oscarayo@gmail.com tsmtsm08@yahoo.es	33	15
H. de Navarra Pamplona	Dr. Jaime Gallego	jgallegc@cfnavarra.es	25	12
H. Germans Trias i Pujol Barcelona	Dr. Antoni Dávalos Dra. Mónica Millan	adavalos.germanstrias@gencat.cat mmillan.germanstrias@gencat.cat	19	12
H. Donostia San Sebastián	Dra. Maite Martínez Zabaleta Dra. Ana María de Arce Borda	martinezzabaleta@gmail.com anamaria.dearceborda@osakietza.net	13	11
H. la Princesa Madrid	Dr. José Vivancos	jjvivancos@neurogps.com.es	12	7
H. Clínic Barcelona	Dr. Ángel Chamorro	achamorro@clinic.ub.es	9	8
H. Nuestra Señora de Sonsoles Ávila	Dra. M ^a Alonso de Leciñana	malecinanacases@salud.madrid.org	8	8
H. General de Castellón Castellón	Dr. Carlos Vilar	jcv@gmail.com	6	4
New York Medical College New York	Dr. Michael Moussotas	missing	4	1
H. del Mar Barcelona	Dr. Jaume Roquer	jroquer@parcdesalutmar.cat	3	1
H. Virgen de la Macarena Sevilla	Dr. Eduardo Durán	eduran@gmail.com	1	1
H. la Fe Madrid	Dr. Exuperio Díez-Tejedor	exuperio.diez@salud.madrid.org	3	1

Table 4. List of potential collaborating hospitals. N and N (<55y) represent the whole number of patients and the number of patients younger than 55 years, respectively, that were included in the original CODICIA study by each one of the hospitals. New York Medical college has been excluded (pink). The hospitals that have already been contacted and agree with their collaboration are represented green.

17.3. Annex 3. Case report forms

17.3.1. Spanish version

SEGUIMIENTO A 15 AÑOS DE PACIENTES CON ICTUS CRIPTOGÉNICO (CODICIA) (CASTELLANO)

CÓDIGO PACIENTE: _____

Fecha de contacto: __/__/____

Tipo de contacto: Historia clínica: Telefónico:

Recurrencia:

NO: Sí:

Fecha de recurrencia: __/__/____

- Infarto cerebral
- AIT
- Embolismo sistémico

Comorbilidades:

- HTA
- DM
- DLP
- FA
- Fumador
- Obesidad
- Neoplasia

Tipo de neoplasia i año de diagnóstico: _____

Tratamiento actual:

- Ningún tratamiento
- AAS
- Otros antiagregantes (no AAS)
- ACO
- Oclusión FOP
- Otros:

mRankin Scale: ____

Exitus: NO: Sí:

Causa de exitus: _____

17.3.2. Catalan version

SEGUIMENT A 15 ANYS DE PACIENTS AMB ICTUS CRIPTOGÈNIC (CODICIA) (CATALÀ)

CODI PACIENT: _____

Data de contacte: __ / ___ / _____

Tipus de contacte: Història clínica: Telefònic:

Recurrència:

NO: Sí:

Data de recurrència: __ / ___ / _____

- Infart cerebral
- AIT
- Embolisme sistèmic

Comorbiditats:

- HTA
- DM
- DLP
- FA
- Fumador
- Obesitat
- Neoplàsia

Tipus de neoplàsia i any de diagnòstic: _____

Tractament actual:

- Cap tractament
- AAS
- Altres antiagregants (no AAS)
- ACO
- Oclusió FOP
- Altres:

mRankin Scale: ____

Exitus: NO: Sí:

Causa d'exitus: _____

17.4. Annex 4. Oral informed consents

17.4.1. Spanish version

HOJA DE INFORMACIÓN AL PACIENTE

Buenos días/tardes,

Nos dirigimos a usted para informarle/a de que se está realizando un estudio y nos gustaría solicitar su participación. Este estudio ha sido aprobado por el Comité Ético de Investigación Clínica del Hospital Josep Trueta.

