Universitat de Girona
Facultat de Medicina

NOVEMBRE 2016

FRANK'S SIGN AND SUBTYPES OF STROKE

Could we have answers only with a glance?

FINAL DEGREE PROJECT

RESEARCH PROTOCOL AND PRELIMINARY RESULTS

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"A quien le daña el saber, Homicida es de si mismo."

P. Calderón de la Barca

Quiero expresar mi más sincero agradecimiento al Dr. Joaquín Serena. Gracias por todos tus consejos, por tu continuo apoyo, por tu paciencia y sobre todo, gracias por transmitirme de una forma tan cercana tu pasión por la neurología y tu entusiasmo por el saber en sí mismo. Ha sido un auténtico placer y una enriquecedora experiencia trabajar contigo.

También quisiera agradecer al equipo de profesionales de la Unidad de Ictus del Hospital Dr. Josep Trueta por todo lo aprendido en el mes de rotación.

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ABSTRACT

BACKGROUND: Frank's sign is a crease in the earlobe, which has been correlated with heart disease by a mechanism of atherosclerosis and with its severity and also correlated with vascular risk factors. There are a few amount of studies that reported an association between this sign and the artery carotid intima media thickness (IMT) and only one that correlated it with stroke in general. Stroke is one of the leading causes of death worldwide and the first cause of long-term morbidity in our country, so it is important making efforts to study this pathology and how to detect it preciously. There are 5 subtypes of ischemic stroke with a different physiopathological mechanism each one. However, there are no studies that reported an association between Frank's sign by subtypes of stroke. If Frank's sign has been associated with an atherosclerosis diseases, the prevalence of this sign between atherotrombotic and lacunar stroke has to be higher as share the same physiopathological mechanism. Cryptogenic stroke has a lack of diagnoses in its underlying causes, the studies suggested that the main causes of them could be cardioembolism or atherotrombosis mechanisms, but the techniques that are used as routine impede the accurate diagnosis. As Frank's sign is related to atherosclerosis, we think that Frank's sign could help to define better the profile (atherotrombotic vs no aherotrombotic) of the patients of cryptogenic stroke to choose better some advanced diagnostic techniques in order to diagnose the real underlying cause of this subtype of stroke, and also orientate a better specific secondary preventive treatment to avoid recurrences.

MAIN OBJECTIVES: The main aims of the study is to establish the prevalence of Frank's sign in patients who suffered a stroke and, especially, to analyse the prevalence of Frank's sign in each etiopathogenic subtype. We also will study specially the prevalence of Frank's sing in patients with cryptogenic stroke, correlating it with the presence or absence of clinical and radiological markers to support a causal atherothrombotic or cardioembolic profile.

METHODE: This protocol is a descriptive cross-sectional study to see the prevalence of Frank's sign in the different subtypes of ischemic stroke, and describe the clinic features in those who have a cryptogenic stroke to reach the main objectives of our study. The study will include 265 patients, 53 of each of the 5 subtype of stroke, that have been hospitalized at Stroke Unit after suffering a stroke. Recruitment of participants will last 4 months. The Frank's sign evaluation is going to be done by taking photos of the both ears of the patients in a blinded way by all the research team.

KEYWORDS: Frank's sign; subtype of stroke; cryptogenic stroke; underlying cause of cryptogenic stroke; artherosclerosis; stroke epidemiology

PROLOGUE

It is 138 BC and in the village of Baie (Italy) there is the great emperor Hadrian.
Who was once an insatiable ambitious, a tireless traveller from every corner of his empire, who managed the flourishment of peace and prosperity in ancient Rome, who encouraged the arts and affirmed military discipline, now, he remains in his chambers, with a pale face, with an exhaustive nosebleeds and swollen legs. Hadrian remains without hope to continue fighting for his life and praying out loud poison or sword to be finally destroyed by himself. Meanwhile, in the same room and away from his bed was his bust, perfectly sculpted, with a millimetric imitation of his features and with his personal and distinguished two ears with a deep wrinkle in his earlobes.
The life of Hadrian was falling slowly and painfully, but inside him, each day, was growing a great conviction that he would be remembered over time.

In these, Adriano was not entirely wrong, many historians since then have been the responsible for giving voice to the Adriano's past. Dion Casio with his History Augusta and Kanngiesser with his history review of the deaths of many Roman emperors have aroused the curiosity of many researchers to discover the real death cause of Adriano.

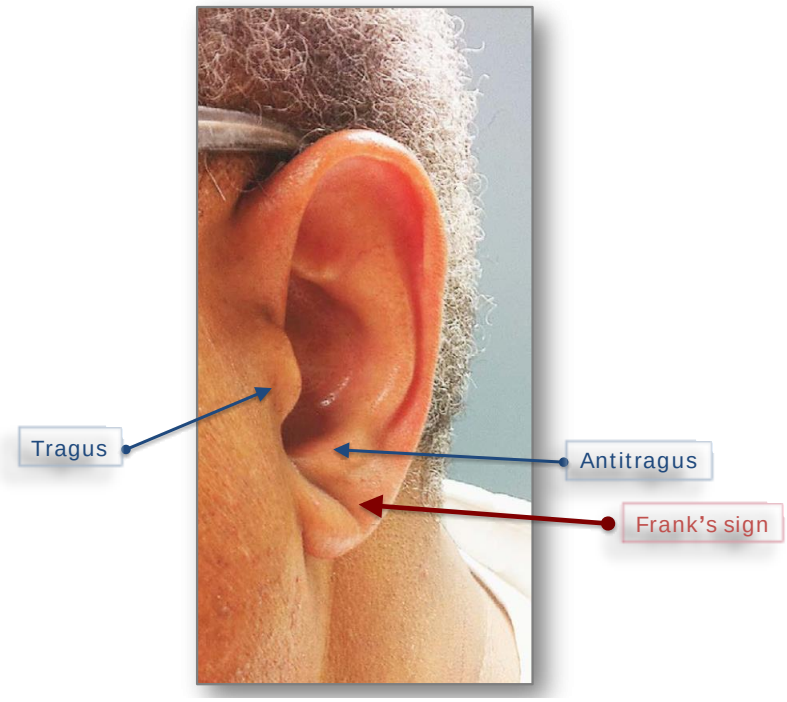
L. Nicholas Petrakis, has been one of those researchers who has been hypothesized that the most likely cause of death of Adriano was congestive heart failure due to coronary atherosclerosis. The story of his recurrent epistaxis and marked edema suggest the possibility of an underlying hypertension progressed to congestive heart failure.
Moreover, a part of the Adriano's disease, have been reported two features in Adriano that have been associated with coronary atherosclerosis: His ambitious, tireless personality and his desire to be eternally recognized, later described as behavior pattern type A. And his distinguished bilateral ear lobes' creases found in his busts that has been described as Frank's sign, by Frank in 1973[1].

[1] *Petrakis NL. Diagonal earlobe creases, type A behavior and the death of Emperor Hadrian. West J Med. 1980;132(1):87–91.*

INTRODUCTION

1. FRANK'S SIGN

The Frank's sign or ear lobe crease (ELC) is a cutaneous clinical sign described as a crease or wrinkle, either unilaterally or bilaterally, that extends approximately 45º diagonally from the tragus towards the outer border of the ear lobe covering at least 1/3 of the ear lobe. (1)(2)



It was first described by Frank in 1973, in this study the author suggested a positive relation between ELC and coronary artery disease (CAD) due to an atherosclerotic mechanism. (3) Several studies since then have been proposed to link ELC with CAD, and many studies show that Frank's sign can be determined as a marker of atherosclerosis(1)(2)(4) and sign of elevated risk of coronary heart disease in asymptomatic individuals with the exception of native American Indians, oriental patients and children suffering from beckwith's syndrome(5), furthermore, different studies suggested the relation of a genetic factor that could be involved in the link between ELC and CAD across different ethnic population(6).

Talking about its physiopathology, in a case report suggested a link between macrophage activity (which involved in artherioesclerosis), aging and maintaining ear lobe collagen (7), the ELC and CAD are apparently related to the loss of elastin and elastic fiber(8), but there are not many studies that can clarify the certain physiopathology of the apparition of ELC, nevertheless, it can be speculated that possibly a diminished blood supply to the ear lobe, a highly vascular area, may contribute to the elastic-fiber tears which become manifest as the early creasing and folding seen by the naked eye(9). It also seems that the prevalence of ELC increases with advancing age and the same is true for the CAD,(6). Although

controversies remain, a recent study found that it is associated not only with the presence of coronary atherosclerosis but also with its extend and severity. It has been postulated that ear lobe and myocardium are supplied by the same genetically originated end arterioles and thus share a common pathway(10)(11).

Talking about vascular risk factors there are some studies that demonstrated the association of Frank's sign with the presence of diabetes, HTA, myocardial infraction and coronary disease in patients of both sexes, for that reason this easily identifiable sign, which may imply the existence of vascular risk factors could be valuable in screening for prospective high-risk coronary patients. Its presence could motivate reduction of these factors, such as smoking and hypertension, which may be instrumental in the precipitation of MI(8)(12)(4).

However, not only studies for CAD are reported, there are some studies that try to make a relation between ELC and other diseases where the physiopathology of them are also artherosclerosis, there are studies that obtain a significant association between ELC and carotid artery IMT (intima-media thickness) and also with the presence of artheriosclerotic plaques in the carotid arteries as a reliable markers of systemic atherosclerosis and as a one of the risk factor of cerebrovascular disease (CVD)(13)(14), furthermore, there are, only one recent study that demonstrated a relation between ELC and ischemic stroke, what is interesting of this study is that the Odds Ratio for ELC for ischemic stroke is even higher than that they found for coronary heart disease (15). There is one study that reveals a significant and independent association between presence of ELC and increased prevalence, extend, and severity of PAD for the first time(16).
In conclusion, although controversies exist, and taking in account what we are interesting on for our study, the presence of diagonal ELC should prompt clinicians to evaluate patients for coronary and carotid atherosclerotic disease, especially when there are other concurrent risk factors for artheriosclerosis.
Furthermore, since artherosclerosis is a generalized disease and as we have observed in the literature review, it could be concluded that Frank's sign occurs more frequently in patients with cerebrovascular disease, and this last affirmation is on what we are going to focus the aims of our study.

In the following part, we are going to explain what stroke is and its subtype to put in context what we are going to search at the objectives and to understand our hypothesis.

2. DEFINITION OF STROKE AND ITS EPIDEMIOLOGY

The terms cerebrovascular disease (CVD) or stroke refer to a **disturbance in the cerebral blood flow that results in** a transient or permanent **change in the function of one or more regions of the brain.** There are different types of stroke, depending on the nature of the lesion:

-Ischemic stroke →that is due to a lack of blood supply to a given area of the parenchyma.

-Hemorrhagic stroke→ that is caused by the rupture of a cerebral blood vessel, with extravasation of blood into the vascular bed.

Strokes are ischemic in 85% of the cases and the 15% remainder are hemorrhagic(17).

Stroke is currently the **first cause of death in Spain in women and the second cause in men**(18), regarding to the top 10 cause of death in the world according to WHO, stroke ranked in the second place(19). Despite this, **in recent years there has been a progressive decrease in stroke mortality** (figure 2), which is related to the improvement in the measures of primary and secondary prevention, and the advances in stroke care in the acute phase. Compared to other European countries, Spain is among those with lower mortality in both men and women. Data-hospital mortality from stroke in Spain range between 16.7% and 25%, being lower in ischemic stroke than in hemorrhagic ones and increases with age(20).

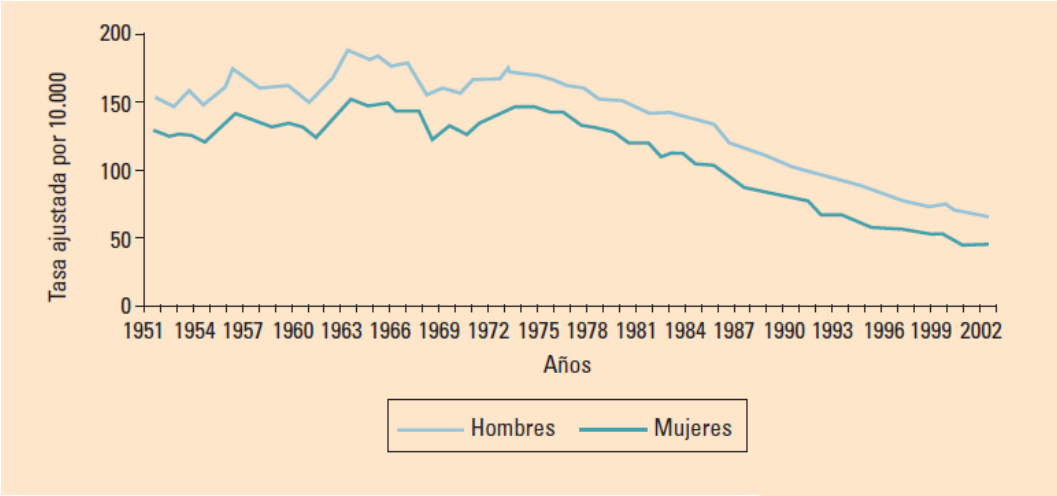


Figure 2. Stroke mortality in Spain, from 1951 to 2002(20)

Its incidence is estimated at 200 cases per 100.000 habitants/year worldwide, according to WHO. The incidence of stroke increases progressively in each decade of life after 55 years old, occurring more than half of cases at age of 75. In Spain, incidence data are based in small population studies and it is found rates of 132-174 cases per 100.000 habitants/year to all ages. Talking **about prevalence in Spain, it is estimated to be at 7% of the urban population older than 65 years old**, this prevalence increases with age and is higher in males(21)(22).

The importance of **stroke** resides in the fact that it **is the first conditioner of disability in adulthood and the second cause of dementia** after Alzehimer's disease and the most common cause of neurological hospitalization, constituting about 70% of revenue at neurological services. A high percentage of patients who have suffered a stroke have disabling sequelae such as paralysis, balance problems, slurred speech, cognitive deficits, or emotional pain. All these problems determine that **35-45% of the cases of stroke are in a situation of partial or total dependence**. Of all patients over 65 with dependency, 73% are due to stroke(20)(23).

The estimation of the economic impact of stroke in Spain believes that **the direct health cost per patient is around 15,268 euros the first year of the stroke**, targeting 70% to the period of hospitalization. Factors that are associated with an increased cost are the length of stay, type of stroke (higher in the HSA and lower in lacunar stroke), stroke severity and intensity of the sequels.
Survival after stroke not means full recovery, because the 90% of the patients remains with sequels, which 35-45% of them could incapacitate the individual for their autonomy in daily life activities, generating a demand for care with considerable health and social spending. This aspect is particularly important, since 25% of strokes affect people still in active employment status(20)(23).

3. ISCHEMIC STROKE

Depending on developments during the initial hours, we differentiate between **2 types** of ischemic cerebrovascular accidents:

1. **The transient ischemic attack (TIA) →** Recently defined as a **brief episode of neurologic dysfunction** caused by focal brain or retinal ischemia, with clinical symptoms typically **lasting less than one hour**, and **without evidence of acute infarction** in the imaging. TIA it should be considered an **important warning sign of cerebral infraction** or other cardiovascular complications and also **have a poor long-term prognosis.** The TIA is referred to as carotid, vertebrobasilar or indeterminate, depending on the vascular territory involved, and on the basis of clinical signs. It can be classified as retinal (amaurosis fugax), cortical hemispheric, lacunar, or atypical. In summary, patients with TIA should be considered **a group at high vascular risk and, once diagnosed, the causative mechanism should be identified** (17)(24)**.**
2. **Cerebral infarction →**Defined as **irreversible damage to the brain parenchyma** or symptoms **lasting more than an hour.** The final cause is the **lack of blood flow** to some part of the brain, **which produces ischemia and, ultimately, infarction** (death of brain cells). The presence of ischemic brain tissue is sufficient **to affect brain function and, thus, produces the typical clinical signs of stroke** (17)(25)**.**

Talking about the risk factors for cerebrovascular diseases, the **most important one** is the **arterial hypertension** (figure 3) and is the one which is highest associated with all types of stroke.

Furthermore, stroke have other risk factors. We can classify them in non-modifiable risk factors and modifiable risk factors, at the same time we can classify the modifiable ones in well documented and less documented risk factors, according to its level of evidence (20)(26).