El objetivo es evaluar después de una media de 15 años el riesgo de recurrencias y pronóstico del ictus criptogénico en pacientes con/sin foramen oval permeable, para tratar de orientar el riesgo-beneficio y el coste-beneficio del tratamiento preventivo de dicha entidad.

Para su realización estamos llamando a los pacientes que, como usted, participaron en el estudio CODICIA, y realizando una serie de preguntas para obtener los datos que necesitamos.

Solicitamos su permiso para realizarle la siguiente entrevista y utilizar los datos obtenidos únicamente para la realización de este estudio, de forma totalmente confidencial y sin acceso a estos por parte de terceros de acuerdo con la legalidad vigente (*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales*).

En caso de publicación de los resultados a través de publicaciones y/o congresos, ya sea a las autoridades sanitarias o a la comunidad científica, siempre se hará de forma global y nunca de forma individualizada, de manera que no será posible la identificación de los participantes.

Su participación es totalmente voluntaria y en caso de no querer participar no tiene por qué dar explicaciones ni tendrá consecuencias en sus cuidados médicos.

Muchas gracias por su atención, si tiene alguna pregunta no dude en realizarla.

HOJA DE CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO: Primera evaluación a largo plazo del riesgo de recurrencia y pronóstico del ictus criptogénico en pacientes con y sin foramen oval permeable.

D/D^a:

Fecha de nacimiento:

Teléfono:

DNI:

Código paciente:

Manifiesta:

- Haber sido debidamente informado/a por parte del Dr./Dra. _____, habiendo entendido toda la información y habiendo contado con la posibilidad de realizar todas las preguntas necesarias.

SÍ

NO

- Saber que puede no participar en este estudio sin la necesidad de dar explicaciones y sin consecuencias en sus cuidados médicos.

SÍ

NO

Consiente:

- La realización de la siguiente entrevista y la utilización de sus datos de forma completamente confidencial y de acuerdo con la legalidad vigente.

SÍ

NO

Fecha:

Firma del investigador/a

Firma del/la paciente*

*En caso de que el/la paciente acuda a la consulta del investigador/a posteriormente a la llamada se le solicitará el consentimiento por escrito.

17.4.2. Catalan version**FULL D'INFORMACIÓ AL PACIENT**

Bon dia/tarda,

Ens dirigim a vostè per informar-li de que s'està realitzant un estudi i ens agradaria sol·licitar la seva participació. Aquest estudi ha estat aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital Josep Trueta.

L'objectiu és avaluar després d'una mitja de 15 anys el risc de recurrències i pronòstic de l'ictus criptogènic en pacients amb/sense foramen oval permeable, per tractar d'orientar el risc-benefici i el cost-benefici del tractament preventiu d'aquesta entitat.

Per la seva realització estem trucant als pacients que, com vostè, van participar a l'estudi CODICIA, i realitzant una sèrie de preguntes per obtenir les dades que necessitem.

Sol·licitem el seu permís per realitzar-li la següent entrevista i utilitzar les dades obtingudes únicament per la realització d'aquest estudi, de forma totalment confidencial i sense accés a aquestes per part de tercers d'acord amb la legalitat vigent (*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales*).

En cas de publicació dels resultats a través de publicacions i/o congressos, ja sigui a les autoritats sanitàries o a la comunitat científica, sempre es farà de manera global i mai de manera individualitzada, de manera que no serà possible la identificació dels participants.

La seva participació és totalment voluntària i en cas de no voler-hi participar no té per que donar explicacions ni hi haurà conseqüències a les seves cures mèdiques.

Moltes gràcies per la seva atenció. Si té alguna pregunta no dubti en realitzar-la.