Table 1. Risk factors for ischemic stroke (20)

Non- modified Risk factors	Modified Risk factors	
	Well documented	**Less documented**
➢ Age ➢ Sex ➢ Race ➢ sociocultural level ➢ Geographic location ➢ Hereditary factors	➢ Arterial hypertension ➢ Smoking habit ➢ Diabetes Mellitus ➢ Carotid stenosis ➢ Atrial fibrillation ➢ Other cardiopathies → infectious endocarditis, mitral stenosis and recent ischemic acute stroke ➢ sickle-cell anemia ➢ Hormonal therapy ➢ Previous stroke or AIT ➢ Sedentary ➢ Dietetic factors	➢ Obesity ➢ Metabolic syndrome ➢ Drug consume ➢ Alcohol habit ➢ Obstructive apnea sleep syndrome ➢ oral contraceptives ➢ Migraine ➢ Hyperhomocisteinemia ➢ Inflamatory states and infections ➢ Hypercoagulability states

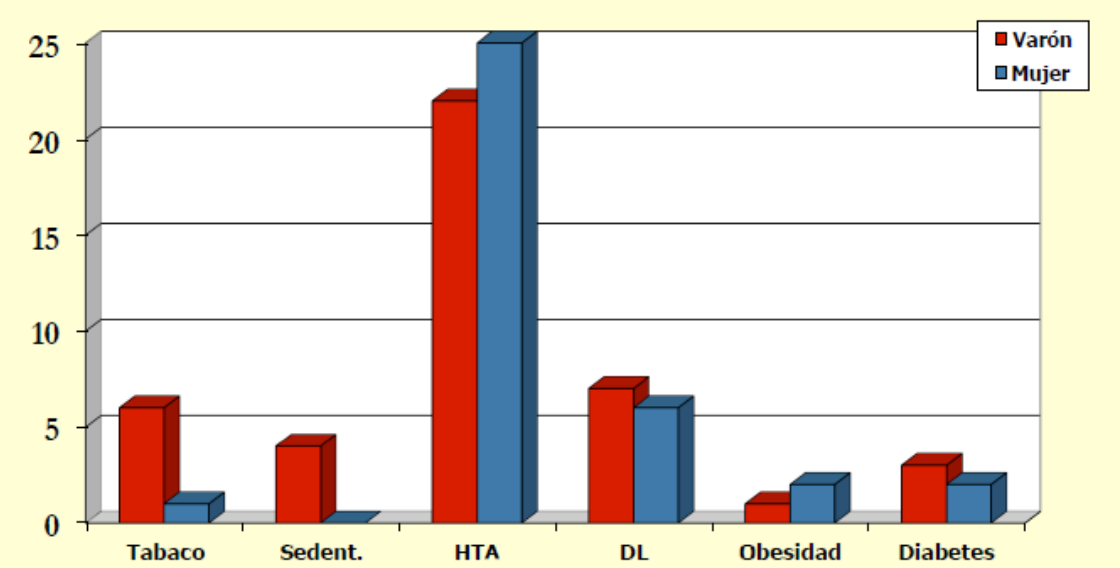


Figure 3. Attributable risk (%) of the principal cerebrovascular risk factors (26)

Talking about the etiology of ischemic stroke, that is the type of stroke that we have focused the objectives of the study, **there is a classification that is the most widely used** to talk about ischemic stroke **due to its evidence-based** and because it is designed to determine the most likely etiology in the presence of multiple competing mechanisms. **This classification is named** Stop Stroke Study TOAST **(SSS-TOAST)** and is based in clinical features and on data collected by tests such as brain imaging (CT/MRI), cardiac imaging (echocardiography), duplex imaging of extracranial arteries, arteriography, and laboratory assessments for a prothrombotic state(17) (27) (28) (29).

The SSS-TOAST classification **divided ischemic stroke in 5 great group**s (figure 5):

1. **Atherotrombotic, or large artery artherosclerosis:**

- This diagnosis requires the Doppler/duplex and/or angiograph study (angio-MRI, angio-TC or arteriography) to detect lesions in the artery wall (stenosis or occlusion) of the big vessels (extracranial and intracranial). The normality, minim alterations or the absence of this techniques exclude the diagnosis.
- **Mandatory criteria:**
  - ≥50% of stenosis, occlusion or ulcerated plaque (>2mm depth) in the ipsilateral intracranial or extracranial artery.
  - Absence of cardiac source of embolism and other etiology
- **Other criteria that also affirm this diagnosis:**
  - Clinical findings
    - Ipsilateral carotid bruit
    - Previous ipsilateral TIA to the infract
    - Evidence of risk factors for accelerated atherosclerosis
    - Symptomatic arteriosclerosis disease → previous story of ischemic cardiopathy and previous history of peripheral artery disease
  - Imaging findings
    - TC/MRI evidence of non-hemorrhagic infract greater than 1.5 cm in diameter of the cortical, subcortical, cerebellar or brain stem structures.
    - In the angiography, stenosis or occlusion of the vascular territory affected

2. Cardioembolic stroke

- **Mandatory criteria**
  - Presence of embolic heart disease (figure 4)
  - Absence of cerebrovascular atheromatous lesions and other possible etiology

    *In the case that the cardioembolic source were minor and in absence of other etiology, the stroke is going to be classified as "possible" cardioembolic etiology.

Major cardioembolic sources
- Atrial fibrillation, including paroxysmal atrial fibrillation
- Sustained atrial flutter
- Valve prostheses, mechanical or biological
- Recent myocardial infarction (<4 weeks)
- Earlier myocardial infarction (>4 weeks) associated with an ejection fraction <28%
- Left ventricular or atrial thrombi
- Left atrial myxoma
- Papillary fibroelastoma
- Endocarditis, infectious, or noninfectious
- Dilated cardiomyopathy
- Symptomatic congestive heart failure with an ejection fraction <30%
- Sick sinus syndrome
- Rheumatic mitral or aortic valve disease

Minor cardioembolic sources
- Patent foramen ovale
- Atrial septal aneurysm, with or without foramen ovale
- Left ventricular aneurysm without thrombus
- Isolated spontaneous echo contrast (without mitral stenosis or atrial fibrillation)
- Mitral annulus calcification, including severe calcification

Figure 4. cardioembolic sources (*17*)

- **Other criteria that also affirm this diagnosis**
  - Clinical findings
    - Abruptly established neurological deficit (in seconds or few minutes)
    - Apparition during wakefulness
    - Transitory loss of consciousness and/or seizures at the beginning of the symptomatology
    - Previous cerebral infraction or TIA in different vascular territories
    - History or coexistence of systemic embolisms
  - Imaging findings
    - Evidence in TC of infract >1.5 cm in diameter, generally cortical, sometimes hemorragic or multiple infracts in different vascular territories.
    - in angiography: evanescent angiographic occlusions, arterial isolated occlusion without evidence of atherosclerotic lesions or defect in center-fill of the proximal portion of one artery without atherosclerotic changes

3. Small Vessel (Lacunar) Disease

- Normal CT/MRI examination or maximum infarct diameter of 1.5 cm, located in arterial territory or perforating cerebral arterioles (the diameter of which is usually less than 200 μm) due to lipohyalinosis or microatheromatosis of said vessels.
- Vascular imaging should not demonstrate findings consistent with large artery atherosclerosis (stenosis >50%) in the clinically relevant vessel.
- The affected structures are restricted to the basal ganglia, internal capsule, thalamus, or brain stem.
- Clinical findings → one of the following classic lacunar syndromes have to be accomplished (figure 5):
  - Pure hemiparesis → it affects at least two of the three parts of the body (face, superior extremities and inferior extremities)
  - Pure sensory syndrome → it affects at least two of the three parts of the body
  - Sensorimotor syndrome → it affects at least two of the three parts of the body
  - Ataxic hemiparesis → ipsilateral weakness with prominent ataxia
  - Dysarthriaclumsy hand syndrome →prominent ataxia with isolated hand weakness
- The presence of hypertension or diabetes mellitus supports the diagnosis.
- By definition, there must be no cortical signs or symptoms
- There should be no potential cardiac sources of embolism or stenosis greater than 50% in ipsilateral extracranial arteries

4. Other determined cause

- This category includes patients with acute cerebral infarction due to infrequent causes, such as:
  - No atherosclerotic vasculopathy → fibromuscular dysplasia, artery ectasia, moya moya disease, Snedon syndrome, arterial dissection and so on.
  - Hypercoagulability states
  - Hematologic disorders
  - Migraine-infarction
  - Vasospasm
  - Other hereditary and metabolic diseases.
- Etiologies of cardioembolic cerebral infarction and the presence of atherosclerosis in extracranial arteries should be ruled out.

5. Stroke of undetermined etiology

- The diagnosis of undetermined cause of stroke reflects the difficulty in making a pathogenic diagnosis in some cases.
- There are 3 scenarios.
  - Incomplete evaluation →some patients may not have a determined cause because the diagnostic evaluation (in particular, cardiac and vascular imaging studies) was not performed.
  - Unclassified → In some cases, conflicting causes are detected. These patients could have clinical features and imaging findings consistent with strokes that would be found with either large or small vessel disease.
  - Cryptogenic stroke →Some patients have no particular identified cause despite an evaluation. These cryptogenic cases, which are often presumed to be secondary to embolization, would be included in the new category of embolic strokes of undetermined source. These strokes may be because of a variety of potential sources in the heart, aorta, or great vessels of the neck but without solid evidence found on evaluation to establish a diagnosis.

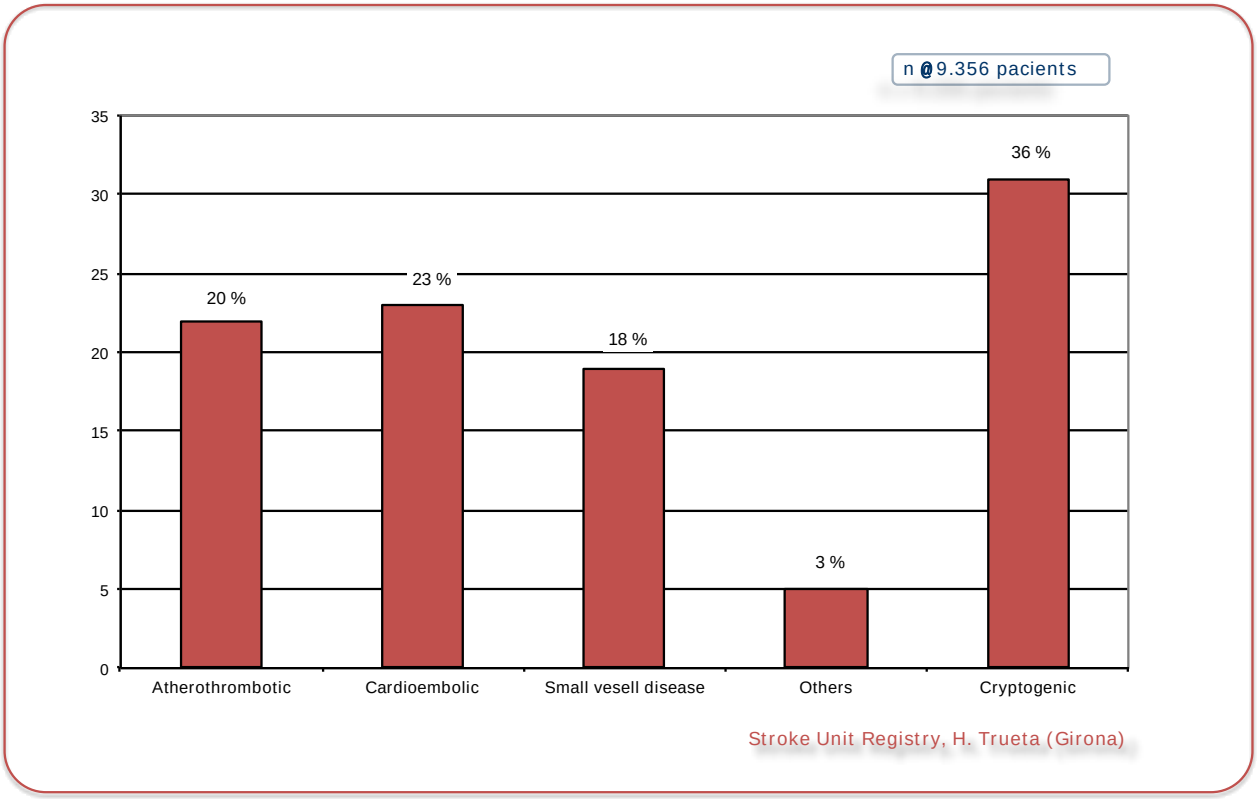


Figure 5. Prevalence of ischemic stroke subtypes in the whole population of consecutive patients admitted to a Stroke Unit in the last 20 years.

3.1 Large artery artherosclerosis or atherotrombotic stroke

We are going to enlarge upon this subtype of ischemic stroke because it is relevant to understand the hypothesis that we will formulate later. As we said before, the main mechanism that leads in a atherotrombotic stroke is the atherosclerosis.

Atherosclerosis is a systemic inflammatory disease that affects mainly arteries of medium and large caliber such as the aorta, coronary arteries, cerebral arteries, renal arteries and the arteries of the extremities. It is a multifactorial process where different environmental and genetic factors are involved. The normal arterial wall is formed by three capes which are named, of lumen to the periphery, as intima, media and adventitia. The part of the intima that is in contact to the blood flux is named endothelium.
Atherosclerosis is developed basically in the intima of the arterial wall by the formation of lesions known as atheroma plaque that protrudes towards to the lumen. It is postulated that the different vascular risk factors joined to the individual susceptibility leads in disequilibrium of some endothelium substances. This disequilibrium predisposes to the development of a chronic inflammation that leads in a major permeability of the endothelium. This permeability facilitates the migration of lipids to the intima and macrophages activation. This macrophage activation leads to foam cell formation, smooth cells migration with abundant intracitoplasmatic cholesterol and an increase of connective tissue such as, collagen and elastic fibers, forming a fibrous plaque. Necrosis of macrophages and smooth muscle cells lead to the formation of necrotic core that contribute to a weakening of the plaque. Plaque rupture exposes all the components of the atheroma formation to blood components, initiating coagulation, platelet adherence and the formation of thrombus. Evolution of advanced plaques involves repetitive cycles of microhaemorrage and thrombosis that can cause occlusive arterial disease(30)(31).

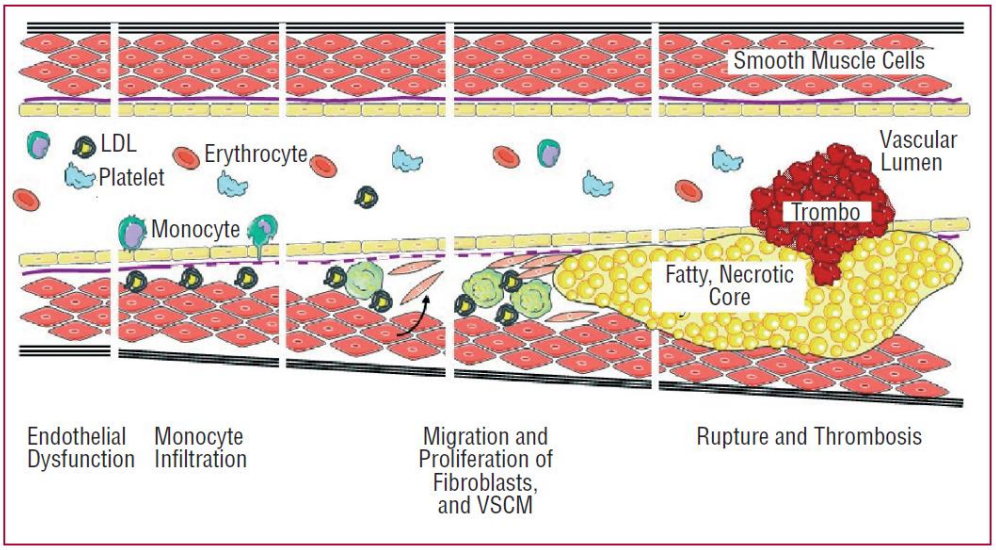


Figure 6. Formation of atherosclerotic plaque (38)

It is known that artherosclerotic burden leads in a poor prognosis to those patients who suffered an ischemic stroke (IS), as we can see in those who suffered an ischemic heart disease (IHD) or peripheral arterial disease (PAD). Atherosclerotic burden (ATB) is a term used to describe the global extension of arteriosclerosis and has been related to poor outcome after IHD, PAD or IS.

However, there are more factors that joined with ATB leads in a great mortality before suffering an ischemic stroke. The most outstanding factors are age, severity of the stroke and the amount of territories that are affected by atherosclerosis. There are studies that found a direct relationship between ATB, a high score at NIHSS and the mortality at 30 days after ischemic stroke, at the same time they affirm that the more territories affected by artheriosclerosis the more risk of mortality they have.

Other factors described that joined with ATB can lead in a bad prognosis of patients that have suffered a stroke included: hyperthermia, hyperglycemia, arterial hypertension, atrial fibrillation, cardiac insufficiency, serologic markers of inflammation, male sex, previous functional status evaluable with the modified Rankin scale and race (31).

3.2. Cryptogenic ischemic stroke

The term cryptogenic stroke generally refers to a stroke for which there is also no specific attributed cause after a comprehensive evaluation for the most common causes.

Cryptogenic stroke account for at least 1/3 of parts of all ischemic stroke, with higher prevalence in young patient population (<55 y.).

The importance of cryptogenic stroke radices in several reasons. Firstly, in its prognosis, because it has a high risk of recurrence, secondly, in its perception, because patients and also physicians have a high level of uncertainty in this subtype of stroke and that leads to a bad therapeutic accomplishment because there is not an evident cause, and thirdly, and perhaps most importantly, that has an insufficient etiological diagnosis technique. For all that reasons, it is necessary making efforts to reduce its percentage of diagnosis.

There are three big groups of potential causes of Cryptogenic stroke:

1. **Artery diseases→** such as atherosclerosis disease, where, as we said before, this disease can lead in an atherotrombotic stroke. Patients diagnosed with a cryptogenic stroke may have evidence of a mild degree of stenosis in vessels corresponding to the area of symptomatic vascular brain injury, however do not accomplish the criteria to being classified as a atherotrombotic stroke, although even an artery with mild degree of stenosis can harbor unstable plaque, which can rupture or erupt, resulting in stroke via arteroembolism. Another problem for diagnosed adequately the underlying atherotrombotic cause in a cryptogenic stroke, might be that, sometimes, this atherosclerotic plaque remains unstable or is so subtle for being detected by the diagnose

techniques that are used as routine, for instance, because the vulnerable atherosclerotic plaques often have well-preserved lumen due to plaque grows outward initially and also, sometimes, the location of the plaque is a problem. This kind of possible etiology of cryptogenic stroke is where we are going to focus an objective of our study on, and we are going to explain it later.

2. **Heart diseases** →The main heart diseases that are underdiagnosed as potential cardioembolic causes of stroke are the transitory or spontaneously reversible ones. The diagnostic workup in these diseases results may be unrevealing if testing is undertaken during the time of reversion to normalcy. It is the case, for instance, of ACXFA paroxysmal (that is more frequent and has worse prognosis as permanent, because its transitory nature leads in a more difficult diagnose), arterial dissection, takotsubo syndrome (that is a vasospasm/reversible vasoconstriction syndrome), patent foramen ovale, aortic arch atheroma and so on.
3. **Blood diseases** → such as malignancy cancer, like lungs or gastrointestinal cancer. These malign cancers secret substances resulting in the activation of factors X and VII of the coagulation and leads in a protrombotic state. In addition, aggressive antitumor therapy may also increase the risk of thrombosis leading on potential stroke origin, for that reason, given that appropriate anticoagulation can effectively prevent cancer-related stroke.

As we can see above, there are some scenarios where the real cause of a stroke may be inadequately investigated or ignored and are directly diagnosed as cryptogenic stroke. The proportion of patients diagnosed with cryptogenic stroke using current classification systems remains high. Being diagnosed as cryptogenic stroke means that, in fact, the real cause of the stroke is not known and it leads to these patients in some disadvantages, as we commented above. Moreover, as no causal relationship is inferred due to low causality grades in this subtype of stroke, leaves the physician with the same uncertainty about secondary preventive treatment. For all these reasons, targeted selection and judicious use of appropriate tests in the workup of cryptogenic stroke are crucial. As such, diagnostic investigations of suspected cryptogenic stroke, particularly advanced diagnostic techniques should be guided and chosen in accordance with patients' characteristics. The cost-effectiveness of advanced diagnostic technologies will greatly depend on the appropriate selection of patients for the various diagnostic tests (32) (33).

JUSTIFICATION

Stroke has a huge worldwide socioeconomic and health impact because of its high prevalence, hospitalization rate and the severity of its long-term squeal in survivors (20), for that reason, it is important to make-efforts to study this pathology and try to clarify how to detect it precociously.

As we say previously, there are some studies that try to make a relation with the ELC or Frank's sign to and atherosclerotic diseases, above all, related to coronary artery disease (CAD) (3). These studies found a strong relation with them. There are also, some studies that compare the same with peripheral artery diseases (PAD) (16), carotid intima-media thickness (IMT)(14) and only two which found a relation between Frank's sign and ischemic stroke (34)(15). As we can observe, the amount of studies that compare the correlation between ELC and stroke is lower than those which compare the Frank's sign with CAD.

Although CAD, PAD, IMT, Frank's sign and stroke, especially atherotrombotic and lacunar subtype, might have a common pathophysiology such as atherosclerosis or vascular changes, no studies have reported a correlation between Frank's sign and stroke by subtypes. This is one of the aspect in which we are going to focus the main objectives of the study.

In other hand, nowadays, there are intensive efforts to clarify the underlying ethiopatogenic mechanism in patients suffering from cryptogenic stroke (30 to 50% of stroke patients). The studies suggested that the main underlying causes of this stroke subtype are cardioembolism or atherotrombosis, but the nature of the diseases that produce the stroke and the techniques that are used as routine impede the accurate diagnosis. It is important to reduce the diagnosis rate of cryptogenic stroke, for the reasons we said at the introduction. The diagnosis of cryptogenic stroke could decrease by applying more advanced diagnostic techniques that increase the certain diagnosis as cardioembolic or atherotrombotic stroke subtype. However, in order to be cost-effectiveness, these techniques have to be applied in the correct chosen patients, according to their characteristics (32).

It is known that Frank's sign is related to atherosclerotic process, for that reason, we think that Frank's sign could help us if we use it as a cutaneous marker that defines better the profile of the patients that have suffered a cryptogenic stroke. Taking into account the Frank's sign, only with a quick glance, we could choose better some advanced diagnostic techniques in order to diagnose the real underlying cause of cryptogenic stroke.

Another issue to be discussed in the study is the atherosclerotic burden. As we said in the introduction, the ATB of a patient joined with other factors can lead in a poor prognosis after suffering a stroke (31). As we know by reading the literature review, Frank's sign is related to atherosclerotic process and even more it is related with its severity, for that reason, it would be interesting if we could use the Frank's sign as a cutaneous marker that help us to predict the prognosis of the patients that have suffered a stroke in those whose etiology is atherotrombotic.

For all these reasons, we consider that analyzing the prevalence of Frank's sign in stroke population and within the different stroke subtypes, particularly in cryptogenic stroke, would be of etiopatogenic and potentiality therapeutic interest. Moreover, we also consider that analyzing the evolution of the patients that have suffered a stroke by taking into account the presence of the Frank's sign, could be of prognosis interest.

HYPOTHESIS

The hypotheses which have generated the main objectives are:

1. The Frank's sign is more prevalent among patients who have suffered an atherotrombotic or lacunar stroke, and less prevalent in those who have suffered a cryptogenic, cardioembolic or infrequent etiology stroke.

2. The Frank's sign can be used as a cutaneous marker that can help us to stratify the underlying etiology in cryptogenic stroke (atherothrombotic profile vs no atherothrombotic profile) more adequately.

The hypothesis that has generated the secondary objective is:

1. The Frank's sign could allow a better risk stratification of stroke, especially in patients with atherothrombotic and lacunar profile. Its presence would indicate a greater burden of atherosclerotic disease and is associated with a worse functional prognosis and increased risk of recurrent vascular events.

OBJECTIVES

Main objectives

1. Establishing the prevalence of Frank's sign in patients who are hospitalized in a stroke unit after suffering a stroke and, especially, to analyze the prevalence of Frank's sign in each etiopathogenic subtype of stroke.

2. We will study specially the prevalence of Frank's sing in patients with cryptogenic stroke, correlating it with the presence or absence of clinical and radiological markers to support a causal atherothrombotic or cardioembolic profile.

Secondary objective

1. We are going to evaluate the functional situation using the Rankin's modified scale and the recurrence of new vascular events at 3 months and at 1 year after their inclusion in the study, correlating it with the presence or absence of Frank's sign in each etiopatogenic subtype of ictus. We are going to focus on atherotrombotic subtype adjusted by confusing habitual factors.

MATERIAL AND METHODS

1. STUDY DESIGN

This study has been designed as a cross-sectional descriptive study.

The patients are going to be evaluated three times.

The first time, the objectives of the patient's evaluation are to see the prevalence of Frank's sign in the different subtypes of ischemic stroke, and describe the clinic features in those who have a cryptogenic stroke to reach the main objectives of our study.

The second and third time that we are going to evaluate the patients are at 3 months and at 1 year after they have been hospitalized. The finality of these evaluations is to check their functional situation and their vascular recurrence to achieve the secondary objective of our study.

The length of the study period since the start of collecting patients until the last 1 year after discharge evaluation will be 1 year and 4 months and it will be performed at hospital Dr. Josep Trueta in charge of the neurological service.

2. STUDY POPULATION

The target population of the study will be patients hospitalized at stroke unit before suffering a stroke, independently its etiology, once they accept and sign de consentient (SEE ANNEX 1) to participate in the study.

Inclusion criteria

- Patient who has suffered a stroke independently its etiology and its age once has been hospitalized at stroke unit of HJT.
- Patient who has accepted and signed the informed consentient to participate in the study.
- Patient who has its both ears photographed and the picture remain clearly visible to determine if the Frank's sign is present.
- If due to some reasons, a patient who has suffered a stroke could not be photographed at stroke unit, but he remains at the neurological ward waiting for some study, he could also participate in the study, after accepting and signing the informed consentient.

Exclusion criteria

- Patients that have been wearing for years or wear at that moment earrings, dilatations, tattoos or any object in the earlobe due to the possibility of potential false Frank's sign.
- Patients that due to an accident or any type of surgery have lost the ears or a part of them, especially the earlobe due to the impossibility of evaluation the Frank's sign.
- Patients whose ears can't be photographed and the evaluation to see the presence or not of the Frank's signs remains impossible

3. SAMPLING

Sample selection

A non-probabilistic consecutive sampling method will be used. This sampling consists of selecting patients diagnosed as stroke, independently of its etiology, who meet the inclusion and exclusion criteria. Candidates will be informed about the study and invited to participate voluntarily by signing the informed consent.

Sample size

A sample size has been calculated using as reference the data found in the literature review (34). This report is the only report we have found that analyzes the prevalence of the Frank's sign in stroke, however, there is not any study that reveals the prevalence of the Frank's sign between subtypes of stroke that is in which we are interested on.

We calculate the sample size using GRANMO based on the prevalence of Frank's sign between stroke in global that is 59%. Accepting an alpha risk of 0.05 and beta risk below 0.2 in a bilateral contrast, we need 53 patients to detect a difference equal or superior to 0.2 unities, we assume, as we said before, that the population reference of 0.59. It has been estimated a loss rate of 10% tacking.

As we need a sample size to detect a difference greater than 0.2 unities, if it exists, between the different subtypes of stroke and Frank's sign to evaluate significantly the importance of the presence of the Frank's sign as risk factor of vascular recurrence to achieve the secondary objective, we assume that we need the same sample size but for each subtype of stroke accepting also an alpha risk of 0.05 and beta risk below 0.2.

We consider that we need a sample formed by:

- 53 patients that have suffered an atherotrombotic stroke
- 53 patients that have suffered a cardioembolic stroke
- 53 patients that have suffered a small sized vessel stroke
- 53 patients that have suffered a cryptogenic stroke

- 53 patients that have suffered a stroke of other etiology, inside this group we introduce those who have suffered a stroke of other determined etiology and hemorrhagic ones.

Taking into account these data, we need a total of 265 patients.

4. VARIABLES AND MESURAMENTS

Since this is a descriptive cross-sectional study, independent and dependent cannot be identified.
However, we define a principal variable that is **Frank's sign** because we are going to focus all our study in it. We define a secondary variable that is the **subtypes of stroke**, because is an important variable to achieve our main objectives too. The rest of variables which are mainly the risk vascular factors of the patients and the clinical or imaging features of their actual stroke, are going to be tertiary variables because we consider that they are not the principal objective of our study but have a high relevance in relation with the presence or not of the Frank's sign to extract posterior conclusions.
All the variables are collected at CRF (SEE ANNEX 2)

Principal variable

- **Frank's sign**: *Nominal categorical variable.* We are going to record this variable as we explain in the evaluation sheet of Frank's sign (SEE ANNEX 3).
    - (yes/no): We consider that Franks sign is present when subjects have a crease or wrinkle extending 45º diagonally from the tragus towards the outer border of the ear lobe covering at least 1/3 parts of the ear lobe.
    - (Bilateral/unilateral): we consider that a Frank sign is present either if its bilateral or unilateral but we have to specify it

Secondary variable

- **Type of stroke →** *Nominal categorical variable.* We are going to consider the type of stroke as a categorical variable, where we can have:
    - Infract → qualitative or quantitative alteration in the input of blood to encephalic territory producing a neurological deficiency that lasts more than 24 hours or a imaging evidence of acute ischemic lesion in the brain.
    - TIA→ Brief episode of neurological dysfunction caused by focal cerebral or retinal ischemic producing clinical symptoms that lasts less than an hour and without an evidence of imaging findings.
    - Haemorragic → bleeding resulting from spontaneous rupture of blood vessels directly into the brain parenchyma

- **Subtypes of ictus (etiology)→** *Nominal categorical variable.* The classification criteria to collect this variable is explained in the ANNEX 4. We can have:
  - Atherotrombotic
  - Cardioembolic
  - Criptogenic or undetermined
  - Infrequent
  - Lacunar

Tertiary variables

- Baseline data
  - **Age →** This variable will be collected as a *discrete quantitative variable* as we show in the CRF. However, to simplify the statistical analyses and because it has a higher clinical relevance, we are going to aggregate the ages of patients in five groups, depending on his range of age. We have patients ≤50 years, 51-59 years, 60-69 years, 70-79 years and ≥80 years, according to that the age is transformed in a *nominal categorical variable.*
  - **Gender→** *nominal categorical variable* (male/female)
- Clinical features
  - **Hypertension→**systolic blood pressure ≥140 mmhg, diastolic blood pressure ≥90 mmhg or history of medical treatment for hypertension. We are going to collect this variable as a *nominal categorical variable* (NO/YES)
  - **Dyslipemia →**total cholesterol ≥200 mg/dl, triglyceride level ≥ 150mg/dl or low-density lipoprotein ≥ 130 mg/dl or history of medical treatment for dyslipemia. We are going to collect this variable as a *nominal categorical one* (NO/YES).
  - **Body mass index→** normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) or obesity (≥30 kg/m^2). We are going to collect this variable as a *nominal categorical one* (normal weight/overweight/obesity). However, to simplify statistical analysis and because is more visual, we are going to analyze the BMI as: No obesity or Obesity.
  - **Diabetes mellitus →** use of hypoglycemic agent, fasting serum glucose >126 mg/dl or HbA1c >6,5%. We are going to collect this variable as a *nominal categorical one* (NO/YES).
- Toxic habits
  - **Smoking habit →**somoker, non-smoker (those have never smoke), ex-smoker (those who have been 5 years without smoking). We are going to collect this variable as a *nominal categorical one* (Non-smoker/smoker/ex-smoker)
  - **Alcohol habi**t → no drunker, sporadic drunker, usually drunker, ex-drunker (those who have been 2 years without alcohol). We are going to collect this variable as a *nominal categorical one* (no drunker/sporadic drunker/usually drunker/ex-drunker). However, to simplify the statistical analyses we are going to analyze this variable as: (No drunker/drunker)

- **Drug habit** →we take in account the type of substance that the patient consume (cocaine, cannabis, opioids, other drugs), no consumer, ex-consumer. We are going to collect this variable as a *nominal categorical one.*

- Previous pathologies
  - **peripherial artery disease** → documented in the clinical history of patients. We are going to collect this variable as a *nominal categorical one* (NO/YES).
  - **heart disease**→ All these data are documented in the clinical history of patients. We are going to collect this variable as a *nominal categorical one* (NO/YES).
  - **previous stroke**→ All these data are documented in the clinical history. We are going to collect this variable as a *nominal categorical one* (NO/YES).
- Presence of atherosclerotic markers in TSA/US
  - **Presence of atherosclerotic plaques** → it is evaluated with Doppler carotid ultrasonography of TSA and transcranial by the neurological vascular specialist during the hospitalization at stroke unit or at its arrive at urgency unit as a routine exploratory technique. We are going to collect this variable as a *nominal categorical one* (NO atherosclerotic plaques/presence of atherosclerotic plaque).
  - **Carotid stenosis** → it is evaluated with Doppler carotid ultrasonography of TSA and transcranial by the neurological vascular specialist during the hospitalization at stroke unit or at its arrive at urgency unit as a routine exploratory technique. We can found no stenosis in carotid arteries, significant stenosis of the carotid artery (>50%) or an occlusion of the carotid artery. We are going to collect this variable as a *nominal categorical one* (NO/stenosis/occlusion).
  - **Other vascular stenosis** → it is evaluated with Doppler carotid ultrasonography of TSA and transcranial by the neurological vascular specialist during the hospitalization at stroke unit or at arrive at urgency unit as a routine exploratory technique. We can found no stenosis in other cerebral vascular territories that are not the carotid arteries. We can found no stenosis in carotid arteries, significant stenosis of the carotid artery (>50%) or an occlusion of the carotid artery. We are going to collect this variable as a *nominal categorical one* (NO/stenosis/occlusion).
- Neurological scales of severity, vascular recurrences and territory affected of actual stroke
  - **Rankin modified scale** → is a neurological scale that evaluate the functional situation of the patients (SEE ANNEX 5). It is going to be evaluated at hospitalization, at discharge, at 3 months after discharge and 1 year after discharged by a specialized neurologist. In the 1 year after discharge evaluation could be assessed by telephone calling by a specialized nurse (SEE ANNEX 6). We are going to collect this variable as a *ordinal categorical variable*.

- **NIHSS** →is a neurological scale that evaluate the severity of the stroke and its disability due to it (SEE ANNEX 7). It is going to be evaluated at hospitalization, at discharge, at 3 months and 1 year after discharged by a specialized neurologist. We are going to collect this variable as a *ordinal categorical variable*.
- **Vascular recurrences** →It is going to be evaluated at 3 months after discharge and a 1 year using a questionnaire (SEE ANNEX 8). We are going to collect this variable as a *ordinal categorical variable*.
- **Territory affected** (TC/MRI) → it is shown in a cranial computed tomography scan or in a magnetic resonance imaging. The imaging technique done is the one the vascular neurological specialist considers adequate to show the territory that is affected. This imaging techniques can be done at urgency department when the patient arrives with a stroke code or when they are hospitalized at stroke unit for control. We can find an affectation of the anterior cerebral vascular system or the posterior cerebral vascular system. We can found an affectation of the anterior cerebral vascular system or the posterior cerebral vascular system. We are going to collect this variable as an *ordinal categorical variable* (anterior cerebral vascular system/posterior cerebral vascular system)

To sum up this part of variables we have to say that finally, all our variables are categorical ones. We have to take in account that as we explained, the age is going to be recorded in CRF as a quantitative variable but for statistically analyses and for the posterior discussion and results we are going to transformed it in a categorical one.