FULL DE CONSENTIMENT INFORMAT	
TÍTOL DE L' ESTUDI: Primera avaluació a llarg termini del risc de recurrència i pronòstic de l'ictus criptogènic a pacients amb i sense foramen oval permeable.	
D/D^a: Data de naixement: Telèfon: DNI: Codi pacient:	
Manifesta: <ul style="list-style-type: none"> Haver estat degudament informat/da per part del del Dr. Dra. _____, havent entès tota la informació i havent comptat amb la possibilitat de realitzar totes les preguntes necessàries. SÍ <input type="checkbox"/> NO <input type="checkbox"/> <ul style="list-style-type: none"> Saber que pot no participar a aquest estudi sense la necessitat de donar explicacions i sense conseqüències a les seves cures mèdiques. SÍ <input type="checkbox"/> NO <input type="checkbox"/>	
Consent: <ul style="list-style-type: none"> La realització de la següent entrevista y la utilització de les seves dades de manera completament confidencial i d'acord amb la legalitat vigent. SÍ <input type="checkbox"/> NO <input type="checkbox"/>	
Data:	
Signatura de l'investigador/a	Signatura del/la pacient*

*En cas de que el/la pacient acudeixi a la consulta de l'investigador/a posteriorment a la trucada se li sol·licitarà el consentiment por escrit.

17.5. Annex 5. Modified Rankin Scale structured evaluation

MODIFIED RANKIN SCALE	
0	No symptoms.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all the previous activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Dead.

17.5.1. Structured evaluation document in Spanish

EVALUACIÓN ESTRUCTURADA DE LA ESCALA MODIFICADA DE RANKIN (CASTELLANO)		
Exitus	El paciente ha fallecido .	SÍ (mRS= 6) NO
Encamamiento	El/la paciente no puede caminar , ni siquiera con la ayuda de otra persona. Si es trasladado 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. <ul style="list-style-type: none"> Si auto propulsa silla mecánica → respuesta NO 	SÍ (mRS = 5) NO
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. <ul style="list-style-type: none"> 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 (aunque no pueda girar esquinas) → respuesta SÍ Si el/la paciente NO necesita asistencia para sentarse en y levantarse de una silla de ruedas → respuesta NO Si el/la paciente utiliza aparatos de asistencia para caminar, pero no necesita la ayuda de otra persona → respuesta NO 	SÍ (mRS = 4) NO
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? <ul style="list-style-type: none"> ¿Es estrictamente necesaria la asistencia para preparar una comida sencilla? Por ejemplo: si el/la paciente puede prepararse el desayuno o un entremés → respuesta NO ¿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 → respuesta NO ¿Es estrictamente necesaria la asistencia para encargarse de los gastos de la casa? Si es el caso → respuesta SÍ ¿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 → respuesta NO ¿Es estrictamente necesaria la asistencia para realizar compras en establecimientos cercanos? Por ejemplo: si el/la paciente puede comprar aunque sea un único artículo → respuesta NO 	SÍ (mRS = 3) NO

Tareas y actividades de rutina	<p>Trabajo: ¿Ha sido reducida de forma sustancial (en comparación con el estado previo del primer accidente cerebrovascular) 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.</p> <p>Responsabilidades familiares: ¿Ha sido reducida de forma sustancial (en comparación con el estado previo del primer accidente cerebrovascular) la capacidad de la persona para hacerse cargo de la familia en casa?</p> <p>Actividades sociales y de ocio: ¿Ha sido reducida de forma sustancial (en comparación con el estado previo del primer 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.</p>	Sí (mRS = 2) NO
Síntomas como consecuencia del accidente cerebrovascular	<p>¿Presenta el/la paciente algún síntoma como resultado del primer 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.</p>	Sí (mRS = 1) NO (mRS = 0)