5. PROCEDURE AND DATA COLLECTION

5.1. Research team

Principal researcher → Specialized vascular neurologist: Dr. Joaquin Serena (JS)
Secondary researchers → Neurologist of the vascular team (NRL2) and Adina Ciscar (AC)
Collaborators → Nurse of the department (NRS) and statistical specialist

First of all, before starting the study there was a meeting of the principal researchers and the secondary ones. The principal researcher explained to the secondary researchers the idea of the study and they decided how the study is going to be conducted.
In this meeting also, JS and AC decided that it could be interesting take an advantage of the AC's rotation at Unit stroke and start collecting patients for the study for the propose to elaborate a preliminary analysis.

5.2 Preliminary analyses

The preliminary analysis has been conducted during the rotation of AC at Unit stroke. The period of the preliminary analysis lasts one month and a half and has been conducted at the same time as the protocol elaboration.

The aims of the preliminary analysis are:

- Check if the first design of the study is correct to achieve the proposed objectives of the study.
- Have some preliminary results to extract preliminary conclusions

To do the preliminary analysis a database with the SPSS has been created. This database is in which all the data of the total length of the study is going to be attached and in which we have based to analysis the preliminary results and in which the final results are going to be analyzed.

5.3 Responsibilities of the team

Principal researcher → Dr. Joaquin Serena, as the principal researcher, has the responsibility of coordinate, supervise and give clarifying ideas to have a quality study. Dr. JS is also the responsible of the visits of the patients at 3 months and a 1 year of being discharged each patient. Moreover, Dr. JS is the responsible of the statistical analysis, interpretations, publication and dissemination of the final results of the study.

Secondary researchers

- NRL 2 → a neurologist of the vascular team is the responsible joined to AC of the total patients' collection for the study, taking photographs, fill the CRF of each patients and introduce the data of the patients in the database.
- Adina Ciscar → as a secondary researcher, AC has the responsibility of the elaboration of the research protocol, the creation of the database and the performance of the preliminary analyses.

Collaborators

- NRS → As nurse of the neurological department, is the responsible of the telephone evaluation of the patients in case that they do not have to come back to the hospital. The nurse is also the responsible of the contact to the patients that for several reasons are lost for the study or do not come to their visits.
- Statistical specialized → Is the responsible of helping to the principal researcher if he have any doubt or problems in the performance of the statistical analyzes of the final results.

5.4 Data collection

Data obtained from participants is registered in the Case Report Form(CRF) (SEE ANNEX 2) and according to this form, reported to the study database. All variables are included.

Data will be collected by the research team, above all by the secondary researchers. All of them are currently working in the HDJT. The principal researcher is going to teach to the secondary researchers how to collect data in the CRF and how to use the Frank's sheet evaluation.

First of all, once the patients are stable and hospitalized at stroke unit, we will explain them about the study that is being conducted, and also offer the possibility to take part of it, if accepted an informed consentient will be given to them in order to be signed.
After signing the informed consent, we will proceed on taking the photographs of their both ears and of their identifying bracelet. All participants must have an identification number attached to their photographs, which remains linked to their medical record number in a protected database to ensure data confidentiality.

As the hospitalization period in Unit stroke is mainly 48 hours, the CRF of each patient has to be filled once the patient is discharged of the Unit Stroke. This procedure will not interfere in the normal function at the Unit stroke because the vascular neurologists will work by following the established protocol for the patients hospitalized at unit stroke.
When a patient is discharged of the Unit stroke his CRF must be filled in, to do that, the researcher has to access by the SAP to the medical history of the patient using the medical history number that appears in the identifying bracelet. The researcher has to look for the discharged inform of the patient and search for the necessary data to fill all the proposed aspects in the CRF. These proposed aspects are: baseline data, such as, the gender and the age; data about the actual stroke, such as, the type of stroke, etiology of the stroke and the location of the stroke; clinical features about the patient, such as, arterial hypertension, diabetes mellitus, dyslipidemia, obesity, if the patient has or has had a smoking, alcoholic and/or drug habit; the presence of previous diseases, such as, heart disease, peripheral artery disease or a previous stroke before the actual one; information about the duplex that has been done during the hospitalization, of this, the researcher has to search only if the patient has an atherosclerotic plaque in their cerebral arteries, if the patient has a stenosis of the carotid artery or the other cerebral vascular territory; the researcher also has to search the modified rankin scale number at hospitalization and when he is discharged and the hospitalization NIHSS punctuation and the discharged one.

Independently of the data collection for the part of the CRF that we have explained above, the presence or not of the Frank's sign of each patient has also to be filled in the CRF. For do this activity there will be

meetings with all the researchers to evaluate the photographs that have been taken. To do that, the researchers have to use the evaluation sheet of Frank's sign (SEE ANNEX 3).
The Frank's sign must be evaluated by the principal neurologist and the secondary ones, for each evaluator there is one evaluation sheet where the expert writes the results and his identification. This process needs to be completed in a blinded way, this means that the evaluators do not know which patient are they evaluating, for that, the researchers have to identify the evaluation Frank's sign sheet using the identification number attached to the photographs of the patients.
First, the principal researcher evaluates the photographs and writes the result and his evaluation number in the evaluating sheet, once his evaluation has done, it is time for the other neurologist and then for the nurse. Once the three researchers have evaluated the photographs of the patients, it is time to put in common and reach consensus, if there is not a consensus who have the last decision is the principal researcher. The consensus result has to be written also in the CRF of each patient. The frequency of these meetings will be when the research team consider that they have a considerable amount of patients, more or less each time that they have 50-60 patients collected.

To end with the first part of the collecting data procedure, the CRF needs to be completed including the evaluation of the Frank's sign. Once all the CRF of all the patients that are included in the study are completely filled, is time to put all the data in the database by the statistical specialist.

The second part of the data collecting for the study consists in a data obtained from the evaluation of all the patients at 3 months and at 1 year after being discharged.
The first evaluation of each patient is going to be at 3 months after being discharged. This evaluation is going to be done in the routine visit that all the patients which were hospitalized in the Unit Stroke have. The responsible of this visit is the principal neurologist, the data that is going to be obtained for the study is the functional status of the patient evaluated by the modified Rankin scale and the presence of any vascular recurrence evaluated by a questionnaire (SEE ANNEX 8). The results of this evaluation must be written in the corresponding part of the CRF.
The second evaluation of each patient is going to be done after one year of being discharged. The second evaluation could be done in two different ways, depending on the conditions of each patient. If the patient has suffered a severe stroke or if in the first visit the neurologist considers that the patient needs a second visit as routine, the second evaluation is going to be done like the first one, the neurologist will evaluate if there are any changes in the functional state of the patient using the modified Rankin scale and also asks for any vascular recurrence using the same questionnaire. However, if the patient has suffered a mild stroke or if in the first visit the neurologist considers that the patient is approved to be discharged, or even if the patient for his own decision does not want to go back to the visit, the evaluation has to be done via telephone call, for that work, the neurological department has a specialized

nurse who is the responsible to do this evaluation. In this evaluation the same data is going to be obtained, for the functional status, the nurse has to use the validate modified Rankin scale via telephone call (SEE ANNEX 6), the nurse also has to ask for any vascular recurrence, using the same questionnaire as in the other parts (ANNEX 8) but ignoring the part of physic exploration . The results of this evaluation must be written in the corresponding part of the CRF.

Once we have all the information of each patient that has been recruited in the study, it is time to fill this part in the database by statistical specialist.

STATISTICAL ANALYSIS

First, we are going to describe all the variables by creating a descriptive table with the different variables. Results will be expressed as frequencies (n) or percentages (%) for categorical variables and as mean ± standard deviation (SD) for continuous variables depending on whether or not they are normally distributed. We will evaluate the normal distribution of the variables by using the kolmogórov-Smirnov test.

Once the description of the variables is done, we will do bivariate statistical study in which we will compare the principal variable that is Frank's sign between the secondary and tertiary ones. Due to we regrouped all the continuous quantitative variables in categorical ones as we explained before, we are going to show the percentages in a contingency table and the analyses is going to be performed in a chi-squared test.

Finally, logistic regression model will be applied to evaluate the independent relation between the frank's sign in stroke recurrence or the modified rankin scale for the functional prognosis adjusted by confounding factors.

For all analyses, a p value of <0.05 is going to be considered.

We also use a kappa index to give reliability to the visual and manually assessment of the Frank's sign because is a categorical variable, using that index we measure the variability between the different observers that are going to perform the evaluation of the sign, as well as we exclude the randomly concordance.

STATISTICAL ANALYSIS FOR PRELIMINARY RESULTS

To assess the preliminary results we are going to describe the variables in a contingency table, expressing the results as frequencies (n) and percentages (%), when variables are categorical and as mean ± standard deviation (SD) when variables are continue. We also are going to assess a bivariate analysis to compare the Frank's sign between all other variable to achieve the main objectives of the study, as the variables are categorical a chi-squared test is going to be performed. P value <0.05 is going to be considered as statistical significant.

ETHICAL CONSIDERATIONS

This project will be evaluated and approved by the Clinical Research Ethics Committee (CEIC) of the "Hospital Doctor Josep Trueta" and by the Autonomous Community Authorities.

Ethical Principles for Medical Research Involving Human Subjects defined in the World Medical Association Declaration of Helsinki will be accurately considered in this study to ensure the human rights and ethical tenets.

All participants will be appropriately informed and will be given an information sheet (Annex 1) about the study before being included. Subjects will have to voluntarily sign the informed consent (Annex 1).

To guarantee and protect confidentiality of all participants, information collection during the course of this study will be performed in accordance to "Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal" and "Real decreto 1720/2007, de 21 de diciembre por el que se aprueba el Reglamento de desarrollo de la Ley Orgánica 15/1999".

This study will respect biomedical regulation according to "Ley 14/2007, de 3 de julio, de Investigación Biomédica" for invasive procedures.

Participants have the right to access, modify, oppose or remove their personal data contained in the file as well as to leave the study at any time.

STUDY LIMITATIONS

Several limitations should be acknowledged

-As this study has a cross-sectional design it will not allow us to establish causal inferences between the principal variable and the secondary and tertiary ones. Therefore, it will be establishing frequencies.

-Since it will be used a non-probabilistic consecutive sampling method a selection bias can be produced.

-We use an hospitalary sample, it means, for example that not all the strokes that arrives at the urgency department are hospitalized at the Unit stroke and also not all the patients who suffered a stroke ask for hospital care, so for that reason we can lose possible participants, but as stroke is a disabling disease and the most of times have an evident clinic, we expect that it will be insignificant.

-Possible loss of participants during the time between the discharged and the evaluation at 3 months at a 1 year may be a limitation in this study, but as we said before, stroke is a disabling disease and at least the evaluation at 3 months of the discharged is part of the medical care and the patients are cited before going home, we expect that it will be insignificant. The death of the participants is possibly the main reason of participants' loss that this study predicts. Ambulance transport will be provided to patients with limited mobility. If the patients do not attend the appointment, the hospital will try to contact with them via phone call to identify the cause of their absence and try to enroll them, and if it is not possible the evaluation could be done via telephone call.

-The part of taking the photographs may be another limitation because the time that patients are hospitalized at the Unit stroke is so short, and is possible that a patient could be hospitalized during the weekend and for many reasons could be overlook, to avoid this, all members of the Unit stroke, including nurses and auxiliaries will be alerted of the existence of this study to take the photographs when is needed.

WORK PLAN

The study has been designed in six stages. There are stages in which the period of time in them overlaps during some weeks, but the activities that are been performed are clearly divided.

- **Stage 0. Introduction meeting (1 week)**
  - **Activity 0. Introduction meeting**. This activity has been accomplished. The proposal of this phase was to coordinate the design of the study, take the decision to make a preliminary study and elaborate the informed consent to start the collection of patients. This meeting was carried out by the principal researcher and the secondary ones.

- **Stage 1. Protocol elaboration and preliminary study (1 month and a half)**
  - **Activity 1. Protocol elaboration.** This activity has been accomplished in a period of one month and a half. The responsible of this activity has been AC.
  - **Activity 2. Start the collection of patients.** This activity starts at the same time that starts the protocol elaboration. The responsible of this activity are the secondary researchers. The secondary researchers were trained by the principal researcher in the use of the Frank's sign sheet evaluation and in the use of the CRF before the star of the patient's collection. During the patients' collection, the CRF of each patient is going to be filled.
  - **Activity 3. Collect patients for the preliminary analysis.** This activity has been accomplished in a period of one month meanwhile AC was rotating in the Unit Stroke with NRL 2. The responsible of this activity has been AC. Moreover, in this period of time AC has created the database with SPSS where all the length of the study is going to be performed. The CRF of the patients had been filled each time each patient was discharged.
  - **Activity 4. Preliminary analysis.** After one month of collecting patients for the study, AC and JS decided to stop collecting patients for the preliminary study. However, the collection of patients for the final study is still ongoing. When they had the patients for the preliminary study, they perform a meet with the NRL2 to evaluate the presence of Frank's sign of those preliminary patients. When they had all the necessary data of each patient of this preliminary analysis, AC introduce the data in the SPSS. AC and JS performed the statistical analysis for the preliminary analyses, interpreted the results and wrote conclusions that have been attached to the protocol.
  - **Activity 5. Obtaining the ethical approval.** The responsible of this activity is the principal researcher, once the protocol had been finished

- **Stage 2. Continue collecting patients (4 months)**[2]
    - **Activity 6. Collecting patients**. As it is said above, the collecting of the patients is still ongoing after the study of the preliminary analyses. The patients collected for the preliminary analyses also will appear in the final results. This activity is responsibility of AC and NRL2.
    - **Activity 7. Fill CRF and Frank's sign evaluation**. The CRF of each patient is going to be filled each time a patient is discharged. When the secondary researchers have more or less 50-60 patients collected they are going to perform a meeting with the principal researcher to evaluate the presence of Frank's sign

- **Stage 3. Evaluation at three months after discharged (4 months)**
    - **Activity 8. Evaluation at 3 months**. The first three months' evaluation is going to start when the first patient collected have three months after its discharged. Each patient that have been recruited in the period of 4 months that we have been explained before is going to be evaluated at 3 months after discharged. This period lasts until the last patient that have been recruited for the study has his three months' evaluation. This activity is responsibility of the principal researcher, Dr.JS. The NRS has the responsibility of contact with the patients that for several reasons does not come to the visit.
    - **Activity 9. Fill CRF**. Each time this three months' after discharged visit is completed, the principal researcher have to put the results in the CRF.

- **Stage 4. Evaluation at one year after discharged (4 months)**
    - **Activity 10. Evaluation at 1 year after discharged**. The first one year' evaluation is going to start when the first patient collected have 1 year after its discharged, as above, this period lasts until the last patient that have been recruited for the study has his 1 years' evaluation. This activity is responsibility of the first researcher, Dr. JS. The NRS is the responsibility of the evaluation via telephone call of those patients that not come to the presencial consult, also is the responsible of contact with the patients that for several reasons do not come to the visit.
    - **Activity 11. Fill the CRF.** Each time each 1 year' after discharge visit is completed, the principal researcher, or the NRS in case that the evaluation is via telephone call, have to put the results in the CRF.

[2] The one month and a half of the stage 1 is also included in this period of 4 months, even the activities that are performed in each stage are independent.

- **Stage 5. Data analysis and interpretation (1 month)**
    - **Activity 12. Statistical analysis.** Once the last one years' visit after discharged is done and all the CRF of each patients are completed, data will be introduced in the database. When all the database of the total length of the study is filled, data will be analysed by the SPSS. This activity is responsibility of the principal researcher, in case of doubts or if the analyses are complicated, the statistical specialist will help Dr. JS to perform all the analysis.
    - **Activity 13. Interpretation and discussion of the results.** The results will be interpreted and discussed by all the team. The principal responsible is the principal researcher.

- **Stage 6. Publication and dissemination of the results (3 months)**
    - **Activity 14. Publication of the results.** Final research findings and conclusions will be written and published in journal articles. The responsible is the principal researcher
    - **Activity 15. Dissemination of the results.** Attendance to conferences to present the results of the study. The responsible is the principal researcher.

FEASEABILITY

The research study will be carried out at HDJT in Girona in which all the study members are currently working. The neurologists' team have fifteen years of experience in the research of cerebrovascular disease and has become a consolidated investigation group being included in the "Red RENEVAS, RD07/OO26/2002 RETICS".

All the parts of the study will be carried out in the HJDT. The patients that will be included in the study only have to permit having their ears photographed and the attendance of a telephone calling if it is not needed that they had to return to the consult at one year after being discharged. All the process of the study is going to be performed using the resources that we have, it is the case of the discharged informed and the visits that we cited as routine to all the patients that have been hospitalized in the Unit Stroke. Furthermore, for the total length of our proposed study, will not need extra resources from hospital as researchers, because all we need is going to be obtained from the exploration and anamnesis that we used to do as routine. For that reason, the study proposed is achievable in economically terms. Moreover, we are not going to need extra researcher personnel, because it is sufficient with the staff that are currently working in the HDJT.

In terms of duration is also feasible, because as in the Stroke Unit there are more than 600 hospitalizations/year, we expect that our total needed sample size can be achievable in a period of 4 months of patients' recruitment.

Another point to take into account is that the statistically analysis that is going to be performed to acquire the proposed objectives is easy and it is competence of the principal researcher, however, he only will resort to the statistical specialist in the case of doubts.

BUDGET

-The major part of the procedures included in this study are already done as routine in the common protocol for diagnosis, treatment and follow up of stroke, for that reason, it will not suppose any additional expenses.
-The personnel that we need for the study are currently working in the hospital and this work is not going to be extra remunerated.
-The photographs that we need to assess the Frank's sign are going to be done in the personal mobile phone or camera of the researcher.

Even so, we have to take into account this possible extra costs:

-The costs of the **telephone calls** to the patients that are not going to come back at 1 year after discharged and the visit has to be done via telephone call:

- Modified Rankin scale formulary via telephone call → 7 minutes to be assessed
- Vascular recurrences questionnaire → 10 minutes to be assessed

➢ 17 min. x 0.12€/min =2.04€ per call. We expect an average of 140 patients that are going to need this assessment. → **204€ x 140 patients = 285.6€**

-The costs of the **paper and tint to print**:

- Information sheet and informed consent → 4 sheets x 265 patients = 1060 sheets
- Frank's sign sheet evaluation → 3 sheets x 3 copy (for each researcher) x 265 patients =2385 sheets
- CRF → 4 sheets x 265 patients =1060 sheets

➢ **Total of 4505 sheets x 0.03€ per sheet =135.15€**

-**Hiring a statistical specialized in case of doubts** of the principal researcher. We expect that we are going to need a statistical assessment only to check if the analysis done is correct. We also expect to solve all the doubts that could have the principal researcher in the same meeting as the check one, so we have supposed that we are going to need his help for a total of 10 hours.

➢ **Total of 10 hours x 30€ per hour =300€**

-finally, we have to consider the expenses from:

- Attending a congress to present the results→ it will cost 500€.
- Publication costs → it will cost 2000€

➢ **Total of 2500€**

We need in total → 285.6 + 135.15 +300 + 2500 = 3220.75€

IMPACT OF THE PROJECT

As we previously discussed in the introduction and justification, ischemic stroke has a huge socioeconomic impact in the national healthcare as it is the first cause of long term morbidities in our country, so it is an important problem where we have to make all necessary efforts to decrease it.

If the results obtained in this study are relevant and our hypotheses are validated, we will have made an important step forward in the identification of a cutaneous marker that, only with a quick glance, could give us lots of answers in terms of the physiopthological process of atherosclerosis involved in the stroke.

- Could help us to identify atherotrombotic subtype of stroke with no more than a glimpse.

- Could help us to guide those patients who have suffered a cryptogenic stroke in the identification of their real physiopathological profile. This identification could allow us to indicate advanced diagnostic techniques to diagnose the most probable cause of their stroke, decreasing the rate of patients diagnosed us cryptogenic stroke, because as we said previously, being diagnosed as cryptogenic stroke have lots of disadvantages.
  The most important aspect that we would improve would be the indication, with a higher security, of a secondary prevention treatment to avoid, as much as possible, the greater rates of recurrences in this subtype of stroke.

- Could help us to predict, with a higher security, the bad prognosis of those patients that have suffered an atherotrombotic stroke.

PRELIMINARY RESULTS

We describe the preliminary results of this ongoing study, analyzing the results in the first 38 included patients when the design of this protocol was closed for evaluation.

Patients were collected between September and October of 2016, during my period of rotation in the Stroke Unit at Hospital Doctor Josep Trueta.

-The mean age of the total population was 70,1 ± 13,5;

-Of the total 38 patients, 30 were male (78,9%) and 8 (21,1%) female.

-The Frank's sign was present in 22 out of 38 patients (57,9%).

Table 1 shows the distribution of patients by age and the prevalence of Frank's sign in every group of age, as explained in methods and materials section.

Table 1. Proportion of patients and prevalence of Frank's sign between range of age

Range of age	Proportion of patients (n, %)	Prevalence of Frank's sign (n, %)
≤ 50 years' old	3 (7,9)	0 (0)
51-59 years' old	7 (18,4)	4 (57,1)
60-69 years' old	8 (21,1)	2 (25,0)
70-71 years' old	7 (18,4)	5 (71,4)
≥80 years old	13 (34,2)	11 (84,6)

-Of the total population, 31 patients (81,6%) suffered an acute ischemic stroke, 3 (7,9%) a TIA, and 4 (10,5%) a hemorrhagic stroke.

Table 2 shows the distribution of ischemic stroke by etiopathogenic stroke subtype.

Table 2. Proportion of patients between etiology of ischemic stroke

Stroke subtype	Proportion of patients (n, %)
Atherothrombotic stroke	7 (20,6%)
Cardioembolic stroke	10 (29,4%)
Lacunar stroke	4 (11,8%)
Cryptogenic stroke	12 (35,3%)
Stroke of other determined etiology	1 (2,9%)

Table 3 shows the bivariate analysis of Frank's sign by clinical variables included in the protocol.

Table 3. *Distribution of Frank's sign between subtypes of stroke*

	Frank's sign		*Total*	**p value**
	YES (n=22)	**NO (n=16)**	*(n=38)*	
Gender				0.27
Male, n (%)	16 (53,3)	14 (46,7)	30 (78.9)	
Female, n (%)	6 (75)	2 (25)	8 (21.1)	
Age, mean ± SD	74,9 ± 12,6	63,6 ± 12,2	70,1 ± 13,5	<0.05
Age, n (%)				<0.05
≤50	0 (0)	3 (100)	3 (7.9)	
51-59	4 (57,1)	3 (42,9)	7(18.4)	
60-69	2 (25)	6 (75,0)	8 (21.1)	
70-79	5 (71, 4)	2 (28,6)	7(18.4)	
≥80	11 (84,6)	2(15,4)	13 (34.2)	
Stroke, n (%)				<0.05
Infarction	20 (64,5)	11 (35,5)	31 (81.6)	
TIA	2 (66,7)	1 (33,3)	3 (7.9)	
Hemorragic	0 (0)	4 (100)	4 (10.5)	
Ischemic Stroke Subtype, n (%)				0.46
Atherothrombotic	5 (71,4)	2(28,6)	7(20.6)	
Cardioembolic	7 (70)	3 (30)	10 (29.4)	
Lacunar	1 (25)	3(75)	4 (11.8)	
Cryptogenic	8 (66,7)	4 (33,3)	12 (35.3)	
Arterial hypertension, n (%)	16 (61,5)	10 (38,5)	26 (68.4)	0.50
Diabetes Mellitus, n (%)	6 (60)	4 (40)	10 (26.3)	0.87
Dyslipidemia, n (%)	9 (47,4)	10 (52,6)	19 (50)	0.19
Obesity, n (%)	4 (66,7)	2 (33,3)	6 (20)	0.63
Smoking, n (%)				0.20
smoker	2 (28,6)	5 (71,4)	7(18.4)	
ex-smoker	9 (60)	6 (40)	15 (39.5)	
Alcohol habit, n (%)	4 (44,4)	5 (55,6)	9 (23.7)	0.11
Heart disease, n (%)	10 (76,9)	3 (23,1)	13 (34.2)	0.08
Previous stroke, n (%)	6 (85,7)	1 (14,3)	7(21.9)	0.10
Atherosclerotic plaque, n (%)	10 (62.5)	6 (37,5)	16(44.4)	0.28
Stenosis carotid arteries, n (%)	6 (85,7)	1 (14,3)	7 (18.9)	0.08
Stenosis other arteries, n (%)	5 (83,3)	1 (16,7)	6 (15.7)	0.15

We can summarize the main results of the bivariate analysis:

-The prevalence of Frank's sign was higher in man than in women (72,2% vs. 27,3%, p=0.2), although non-statistically significant in this partial and small sample size.

-We detected a significant association between the presence of Frank's sign and age, being more prevalence in older patients (74.9 ± 12.6 vs. 63.6 ± 12.2, p<0.05).

-An interesting finding, non-previously described, was the low prevalence of Frank's sing in hemorrhagic stroke in comparison with ischemic stroke (0% vs 64,5%, p=0.04) as well as the distribution of Frank's sign by etiopathogenic subtypes in ischemic stroke. The prevalence of Frank sign was extremely low in lacunar infarction (25%) with similar prevalence in atherothrombotic, cardioembolic and cryptogenic stroke (71,4%, 70%, 66,7% respectively, table 3 and figure 1).

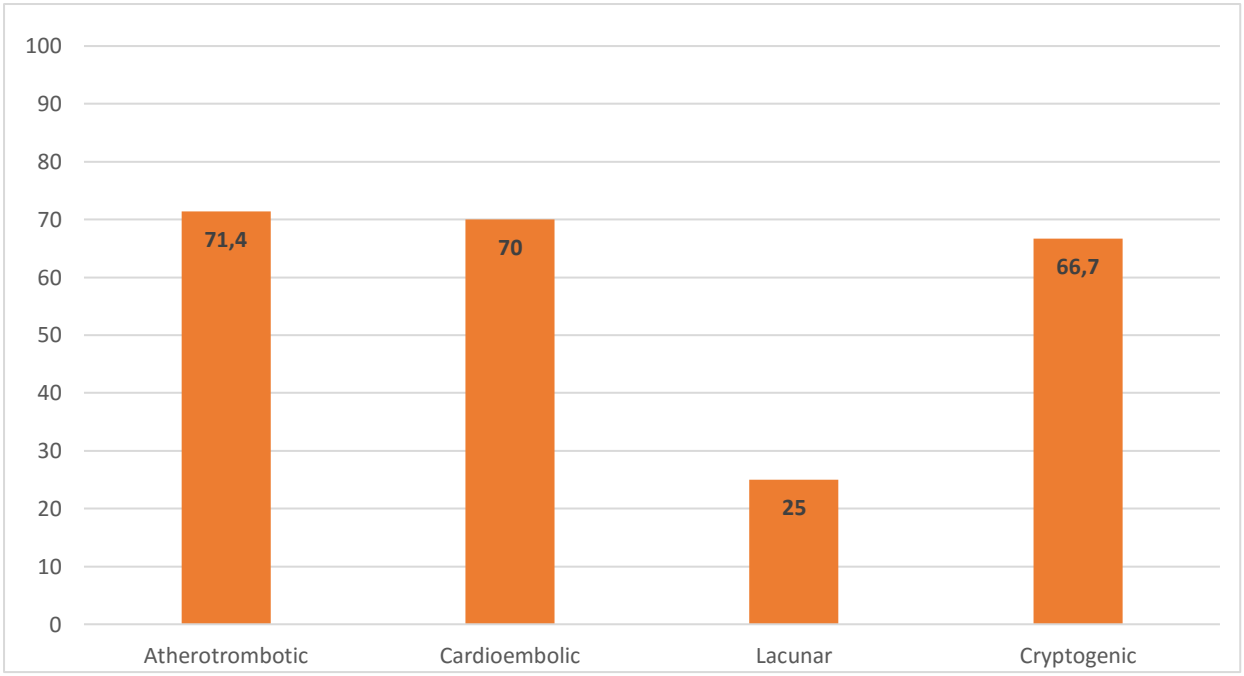


***Figure 1**. prevalence of Frank's sign between subtypes of stroke*

-With respect to classical stroke risk factors, we found no statistical association with the presence of Frank's sign, although, the proportion of patients that have a Frank's sign was higher in those with classical stroke risk factors, such as arterial hypertension, diabetes, obesity and ex-smoking habit (61,5%, 60%, 66.7%, 60%, respectively, table 3, figure 2). The prevalence of dyslipidemia and an alcoholic habit between those patients who have Frank's sign was lower than in those without Frank's sign (47.4%, 44.4%, respectively, table 3 figure 2)

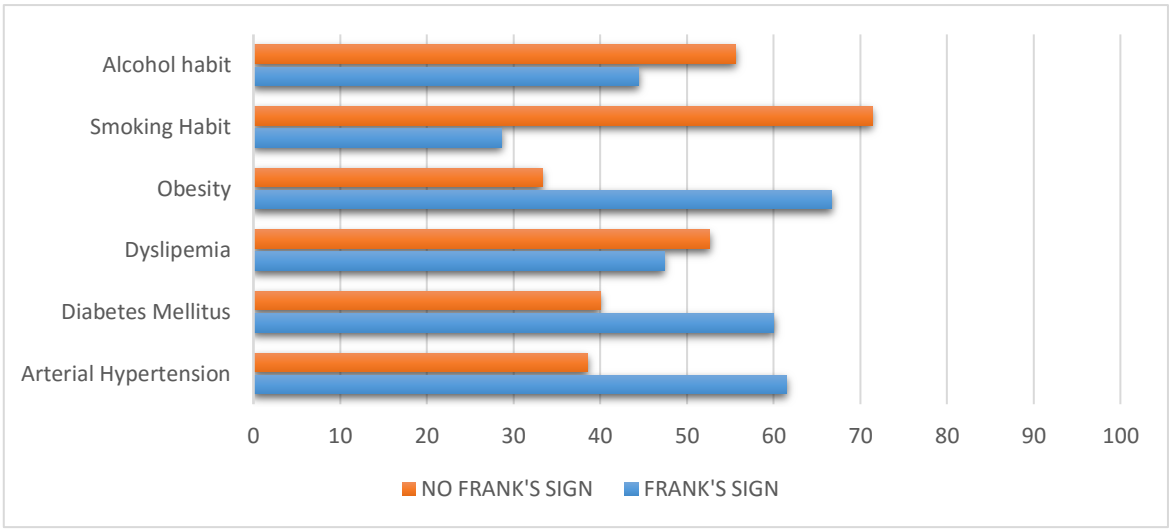


Figure 2. Frank's sign between Risk Vascular Factors

-With respect to Frank's sign and previous diseases, we found a clear tendency to the association between, previous history of ischemic heart disease and the presence of Frank's sign (76,9% vs. 23,1%, p=0.08, table 3), as well as with previous ischemic stroke (85,7% vs 14,3%, table 3)

-The analysis of three classical carotid duplex markers of vascular atherosclerosis (presence of atherosclerotic plaques, stenosis or occlusion of carotid arteries and stenosis or occlusion of other vascular cerebral territories), we detect a non-statistically significant association but as well with a clear tendency, between the presence of these duplex markers and the presence of Frank's sign (62,5% vs. 37,5%, p=0.28; 87,7% vs. 14%, p=0.08; 83,3% vs. 16,7%, p=0.1 respectively, table 3, figure 3).

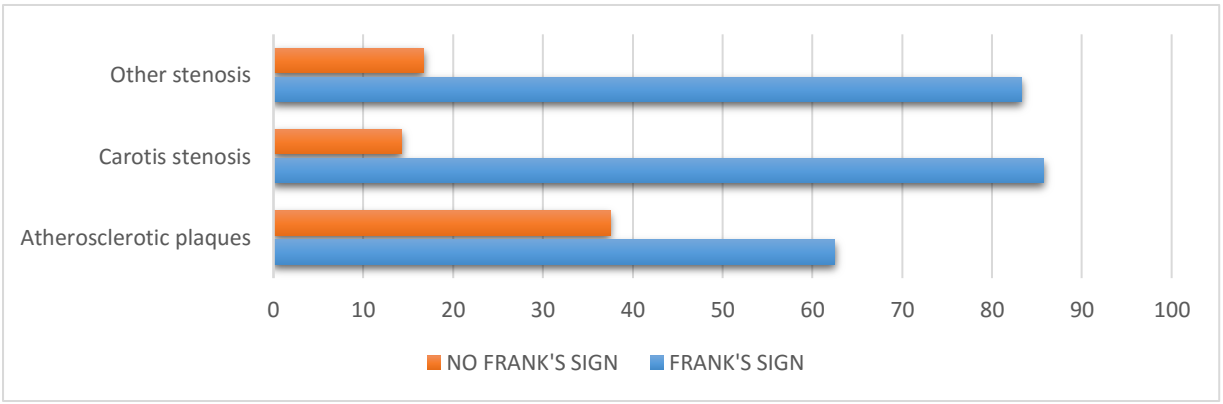


Figure 3. Frank's sign and atherosclerotic dupplex markers

Distribution of Frank's sign in cryptogenic stroke

Although the actual small sample is insufficient to obtain solid conclusion, in Table 4 we show the bivariate analyses of Frank's sign in the etiopathogenic subgroup of patients suffering from a cryptogenic stroke by clinical variables included in the protocol.

Table 4. Frank's sign and cryptogenic stroke

	Frank's sign		Total	P
	YES (n=8)	NO n=4)	(n=12)	value
Gender, n (%)				0.27
Males	6 (60)	4 (40)	10 (83.3)	
Females	2(100)	0 (0)	2 (16.7)	
Age, mean ± SD	79,7 ± 9,7	58,5 ± 8,8	72,7 ± 13,8	<0.05
Age				<0.05
≤50 years old	0 (0)	1 (100)	1 (8.3)	
51-59 years' old	1 (50)	1 (50)	2 (16.7)	
60-69 years' old	0 (0)	2 (100)	2 (16.7)	
70-79 years' old	1 (100)	0 (0)	1 (8.3)	
≥80 years old	6 (100)	0 (0)	6 (50.0)	
Location n (%)				0.21
Anterior cerebral circulation	4 (66,7)	2 (33,3)	6 (85.7)	
Posterior cerebral circulation	0 (0)	1 (100)	1 (14.3)	
Arterial Hypertension, n (%)	5 (71,4)	2 (28,6)	7 (58.3)	0.67
Diabetes Mellitus, n (%)	3 (75)	1 (25)	4 (33.3)	0.66
Dyslipidemia, n (%)	4 (66,6)	2 (33,3)	6 (50)	1.00
Smoking habit, n (%)				0.16
Smoker	1 (33.3)	2 (66.7)	3 (25)	
Ex-smoker	3 (60)	2 (40)	5 (41.7)	
Alcohol habit, n (%)	2 (40)	3 (60)	5 (41.7)	0.09
Heart disease, n (%)	2 (100)	0 (0)	2 (16.7)	0.27
Previous stroke, n (%)	1 (100)	0 (0)	1 (8.3)	0.46
Atherosclerotic plaques, n (%)	3 (50)	3 (50)	6 (50)	0.22
Stenosis carotid arteries, n (%)	1 (100)	0 (0)	1 (8.3)	0.46
Stenosis other arteries, n (%)	2 (100)	0 (0)	2 (16.7)	0.51

We are going to summarize the main results of the bivariate analyses between Frank's sign and cryptogenic stroke by clinical variables included in protocol:

-Of the total 38 patients, 12 (35.3%) of them have suffered a cryptogenic stroke.
-Among the patients who has suffered a cryptogenic stroke, we can found a highly prevalence of the Frank's sign in them. (66.7% vs 33.3%).
-We found a statistically significant association between Frank's sign and age in cryptogenic stroke, being older those who have Frank's sign, and its prevalence increase with age.
-Frank's sign is more frequent in anterior cerebral circulation territory (66.7% vs 33.3%).
-Patients who have Frank's sign in cryptogenic stroke have a higher prevalence in arterial hypertension, as well as diabetes and dyslipidemia (71,4%, 75%, 66%, respectively, figure 4).
-The smoking habit and alcohol habit seems to be related with the absence of Frank's sign in those who have cryptogenic stroke (33.3%, 40%, respectively, figure 4)
-Patients who have suffered a cryptogenic stroke and have Frank's sign, have a higher prevalence of previous history of heart disease and previous stroke before the actual one.
-As in the total population, we observe a trend to a high prevalence of the three analyzed markers of atherosclerosis in the carotid duplex study in those patients who have a cryptogenic stroke and Frank's sign.