17.5.2. Structured evaluation document in Catalan

AVALUACIÓ ESTRUCTURADA DE L'ESCALA MODIFICADA DE RANKIN (CATALÀ)		
Exitus	El pacient ha mort .	Sí (mRS= 6) NO
Enllitament	<p>El/la pacient no pot caminar, ni tan sols amb l'ajuda d'una altra persona. Si és traslladat a una cadira de rodes, no és capaç de moure-la per sí mateix/a adequadament. Generalment requereix una cura quasi constant – quasi tota l'estona hi ha d'haver algú disponible.</p> <ul style="list-style-type: none"> • Si auto propulsa cadira mecànica → respongui NO 	Sí (mRS = 5) NO
Assistència per caminar	<p>És essencial l'assistència d'una altra persona per caminar. Requerir l'assistència d'una altra persona significa necessitar que hi hagi una altra persona constantment present al caminar, per donar ajuda física o supervisió.</p> <ul style="list-style-type: none"> • Si el/la pacient necessita assistència per seure i aixecar-se d'una cadira de rodes, però, un cop assegut a la mateixa, pot traslladar-se per sí mateix/a de manera adequada (encara que no pugui girar cantonades → respongui Sí • Si el/la pacient NO necessita assistència para seure i aixecar-se d'una cadira de rodes → respongui NO • Si el/la pacient utilitza aparells d'assistència per caminar, però no necessita l'ajuda d'una altra persona → respongui NO 	Sí (mRS = 4) NO
Assistència per l'acompliment de tasques personals	<p>Assistència inclou assistència física, instruccions orals o supervisió d'una altra persona. Qüestió principal: si fos estrictament necessari, el/la pacient podria viure sol, durant una setmana?</p> <ul style="list-style-type: none"> • És estrictament necessària l'assistència per preparar un àpat senzill? Per exemple: si el/la pacient pot preparar-se l'esmorzar o un entremès → respongui NO • És estrictament necessària l'assistència per realitzar a diari les tasques domèstiques bàsiques? Per exemple: si el/la pacient pot trobar i guardar la roba, netejar la taula després dels àpats → respongui NO • És estrictament necessària l'assistència per encarregar-se de les despeses de la casa? Si es el cas → respongui Sí 	Sí (mRS = 3) NO

	<ul style="list-style-type: none"> • És estrictament necessària l'assistència per realitzar desplaçaments locals? Per exemple: si el/la pacient pot conduir o utilitzar el transport públic; o trucar un taxi i donar instruccions al conductor → respongui NO • És estrictament necessària l'assistència per realitzar compres a establiments propers? Per exemple: si el/la pacient pot comprar encara que sigui un únic article → respongui NO 	
Tasques i activitats de rutina	<p>Feina: ha estat reduïda de manera substancial (en comparació amb l'estat previ del primer accident cerebrovascular) la capacitat de la persona per treballar (o, per un estudiant, la capacitat d'estudiar)? Per exemple: canvis de temps complert a temps parcial, canvis a nivell de responsabilitat, o ja no és capaç de treballar.</p> <p>Responsabilitats familiars: ha estat reduïda de manera substancial (en comparació amb l'estat previ del primer accident cerebrovascular) la capacitat de la persona per fer-se càrrec de la família i la casa?</p> <p>Activitats socials i d'oci: ha estat reduïda de manera substancial (en comparació amb l'estat previ del primer accident cerebrovascular) la frequència de les activitats habituals de la persona durant el seu temps lliure a menys de la meitat? Activitats socials i d'oci inclouen aficions i interessos, activitats dins i fora de casa. Activitats fora de casa: anar a prendre un cafè, a un bar, restaurant, club, església, cinema, visitar amics, passejar. Activitats dins de casa: aquelles que impliquen una participació "activa" com teixir, cosir, pintar, jugar, llegir, realitzar millories de la casa.</p>	SÍ (mRS = 2) NO
Síntomes com a conseqüència de l'accident cerebrovascular	<p>¿Presenta el/la pacient algun símptoma com a resultat del primer accident cerebrovascular Per exemple, problemes a l'hora de: llegir, escriure, parlar, mantenir l'equilibri o coordinar moviments, veure-s'hi, empassar; o: entumiment, debilitat, pèrdua de mobilitat o altres símptomes.</p>	SÍ (mRS = 1) NO (mRS =0)