However, we must to reanalyze these tendencies when the study ends and the sample of cryptogenic stroke would be greater.

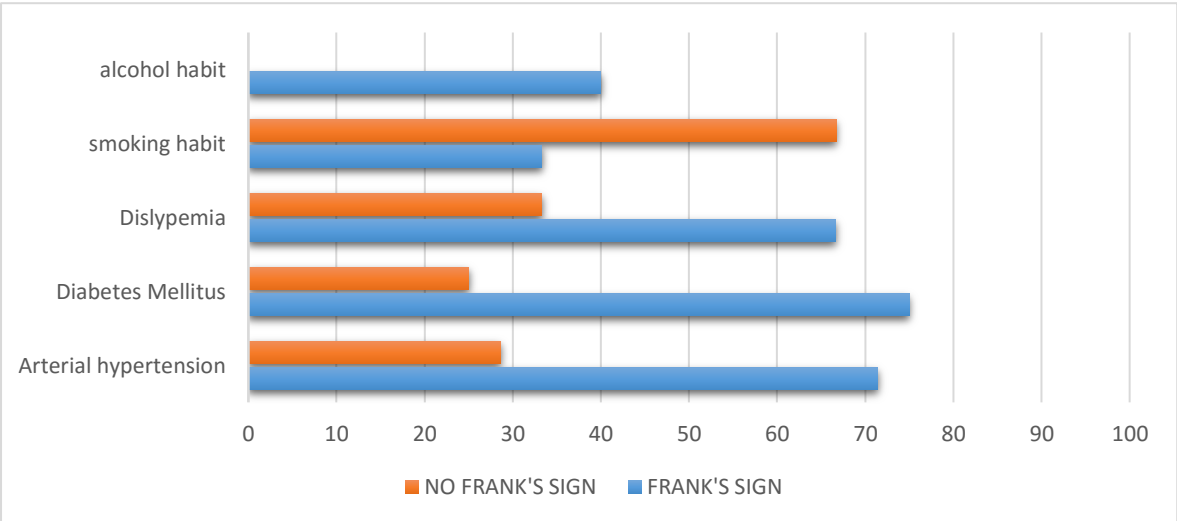


Figure 4. Frank's sign and risk vascular factors in cryptogenic stroke

DISCUSSION

1. FRANK'S SIGN BETWEEN SUBTYPES OF STROKE

The association between Frank's sign and cardiovascular artery disease (CAD) has been reported several times since Frank, in 1973, noticed that many cardiac patients had earlobe crease(3). In these studies, the prevalence of Frank's sign between patients that have suffered a myocardial infraction is higher than between the group of controls(9)(2)(1), for instance, in a study performed by *Shoenfeld et al.* found a higher prevalence (77%) of Frank's sign in 421 patients with MI when compared with a 40% prevalence rate of 421 controls (8). Some of these studies, and other authors also found a prevalence of the classical risk factors of vascular diseases between subjects who have Frank's sign (35)(4). Although there are few studies that assessed the prevalence of Frank's sign between cerebrovascular diseases, those who reported a relation between Frank's sign and the carotid artery intima-media thickness (IMT) as a risk factor for cerebrovascular disease, show a high IMT in the Frank's sign group than in controls (0.90±0.24 vs 0.77±0.15, respectively, $p<0.001$)(13) and (0.88±0.14 vs 0.69±0.14mm, respectively, $p<0.0001$)(36). Moreover, there is one preliminary report that found a prevalence of 59% of the Frank's sign between a group of 116 (68 of 116 patients) patients that has ischemic stroke, whereas 41% of those 116 patients (48 of 116) did not have Frank's sign ($p<0.05$)(34). However, there are no studies that assessed the prevalence of Frank's sign between subtypes of stoke, and show this prevalence is one of the aims of our study.
In our series of preliminary results, we found a high prevalence, 57.9%, of Frank's sign in stroke. (22 out of 38 patients,)

As we explained before, this is a preliminary study and for that reason our current sample (n=38) is insufficient. However, we have thought that could be interesting perform a preliminary analysis and extract preliminary conclusions using the patients that we have collected in the month of my rotation in the stroke unit. This study that we have designed, as we also say, is still ongoing. The final results with the correct sample size are pending to be realized.

In our series we can observe that Frank's sign has a high prevalence between females that have suffered a stroke. The Frank's sign is being more prevalent as the patients increased their age, in agreement with -previous studies(6).

An interesting finding of our study, not previously referred in the literature, is the absence of Frank's sign in haemorrhagic strokes. Focusing in the main objective of our study and with respect to stroke subtypes, we have observed that the Frank's sign have a similar distribution in atherotrombotic and cardioembolic aetiology. A potential explanation for this findings, as we initially expected a lower prevalence of Frank's sign in cardioembolic stroke may be that cardiac sources of embolism (akinetic left ventricular segment, dilated cardiomyopathy, arrhythmias, such as atrial fibrillation)(27)(29), are at the same time a consequences of ischemic heart disease (myocardial infraction) a disease of atherotrombotic pathogenesis. As we have commented on, there are many studies that related the Frank's sign with coronary artery diseases, so it is possible that the presence of the Frank's sign in cardioembolic stroke is due to the concomitant presence of coronary artery disease and stroke in this patients.

We first describe a low prevalence of Frank's sign in lacunar stroke subtype, only 25% of patients suffering lacunar strokes have Frank's sign and, within patients with Frank's sign, the prevalence of lacunar stroke was extremely and significantly low (4.5%). One potential explanation for this interesting finding could be that the physiopathology of lacunar stroke is not the same as the atherotrombotic one. The vessels that are involved in lacunar stroke are small (often described as "small vessel disease" rather than as lacunar stroke), with less than 200 μm of diameter and have a lack of tunica media. The tunica media is the part of the vessel where we can found the elastic fiber that are involved in the physiopathology of the Frank's sign and atherosclerosis disease. In lacunar stroke the pathophysiological underlying disease in lipohialinosis and fibrinoid necrosis involving essentially intima layer, whereas in atherotrombotic diseases, tunica media is involved, affecting larger vessel such us carotid arteries, mean cerebral artery or coronary arteries (37)(31). The absence of tunica media of the vessel in the arteries involved in lacunar strokes and the different stroke mechanism could explain the low association between the presence of Frank's sign and this subtype of stroke. These hypothesis are agree with ours results and reinforce that the Frank's sign is related to the atherosclerotic process.

Frank's sign is associated to classical vascular risk factors, also involved in atherosclerotic process(8). In our preliminary results we found an association between Frank's sign and hypertension and also with diabetes and smoking habit. However, it seems that Frank's sign is not related with dyslipidaemia and alcohol habit. We found a relationship between previous

clinical history of heart disease and previous stroke and the presence of Frank's sign, in agreement with previous published studies and the hypothesis of Frank's sign as a marker of atherosclerotic disease(2). In this same line, we observe a highly prevalent association of three markers of atherosclerotic disease analysed in the carotid ultrasonography study with Frank's sign.

2. FRANK'S SIGN BETWEEN CRYPTOGENIC STROKE

Frank's sign is prevalent in those patients who have suffered a cryptogenic stroke, being present in 2/3 parts of them. This is compelling because we have focused in this particularly important subtype of stroke to study the characteristics of those patients in order to achieve the second main objective of our study. The high prevalence of Frank's sign in this stroke subtype suggest that Frank's sign is an important marker to take into account in the study in this subtype of stroke. Frank's sign could be of clinical utility to stratify more adequately the real underlying cause in cryptogenic stroke

We found that the profile of those patients who have suffered a cryptogenic stroke and have the presence of Frank's sign shows a more atherosclerotic outline than those without-Frank's sign. Cryptogenic stroke with Frank's sign have more prevalence of hypertension, diabetes and dyslipidaemia, they have also more prevalence of previous history of heart diseases and previous stroke, as well as the three duplex markers of atherosclerotic process we have mentioned above. These preliminary results suggest that we could guide us to make plus advanced diagnosed tests to search for atherotrombotic underlying causes among those cryptogenic stoke with Frank's sign and emphasize in the type of treatment. One type of advanced test that could be useful for those patients who have Frank's sign and cryptogenic stroke is the high-resolution-MRI techniques. Using this technique is easier to find the burden and the distribution of the vulnerable atherosclerotic plaque that cannot be find by the habitual techniques. This technique has a clinical relevance and also can be used in monitoring the effect of treatment, such as statins. Talking about the treatment, as we detect that these patients with cryptogenic stroke and Frank's sign are closer to have more atherosclerotic profile, using an intensive treatment with antiplatelet drugs and statins could decrease the high rates of recurrences found in these patients because the secondary prevention is more targeted in the underlying cause of their stroke.

To sum up, we have to say that, as we say above, our preliminary study has some obvious limitations. These results are very preliminary because the sample size is still insufficient and the total length of the collection of the patients is ongoing. However, if we confirm all these results once the sample size will be correct, are very encouraging.

We also have to say that although our sample size is very small, the results that we have found are congruent and concordant with the previous studies reported, in this line we expect that some of the suggested results in our preliminary study could be confirmed when we have all the necessary sample size.

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ANNEXES

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ANNEX 1: INFORMATION SHEET AND INFORMED CONSENT

HOJA DE INFORMACIÓN AL PACIENTE

EL SIGNO DE FRANK Y LOS DIFERENTS SUBTIPOS DE ICTUS ISQUÉMICO.

PODRÍAMOS TENER RESPUESTAS CON SOLO UN VISTAZO?

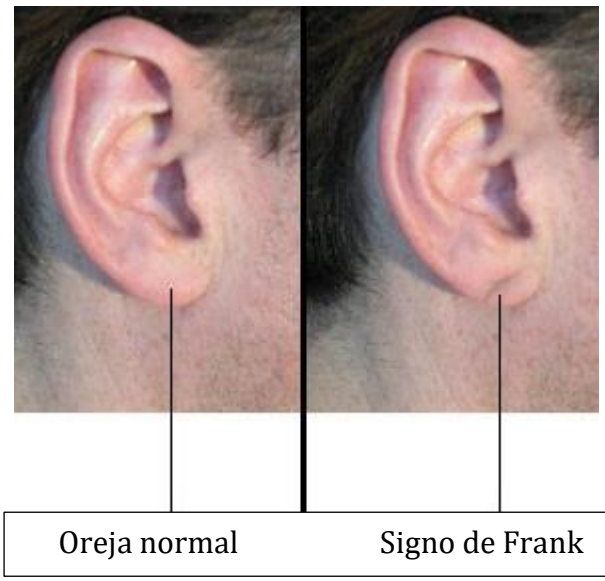
Estimado/a,

El Ictus es una de las principales causas de mortalidad e invalidez en nuestro entorno, lo que conlleva un gran sufrimiento personal, familiar y no pocas veces elevadas cargas sociales. Por tanto, se deben hacer todos los esfuerzos necesarios para disminuir la aparición de esta enfermedad.

Los Ictus representan un conjunto de trastornos del cerebro transitorios o permanentes que son producidos por un trastorno de la circulación cerebral. La palabra **ICTUS** (golpe o ataque) remarca la habitual instauración rápida de sus síntomas. Los Ictus pueden producirse por diversos mecanismos. Los principales son la obstrucción de una arteria que produce un **INFARTO** cerebral o bien la rotura de una arteria cerebral que produce las **HEMORRAGIAS** cerebrales.

Las causas de los Ictus son variadas. Una de las principales causas es la **ARTERIOSCLEROSIS.** La arteriosclerosis es una enfermedad relacionada con el envejecimiento de las arterias que ocurre con la edad, no obstante algunos factores la aceleran: la hipertensión arterial, la diabetes, el aumento del colesterol en la sangre y el consumo de tabaco. Estas enfermedades o hábitos se denominan factores de riesgo vascular. El adecuado control de estos factores disminuye la probabilidad de tener un nuevo Ictus.

El **SIGNO DE FRANK** es un surco que aparece en el lóbulo de la oreja (foto) y se ha relacionado con la arteriosclerosis, mayoritariamente con la de las arterias del corazón, y también con los factores de riesgo vascular. Hoy en día se desconoce con exactitud si este signo también podría estar relacionado con la arterioesclerosis de las arterias del cerebro. Estudiar esta relación es el objetivo del presente estudio



Oreja normal Signo de Frank

Le/la invitamos a participar en un estudio de investigación sobre el análisis de la posible relación entre el signo de Frank y el ictus. La duración del mismo será de 1 año y se realizara en el Hospital Dr. Josep Trueta de Girona.

A continuación le presentamos un formulario en el que se incluye un resumen con la información sobre el estudio para que pueda decidir si está interesado/a o no en colaborar. Lea detenidamente y tómese el tiempo que crea necesario. Le recordamos que su participación es totalmente voluntaria, y que si decide no participar, esto no afectará al trato de los profesionales sanitarios hacia su persona.

1. **¿Cuál es la finalidad del estudio?**

Como acabamos de comentar, la finalidad del estudio es estudiar si existe una relación entre el signo de Frank y el ictus. Pensamos que determinar si existe una relación entre el signo de Frank y el ictus sería interesante ya que con un simple vistazo a las orejas podríamos sacar mucha información sobre las características y el perfil de ictus que ha sufrido la persona que tenemos delante. Esto nos serviría para orientar más la causa que le ha producido el ictus y plantear un tratamiento más concreto y agresivo para evitar recurrencias. Además, nos podría ayudar a predecir el pronóstico de aquellos pacientes que han sufrido un ictus.

2. **¿En qué consistiría mi participación?**

Usted se encuentra ingresado en la unidad de ictus como consecuencia de que ha sufrido un ictus.
Su participación en este estudio constará de varias partes:

-Para empezar, uno de los neurólogos del equipo de investigación le tomara unas fotos de sus dos orejas y de su pulsera identificativa con la cámara de fotos de un teléfono móvil. Los neurólogos que forman parte del equipo de investigación, analizaran las fotos y determinaran, siguiendo unos pasos, si usted presenta o no signo de Frank. Firmando el consentimiento informado, accede a dejar-nos utilizar las fotos y el resultado obtenido.

-Una vez usted haya sido dado de alta de la Unidad de ictus, se le entregará el informe de alta donde quedará explicado todas las pruebas y tratamientos llevados a cabo durante su estancia. Firmando el consentimiento informado usted accede a dejarnos utilizar los datos que aparecen en dicho informe de alta para el estudio.

-A los 3 meses de haber estado dado de alta tendrá una cita en la consulta de vascular. Esta cita se concierta por rutina a todos los pacientes que han sufrido un ictus y han sido ingresados en la unidad de ictus, como revisión, independientemente de que acepte o no formar parte del estudio. Sin embargo, si usted participa en el estudio, en esta misma cita se le evaluara su estado funcional

mediante una escala neurológica ya validada para este propósito y se le preguntará por la existencia de recurrencias vasculares. Firmando el consentimiento informado usted también accede a dejarnos utilizar sus datos obtenidos en esta revisión.

-Finalmente, dependiendo de lo que se decida en esta revisión a los 3 meses en la consulta de vascular, se le concertará una nueva cita al cabo de 1 año de haber sido dado de alta (es decir, a los 9 meses de dicha visita) o se le hará una llamada telefónica al teléfono de contacto que nos facilitará en la hoja de consentimiento informado. En esta visita (en caso de no tener que acudir a consultas se le evaluará lo mismo por teléfono) se le evaluará de nuevo su estado funcional y la existencia de recurrencias vasculares. Firmando el consentimiento informado usted accede a dejarnos utilizar los datos y resultados obtenidos en esta evaluación.

3. ¿Mi participación será confidencial?

Todos los datos recogidos para este estudio, así como las fotos que le realicemos, serán introducidos en una base de datos computerizada para su posterior análisis. Los datos de carácter personal, las fotos realizadas y la información recogida tanto de su informe de alta como la de las evaluaciones posteriores es totalmente confidencial y quedan protegidos de acuerdo con la legislación vigente sobre la protección de datos de carácter personal (Ley Orgánica 15/1999 del 13 de diciembre).
Los resultados de este estudio se utilizaran para su presentación en congresos médicos o la publicación en revistas científicas.

4. ¿Cuáles son los posibles riesgos o inconvenientes de participar en este estudio?

No se prevén riesgos ni inconvenientes para participar en este estudio

5. ¿Puedo retirarme o cambiar de opinión una vez empezado el estudio?

Si, su participación en este estudio es voluntaria, por lo que puede pedir la eliminación de las fotografías realizadas que estén almacenadas y de la información relacionada con las mismas en cualquier momento del estudio y sin necesidad de especificar el motivo. Si así lo decidiese, esto no repercutiría en sus curas médicas.

6. ¿A quién puedo pedir más información?

En caso de duda o que quiera más información, no dude en contactar con su médico investigador de referencia o llame al siguiente número de teléfono: 972257638 (de 8.00h a 17.00h)

HOJA DE CONSENTIMIENTO INFORMADO

EL SIGNO DE FRANK Y LOS DIFERENTS SUBTIPOS DE ICTUS ISQUÉMICO.

PODRÍAMOS TENER RESPUESTAS CON SOLO UN VISTAZO?

YO (Nombre y Apellidos):_____

- He leído detenidamente y he entendido toda la hoja de información que se me han entregado.
- He recibido suficiente información sobre el estudio.
- El investigador me ha explicado de manera clara todo el procedimiento.
- He podido realizar preguntas sobre el estudio y todas mis dudas han sido resueltas de manera satisfactoria.
- Entiendo que todos mis datos serán tratados de forma estrictamente confidencial.
- Entiendo cuál será mi papel como participante del estudio.
- Entiendo que mi participación es voluntaria, y que en cualquier momento del estudio puedo cambiar de opinión sin tener que dar ninguna explicación y que, independientemente de mí decisión, mi atención médica y mis derechos legales no se verán afectados.

Por lo tanto, acepto voluntariamente participar en este estudio de investigación i permito que me sean realizadas las fotografías necesarias y mis datos introducidos en la base de datos para su análisis.

Firma del participante

_____

Firma del investigador

_____

Girona, _____de_____de 20_____

Número de teléfono de contacto_____

ANNEX 2: CASE REPORT FORM (CRF)

CASE REPORT FORM

FRANK'S SIGN AND SUBPTYPES OF STROKE

IDENTIFICATION DATA

Name and surnames:_____

Patient's SAP number:_____ **Patients number identification:**_____

BASELINE DATA

Age: _____ **Gender:** □ 1. Male □ 2. Female

DATA ABOUT CURRENT STROKE

Type of stroke

- □ 1. Infarct
- □ 2. AIT
- □ 3. Haemorragic

Etiology of ischemic stroke

- □ 1. Atherotrombotic, or large artery artherosclerosis
- □ 2. Cardioembolic
- □ 3. Lacunar or occlusive disease of the small vessels
- □ 4. Stroke of undetermined etiology or cryptogenic
- □ 5. Acute stroke of other determined etiology.
- □ 6. Hemorragic etiology
- □ 9. Missing

Territory affected of the stroke

- □ 1. Anterior cerebral system
- □ 2. Posterior cerebral system
- □ 9. Missing

CLINICAL FEATURES

Frank's sign

- □ 1. No
- □ 2. Yes
- □ 3. Unspecific

Frank's sign (lateralitat)

- □ 1. Unilateral
- □ 2. Bilateral

Arterial Hypertension

- □ 1. No
- □ 2. Yes
- □ 9. Missing

Diabetes Mellitus

- □ 1. No
- □ 2. Yes
- □ 9. Missing

Dyslipidemia

- □ 1. No
- □ 2. Yes
- □ 9. Missing

Body Mass Index

- □ 1. Normal weight
- □ 2. Overweight
- □ 3. Obesity
- □ 9. Missing

TOXIC HABITS

Smoking habit

- □ 1. Non-smoker
- □ 2. Smoker
- □ 3. Ex-smoker (>5 years)
- □ 9. Missing

Alcohol habit

- □ 1. Non-drunker
- □ 2. Sporadic-drunker
- □ 3. Usually drunker
- □ 4. Ex-alcohol
- □ 9. Missing

Other drug habit

- □ 1. No drugs
- □ 2. Cocaine
- □ 3. Cannabis
- □ 4. Opioids
- □ 5. Other drugs
- □ 6. Ex-consumer
- □ 9. Missing

PREVIOUS PATHOLOGIES

Peripheral artery disease

- ☐ 1. No
- ☐ 2. Yes
- ☐ 9. Missing

Heart disease

- ☐ 1. No
- ☐ 2. Yes
- ☐ 9. Missing

Previous stroke

- ☐ 1. NO
- ☐ 2. Yes
- ☐ 9. Missing

PRESENCE OF ATHEROSCLEROTIC MARKERS IN TSA/US

Presence of atherosclerotic plaques

- ☐ 1. No atherosclerotic plaques
- ☐ 2. Presence of atherosclerotic plaques
- ☐ 9. Missing

Carotid stenosis

- ☐ 1. NO
- ☐ 2. Significant stenosis (>50%)
- ☐ 3. Occlusion
- ☐ 9. Missing

Other vascular stenosis

- ☐ 1. No
- ☐ 2. Significant stenosis (>50%)
- ☐ 3. Occlusion
- ☐ 4. Missing

NEUROLOGICAL SCALES AT DISCHARGE

Modified Rankin Scale at hospitalization: _____

Modified Rankin Scale at hospital discharge: _____

NIHSS at hospitalization: _____

NIHSS at hospital discharge: _____

EVALUATION AT 3 MONTHS AFTER DISCHARGE

Modified Rankin Scale at 3 months: _____

Vascular Recurrences

- 1. NO
- 2. YES, Cardiac artery disease
- 3. YES, Peripheral artery disease
- 4. YES, Stroke or TIA
- 9. Missing

NIHSS scale at 3 months:_____

EVALUATION AT 1 YEAR AFTER DISCHARGE

Modified Rankin Scale at 1 year: _____

Vascular Recurrences

- 1. NO
- 2. YES, Cardiac artery disease
- 3. YES, Peripheral artery disease
- 4. YES, Stroke Or TIA
- 9. Missing

NIHSS scale at 1 year: _____

EVALUATION SHEET FOR THE FRANK'S SIGN

NAME:_____ **GENDER:**_____

AGE:_____ **NUMBER OF PATIENT:**_____

Ear lobe crease or Frank's sign is a crease or wrinkle extending 45º diagonally from the tragus towards the outer border of the earlobe

HOW TO TAKE THE PHOTOGRAPH OF THE EARS

-The bilateral ear lobes photographs are going to be assessed manually with the researcher's mobile phone or with a camera.

-The patient in sitting or supine decubitus position.

-The earlobes have to remain clearly visible at inspection and at the photograph without any disturbance for its vision.

-You have to take in account that the photograph is well done for its posterior evaluation

EVALUATION OF THE PHOTOGRAPH OF THE EARS [1] [2]

	RIGHT EAR	LEFT EAR
Ear lobe structure (figure 1)	☐ Normal and evaluable ☐ Absent or altered due to an accident or surgery ☐ With earrings, tattoos or some objects	☐ Normal ☐ Absent or altered due to an accident or surgery ☐ With earrings, tattoos or some objects
Ear lobe Crease (figure 2)	☐ Present ☐ Absent ☐ Not clear	☐ Present ☐ Absent ☐ Not clear
Grade of length of ELC (Figure 3)	☐ **Grade 0:** not crease at all ☐ **Grade 1:** any crease <50% across the lobe ☐ **Grade 2:** crease less than 100% across the lobe ☐ **Grade 3:** deep and prominent crease across the whole lobe	☐ **Grade 0:** not crease at all ☐ **Grade 1:** any crease <50% across the lobe ☐ **Grade 2**: crease less than 100% across the lobe ☐ **Grade 3:** deep and prominent crease across the whole lobe

[1] *Shrestha I, Ohtsuki T, Takahashi T, Nomura E, Kohriyama T, Matsumoto M. Diagonal ear-lobe crease is correlated with atherosclerotic changes in carotid arteries. Circ J [Internet]. 2009 Oct [cited 2016 Oct 10];73(10):1945–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19644217*

[2] *Rodriguez-Lopez C, Garlito-Diaz H, Madronero-Mariscal R, Sanchez-Cervilla PJ, Graciani A, Lopez-Sendon JL, et al. Earlobe Crease Shapes and Cardiovascular Events. Am J Cardiol [Internet]. 2015;116(2):286–93. Available from: http://dx.doi.org/10.1016/j.amjcard.2015.04.023*

Grade of depth of ELC (Figure 4)	□ Without crease □ Mild □ Moderate □ Sever	□ without crease □ Mild □ Moderate □ sever
Inclination of crease (Figure 5)	□ Without crease □ Vertical □ Diagonal or Oblique	□ Without crease □ Vertical □ Diagonal or Oblique
Bilateralism	□ YES □ NO □ Neither	

WHAT CONSIDER FRANK'S SIGN

We are going to consider that a patient has Frank's sign when complete all the following points:

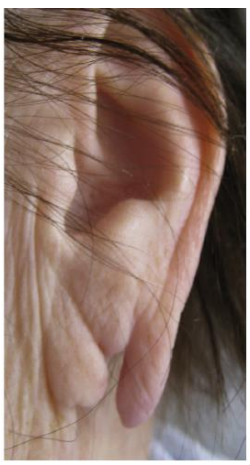
- ✓ The patient's earlobe is normal and evaluable
- ✓ The ear lobe crease is present in one of two ears or in both
- ✓ The grade of length of ELC could be grade 1, 2 or 3
- ✓ The grade of depth could be mild, moderate or sever
- ✓ The inclination of the crease if it is present has to be diagonal or oblique
- ✓ Whenever there was more than 1 crease, at least 1 have met the previous criteria

Conclusions:

1. Has this patient a Frank's sign?
   - □ YES
   - □ NO
2. If the previous question is yes, it is bilateral or unilateral?
   - □ Bilateral
   - □ Unilateral
     - Left
     - Right

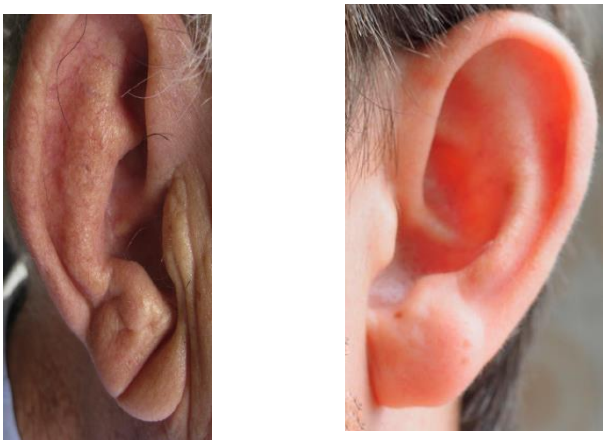
FIGURES AS AN EXAMPLES

FIGURE 1. EAR LOBE STRUCTURE: A) normal and evaluable. B) altered C)with earrings



A B C

FIGURE 2. EAR LOBE CREASE. A)present B) absent



A B

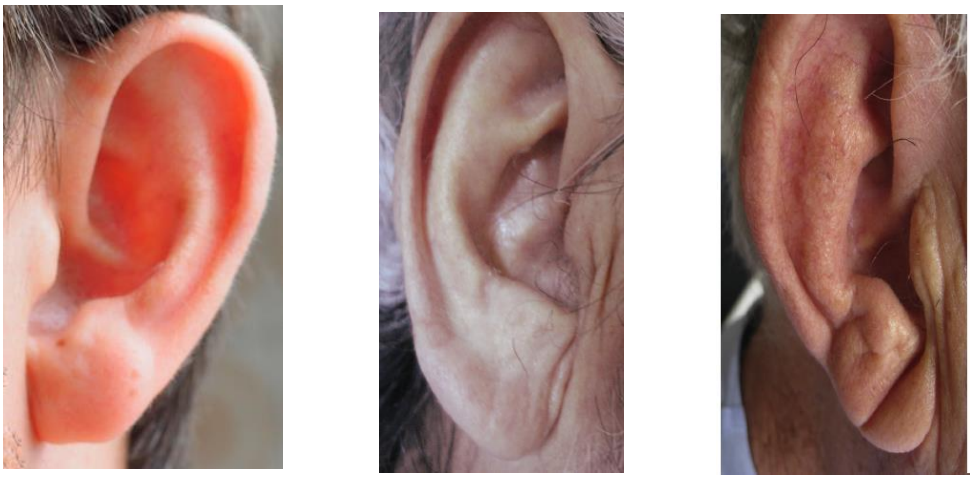
FIGURE 3. GRADE OF LENGTH OF ELC. A) Grade 0. B) Grade 2 C)Grade 3

A B C

FIGURE 4. GRADE OF DEPTH OF ELC. A) without crease B)Mild C)Moderate D)severe

A B C D

FIGURE 5. INCLINATION OF CREASE. A)Without crease B)Vertical C)diagonal or oblique



A	B	C

ANNEX 4: CLASSIFICATION CRITERIA OF ISCHEMIC STROKE

Atherothrombotic Infarct (Large Vessel Atherosclerosis)	Criteria for Cardioembolic Ischemic Stroke	Small Vessel (Lacunar) Disease	Infarction of Other Etiologies or Uncommon Causes	Stroke of undetermined etiology
-stenosis (>50%), occlusion, or an ulcerated plaque (> 2 mm thick) in intracranial artery or ipsilateral extracranial artery, demonstrated by duplex Doppler or angiographic study -Absence of cardiogenic embolism or heart disease of some other etiology **Clinical criteria.** – Presence of murmur, ipsilateral to the infarct – Presence of previous TIA, ipsilateral to the infarct – History of ischemic heart disease – History of intermittent claudication of lower limbs **Imaging criteria.** – Presence in CT and/or MR of cortical, or subcortical nonhemorrhagic infarction measuring over 1.5 cm in carotid, or vertebrovasilar territory – Stenosis or occlusion of the involved vascular territory in angiography	– The presence of cardiogenic embolism – The presence of significant cerebrovascular atheromatous lesions and other possible etiologies must be ruled out **Clinical criteria.** – Sudden maximum neurological deficit (occurring in seconds or a few minutes) – Onset during fasting – Loss of consciousness (transient) and/or seizures at onset – Multiple simultaneous cerebral infarctions – Previous cerebral infarctions or TIA in different vascular territories - History or coexistence of systemic emboli **Imaging criteria.** – TC images showing infarction >1.5 cm, usually cortical, sometimes hemorrhagic, or multiple infarcts in different vascular territories – Angiographic evidence of transient angiographic occlusions, isolated arterial occlusion with no evidence of atherosclerotic lesions, or central filling defect in the proximal portion of an artery with no atherosclerotic changes	-< 1.5 cm infract diameter -Located in arterial or perforating cerebral arterioles (< 200 µm diameter) -Due to lipohyalinosis or microatheromatosis of said vessels – The clinical course is that of one of the classic lacunar syndromes: -pure hemiparesis -pure sensory syndrome -sensorimotor syndrome -ataxic hemiparesis -dysarthria clumsy hand syndrome – Hypertension or diabetes mellitus supports the diagnosis – No cortical signs or symptoms –No potential cardiac sources of embolism or stenosis greater than 50% in ipsilateral extracranial arteries –Stenosis greater than 50% or atheromatous plaques in medium-sized, or large arteries does not rule out the presence of lacunar infarction	-Patients with acute cerebral infarction due to infrequent causes, such as: -nonatherosclerotic vascular diseases (inflammatory, noninflammatory, infectious, hereditary), -hypercoagulability states -hematologic disorders -migraine-infarction -vasospasms -hereditary and metabolic diseases. -Cardioembolic cerebral infarction and the presence of atherosclerosis in extracranial arteries should be ruled out.	-Medium and large sized infract -cortical or subcortical -Carotid or vertebrobasilar location -That happens one of the following situations: -Inadequate or insufficient evaluation -Absence or a determined etiology in spite of an exhaustive study -Conflictive data due to the simultaneous presence of two possible etiologies of infract

ANNEX 5. MODIFIED RANKIN SCALE

Is a clinician-reported measure of global disability that has been widely applied for evaluating recovery from stroke and as a primary end point in randomized clinical trials (RCTs) of emerging acute stroke treatments.

The mRS was published in 1988 and consists of 6 categories (grades 0 to 5) rather than 5 for the RS (original Rankin Scale); an additional category, grade "6" denoting death, is usually incorporated into the mRS for RCT purposes.

In the mRS: grade 1 of the original RS ("no significant disability") is replaced by 2 grades, 0 and 1, with grade 0 describing patients without symptoms and grade 1 describing patients without significant disability "despite symptoms." This finer discrimination of mild strokes increases the usefulness of the mRS in evaluating RCTs of acute stroke interventions. Additionally, grade 2 in the mRS ("unable to perform all previous activities") is more definitive compared with that grade of the RS ("unable to carry out some of previous activities"). A "favourable" outcome defined as mRS grade 1 or 2 was estimated to be more powerful than dichotomization at higher grades. Inter-rater reliability with the mRS is moderate and improves with structured interviews (K= 0.56 versus 0.78); strong test-re-test reliability (k=0.81 to 0.95) has been reported. Numerous studies demonstrate the constructed validity of the mRS by its relationships to physiological indicators such as stroke type, lesion size, perfusion and neurological impairment.

Score Description *Banks JL, Marotta C a. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007 Mar; 38(3):1091–6.)*

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all 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

TOTAL (0–6): _____

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***Stroke* 1988;19(5):604-7**

ENSAYO IMPACT-24	
FORMULARIO DE ESCALA DE RANKIN MODIFICADA **Esta es la única fuente aceptable de puntuación ERm del ImPACT-24** Envíe la evaluación de 90 días a BrainsGate por fax en un periodo de 5 días	ID DEL PACIENTE: ☐ CÓD. SITIO CÓD. PACIENTE

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

Fase del estudio: ☐ Día 5 ☐ Día 30 ☐ Día 60 ☐ Día 90

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

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

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

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

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

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

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

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

ENSAYO IMPACT-24	
FORMULARIO DE ESCALA DE RANKIN MODIFICADA **Esta es la única fuente aceptable de puntuación ERm del ImPACT-24** Envíe la evaluación de 90 días a BrainsGate por fax en un periodo de 5 días	ID DEL PACIENTE: ☐ CÓD. SITIO CÓD. PACIENTE

3.5	**¿ Es estrictamente necesaria la asistencia para realizar compras en establecimientos cercanos?** Por ejemplo: si el/la paciente puede comprar aunque sea un único artículo → responda NO	☐ Sí (ERm = 3) ☐ No

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

_____

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

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

_____

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

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

_____

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

Puntuación ERm: _____ Firma del evaluador/a: _____

ANNEX 7. EVALUATION OF NIHSS SCALE

NATIONAL INSTITUTE OF HEALTH STROKE SCALE

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit.

It is the main neurologic evaluation tool used in our hospital. It is a 15-item clinical deficit scale that was first described in 1989 and assesses levels of consciousness, gaze, vision, facial palsy, arm and leg strength, limb ataxia, sensory loss, neglect, dysarthria, and aphasia. The possible punctuation goes from 0 to 42.[1]

The NIHSS was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. Now, the scale is also widely used as a clinical assessment tool to evaluate acuity of stroke patients, determine appropriate treatment, and predict patient outcome. In fact, baseline severity as measured by the NIHSS is the most important predictor of ultimate outcome.

Initial evaluation of the scale confirmed that it could be administered in a mean of 6.6 minutes across a range of severities. Inter-rater agreement is excellent (mean k = 0.69) and intra-rater agreement is also good, especially when the rater is a neurologist (k = 0.77).[2]

The scale is designed to be a simple, valid, and reliable tool that can be administered at the bedside consistently by physicians, nurses or therapists with the correct training.

However, in our case all the NIHSS's punctuations used are performed by the neurologists of our department

[1] Stroke Clinical Updates: http://www.stroke.org/site/DocServer/SCU_-_Jan-Feb_2006.pdf?docID=5166

[2] Kasner, S. E., Chalela, J. a., Luciano, J. M., Cucchiara, B. L., Raps, E. C., McGarvey, M. L., Localio, a. R. (1999). Reliability and Validity of Estimating the NIH Stroke Scale Score from Medical Records. Stroke, 30(8), 1534–1537. doi:10.1161/01.STR.30.8.1534

NIH Stroke Scale

The NINDS tPA Stroke Trial No. ___ ___ - ___ ___ ___ - ___ ___ ___

Pt. Date of Birth ___ ___ / ___ ___ / ___ ___

Hospital _____ (___ ___ - ___ ___)

Date of Exam ___ ___ / ___ ___ / ___ ___

Interval: 1 ☐ Baseline 2 ☐ 2 hours post treatment 3 ☐ 24 hours post onset of symptoms 6 minutes
4 ☐ 7–10 days 5 ☐ 3 months 6 ☐ Other _____ (___ _____)

Time: ___ ___:___ ___ 1 ☐ am 2 ☐ pm

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

IF ANY ITEM IS LEFT UNTESTED, A DETAILED EXPLANATION MUST BE CLEARLY WRITTEN ON THE FORM. ALL UNTESTED ITEMS WILL BE REVIEWED BY THE MEDICAL MONITOR, AND DISCUSSED WITH THE EXAMINER BY TELEPHONE.

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct — there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one-step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	_____

NIH Stroke Scale

The NINDS tPA Stroke Trial No. ___ ___ - ___ ___ ___ - ___ ___ ___

Pt. Date of Birth ___ ___ / ___ ___ / ___ ___

Hospital _____ (___ ___ - ___ ___)

Date of Exam ___ ___ / ___ ___ / ___ ___

Interval: 1 ☐ Baseline 2 ☐ 2 hours post treatment 3 ☐ 24 hours post onset of symptoms 6 minutes
4 ☐ 7–10 days 5 ☐ 3 months 6 ☐ Other _____ (___ _____)

Instructions	Scale Definition	Score
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	_____
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to answer question 11.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)	_____
4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.	0 = Normal symmetrical movement 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	_____

NIH Stroke Scale

The NINDS tPA Stroke Trial No. ___ ___ - ___ ___ ___ - ___ ___ ___

Pt. Date of Birth ___ ___ / ___ ___ / ___ ___

Hospital _____ (___ ___ - ___ ___)

Date of Exam ___ ___ / ___ ___ / ___ ___

Interval: 1 ☐ Baseline 2 ☐ 2 hours post treatment 3 ☐ 24 hours post onset of symptoms 6 minutes
4 ☐ 7–10 days 5 ☐ 3 months 6 ☐ Other _____ (___ _____)

Instructions	Scale Definition	Score
5 & 6. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "9" and the examiner must clearly write the explanation for scoring as a "9."	0 = No drift, limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift, Limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement 9 = Amputation, joint fusion explain: _____ **5a. Left Arm**	_____
	5b. Right Arm	_____
	0 = No drift, leg holds 30 degrees position for full 5 seconds. 1 = Drift, leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity, leg falls to bed immediately. 4 = No movement 9 = Amputation, joint fusion explain: _____ **6a. Left Leg**	_____
	6b. Right Leg	_____

NIH Stroke Scale

The NINDS tPA Stroke Trial No. ___ ___ - ___ ___ ___ - ___ ___ ___

Pt. Date of Birth ___ ___ / ___ ___ / ___ ___

Hospital _____ (___ ___ - ___ ___)

Date of Exam ___ ___ / ___ ___ / ___ ___

Interval: 1 ☐ Baseline 2 ☐ 2 hours post treatment 3 ☐ 24 hours post onset of symptoms 6 minutes
4 ☐ 7–10 days 5 ☐ 3 months 6 ☐ Other _____ (___ _____)

Instructions	Scale Definition	Score
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9," and the examiner must clearly write the explanation for not scoring. In case of blindness, test by touching nose from extended arm position.	0 = Absent 1 = Present in one limb 2 = Present in two limbs If present, is ataxia in Right arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain _____ Left arm 1 = Yes 2 = No 9 = amputation or joint fusion, explain _____ Right leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain _____ Left leg 1 = Yes 2 = No 9 = amputation or joint fusion, explain _____	_____ _____ _____ _____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick but patient is aware he/she is being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = No aphasia, normal 1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided material difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	_____

NIH Stroke Scale

The NINDS tPA Stroke Trial No. ___ ___ - ___ ___ ___ - ___ ___ ___

Pt. Date of Birth ___ ___ / ___ ___ / ___ ___

Hospital _____ (___ ___ - ___ ___)

Date of Exam ___ ___ / ___ ___ / ___ ___

Interval: 1 ☐ Baseline 2 ☐ 2 hours post treatment 3 ☐ 24 hours post onset of symptoms 6 minutes
4 ☐ 7–10 days 5 ☐ 3 months 6 ☐ Other _____ (___ _____)

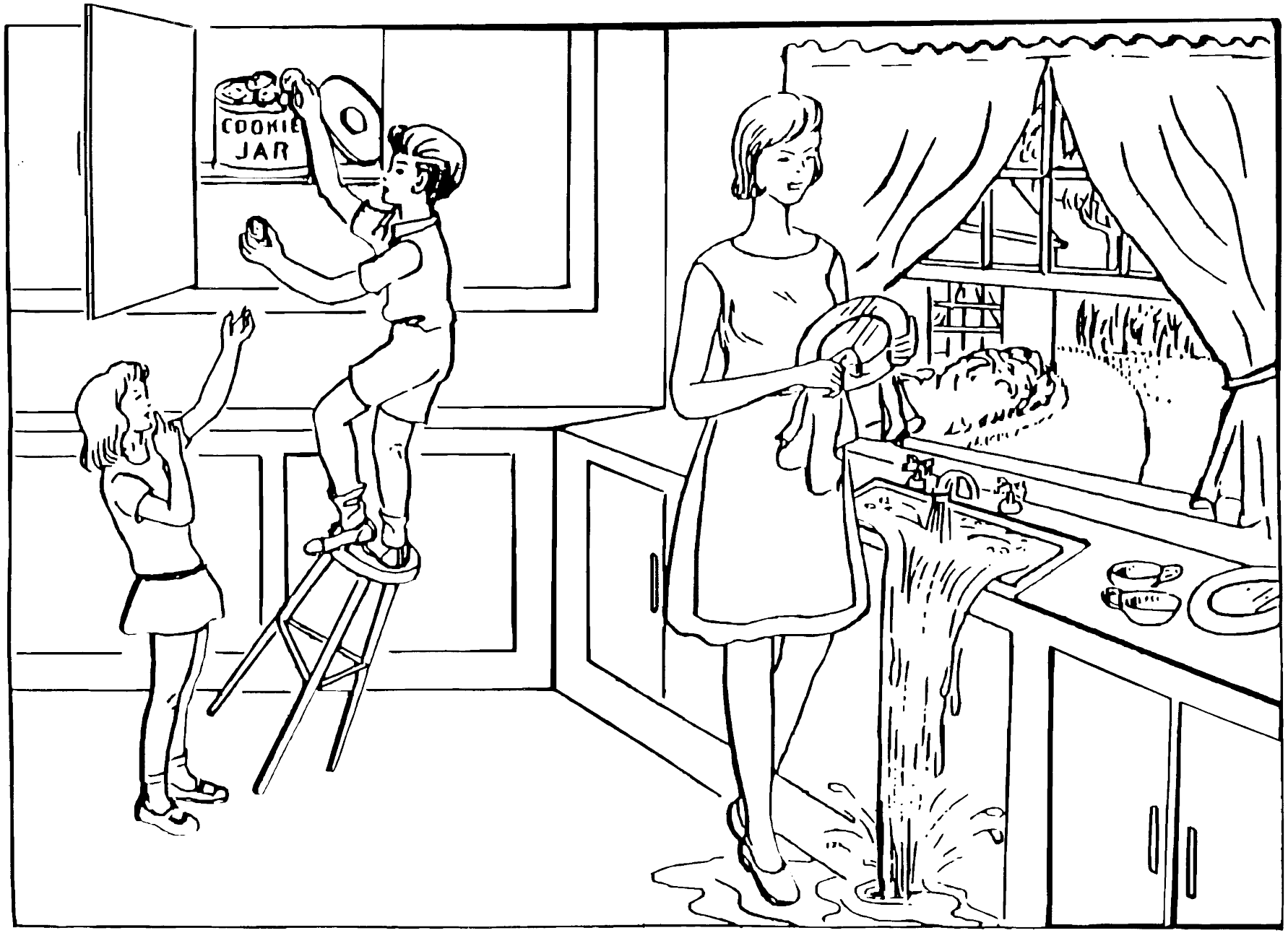
Instructions	Scale Definition	Score
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech may the item be scored "9," and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.	0 = Normal 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. 9 = Intubated or other physical barrier, explain _____	_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	_____

Additional item, not a part of the NIH Stroke Scale score.

A. Distal Motor Function: The patient's hand is held up at the forearm by the examiner and patient is asked to extend his/her fingers as much as possible. If the patient can't or doesn't extend the fingers, the examiner places the fingers in full extension and observes for any flexion movement for 5 seconds. Only the patient's first attempts are graded. Repetition of the instructions or of the testing is prohibited.	0 = Normal (No flexion after 5 seconds) 1 = At least some extension after 5 seconds, but not fully extended. Any movement of the fingers which is not upon command is not scored. 2 = No voluntary extension after 5 seconds. Movements of the fingers at another time are not scored. **a. Left Arm** **b. Right Arm**	_____ _____

12. _____ (___ ___ ___)

Person Administering Scale Code


COOKIE
JAR

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

MAMA

TIP-TOP

FIFTY-FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

ANNEX 8. QUESTIONARIO DE RECURRENCIA O APARICIÓN DE CLÍNICA VASCULAR POST-ICTUS

EVALUACIÓN RECURRENCIAS VASCULARES

CARDIOPATIA ISQUÉMICA

1. Desde que estuvo ingresado. ¿Ha tenido sensación de dolor en el pecho, más bien en el lado izquierdo, que se le haya aumentado o aparecido en el transcurso de la realización de algún esfuerzo físico o después de una comida copiosa?
   - SI
   - NO
   - Respuesta inespecífica

2. Si la respuesta anterior es si, este dolor ha cedido en menos de 15 minutos con el reposo o tras la ingesta de una pastilla sublingual (Nitroglicerina)?
   - SI
   - NO
   - Respuesta inespecífica

3. Desde que estuvo ingresado. ¿ha tenido alguna vez que pedir atención sanitaria por dolor en el pecho que no le cedía hasta la intervención del personal sanitario?
   - SI
   - NO
   - Respuesta inespecífica

4. Desde que estuvo ingresado. ¿Ha sido usted diagnosticado de infarto de miocardio o angina inestable por un especialista?
   - SI
   - NO
   - Respuesta inespecífica

5. *En caso de visita presencial.* Anotar si al realizar exploración física detecta algún signo de cardiopatía isquémica.
   - SI
   - NO

-**Recurrencia Cardiopatía isquémica**:

- NO (cuando todas las respuestas anteriores sean negativas)
- SI (cuando al menos una respuesta de las anteriores sea afirmativa)
- No valorable (cuando la mayor parte de las respuestas sean inespecíficas)

ARTERIOPATIA PERIFÉRICA

1. Desde que estuvo ingresado. ¿Ha notado algún tipo de dolor en las piernas al caminar que le ha llevado a detenerse para que cediera?.
   Pregunta en caso de que el paciente tenga antecedentes de claudicación intermitente. Desde que estuvo ingresado. ¿Ha notado que la aparición de dolor en las piernas al caminar haya sido en distancias más cortas y de aparición más precoz?
   - SI
   - NO
   - Respuesta inespecífica
2. Desde que estuvo ingresado. ¿Ha notado aparición de algún tipo de dolor en las piernas con el reposo o que le incapacite para caminar más de 150 metros?.
   - SI
   - NO
   - Respuesta inespecífica
3. Desde que estuvo ingresado. ¿Ha sido diagnosticado por un especialista de claudicación intermitente o isquemia crónica de las extremidades inferiores?
   - SI
   - NO
   - Respuesta inespecífica
4. *En caso de visita presencial.* Anotar si al realizar exploración física detecta algún signo de arteriopatia periférica.

Recurrencia Cardiopatía isquémica:

- NO (cuando todas las respuestas anteriores sean negativas)
- SI (cuando al menos una respuesta de las anteriores sea afirmativa)
- No valorable (cuando la mayor parte de las respuestas sean inespecíficas)

RECURRENCIA ENFERMEDAD CEREBROVASCULAR

STRUCTURED QUESTIONNAIRE FOR VERIFYING STROOK-FREE STATUS [1]

1. Desde que fue ingresado por el episodio que tuvo. ¿Alguna vez le ha dicho a algún médico que usted ha tenido un ictus o un AIT?
   - SI
   - NO
   - Respuesta inespecífica

2. Desde que fue ingresado por el episodio que tuvo. ¿Alguna vez ha tenido debilidad repentina indolora en un lado de su cuerpo?
   - SI
   - NO
   - Respuesta inespecífica

[1] *Meschia JF, Brott TG, Chukuwudelunzu FE, Hardy J, Brown RD, Meissner I, et al. Structured Telephone Interview. 2011;1076-80.*

3. Desde que fue ingresado por el episodio que tuvo. ¿Alguna vez ha tenido un entumecimiento repentino o un sentimiento de muerte en un lado de su cuerpo?
    - SI
    - NO
    - Respuesta inespecífica

4. Desde que fue ingresado por el episodio que tuvo. ¿Alguna vez ha tenido pérdida de visión repentina e indolora en uno o ambos ojos?
    - SI
    - NO
    - Respuesta inespecífica
5. Desde que fue ingresado por el episodio que tuvo. ¿Alguna vez has perdido la mitad de tu visión?
    - SI
    - NO
    - Respuesta inespecífica

6. Desde que fue ingresado por el episodio que tuvo. ¿Alguna vez has perdido la habilidad de entender lo que la gente estaba diciendo?
    - SI
    - NO
    - Respuesta inespecífica

7. Desde que fue ingresado por el episodio que tuvo. ¿Alguna vez ha perdido la capacidad de expresarse verbalmente o por escrito?
    - SI
    - NO
    - Respuesta inespecífica

8. Des de que fue ingresado por el episodio que tuvo ¿Alguna vez ha vuelto a estar ingresado por otro episodio de ictus o AIT?
    - SI
    - NO
9. *En caso que la visita sea presencial. R*ealizar una exploración neurológica completa y anotar si ha variado la puntuación en la escala de la NIHSS respecto a la previa
    - SI
    - NO
10. *En caso que la visita sea presencial.* Anotar la puntación para la escala NIHSS: _____

-Recurrencia sintomatología enfermedad cerebrovascular

- NO (Cuando todas las preguntas sean negativas)
- SI (cuando al menos una de las respuestas anteriores sea afirmativa)