



**EVERSION VERSUS CONVENTIONAL  
ENDARTERECTOMY IN FEMALES AS  
SECONDARY PREVENTION OF STROKE  
CAUSED BY CAROTID STENOSIS:  
A RANDOMIZED, CONTROLLED TRIAL**

FINAL DEGREE PROYECT

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*"Do not go where the road takes you. Go where there is no one and leave a path"*

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## 1. ABSTRACT

**BACKGROUND:** Stroke is one of the leading causes of death worldwide and the first cause of long-term morbidity in western world. In our country, it's the first cause of death in females over 65 years. The main risk factor to develop an ischemic stroke is the presence of an atherosclerotic plaque in the wall of the carotid artery.

It has been shown that, by sex, there are different anatomopathological characteristics in the atheroma plaques and in the size and diameter of the arteries. These influence the risk of stroke and could also explain why the treatment proposed so far do not benefit females as much as men.

In addition, we must keep in mind that the current guidelines for the treatment of stenosis are based on studies where females are underrepresented. Because of this, although largest meta-analysis comparing e-CEA with c-CEA do not show significant differences, we cannot discard the idea that e-CEA may have advantages in females.

**OBJETIVES:** To compare the proportion of postoperative ischemic strokes in the first 30 days after conventional endarterectomy or eversion in females. They undergo it as secondary prevention of an ischemic stroke caused by carotid stenosis.

Secondary objectives are to evaluate and compare: total procedure time, mortality within the first 30 days, restenosis of the carotid artery, occurrence of long-term ischemic stroke, onset of hypertension/hypotension after surgery, development of a carotid pseudoaneurysm.

**DESING:** A multicenter randomized controlled single-blind with external blind review clinical trial will be carried out in 7 hospitals through Catalonia, conducted between 2019 and 2023. We will use a non-probabilistic, consecutive and proportional sampling.

**PARTICIPANTS:** Females that undergo an endarterectomy, as secondary prevention after suffer an ischemic stroke with significant carotid stenosis, in the hospitals included in our study. The study will include 396 participants.

**KEYWORDS:** Management of carotid stenosis, carotid endarterectomy, e-CEA, c-CEA, complications, sex factors, carotid disease in females, ischemic stroke prevention.

## 2. INTRODUCTION

### 2.1. STROKE: EPIDEMIOLOGY AND DEFINITION

#### 2.1.1. EPIDEMIOLOGY:

The stroke is public health problem of the first order, being the second leading global cause of death. (1)

In Europe, about 1.4 million strokes occur every year. Stroke causes 1.1 million deaths annually in Europe, being the second cause of death. Stroke imposes an enormous financial burden on health systems, exceeding costs more than 38 billion Euros. (2)

In Spain, it supposes the leading cause of death in females over 65 and males over 75 years. (3–5)

80% are of ischemic origin, with carotid atherosclerosis in 20-30% of cases. It is estimated that at least one million Europeans have severe carotid stenosis. (6,7)

After a first episode, a third of patients will recover, a third will die and a third will suffer sequelae, being the main cause of disability in adults, which will involve primary and specialized health care, and dependence on others for some aspect of everyday activities. (2–4,6)

They also represent the second most frequent cause of dementia, the most frequent cause of epilepsy in the elderly and a frequent cause of depression.

It should also be noted that demographic changes will lead to an increase in both incidence and prevalence, due to the aging of population. In the other hand, we have to take into account that, over the years, there has been a reduction in mortality in both males and females, thanks to advances in diagnostic techniques and treatments. (3,4)

### 2.1.2. DEFINITION:

Stroke is a clinical syndrome, presumably of vascular origin, characterized by the rapid development of signs of focal neurological involvement (sometimes global) that last more than 24 hours or lead to death. (3,4)

Transient ischemic attack (TIA) consists of a brief episode of neurological dysfunction caused by a cerebral or retinal focal ischemia, which produces clinical symptoms typically less than 1 hour long and without evidence of cerebral brain in sequences of DWI (Diffusion-Weighted Magnetic Resonance Imaging). (3)

There are two types of stroke: ischemic and hemorrhagic. Cerebral infarction or ischemic stroke is caused by the qualitative or quantitative alteration of the blood supply to the brain. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue, which produces a neurological deficit for more than 24 hours or there is neuroimaging evidence of the appearance of an acute ischemic lesion and, consequently, implies the presence of a necrosis tissue. (2,3)

The most common symptom of a stroke is a sudden weakness or numbness of the face, arm or leg, most often on one side of the body. Other symptoms include: confusion, difficulty speaking or understanding speech; difficulty seeing with one or both eyes; difficulty walking, dizziness, loss of balance or coordination; severe headache with no known cause; fainting or unconsciousness. Sometimes, the symptoms may have been preceded by episodes of TIA.

The effects of a stroke depend on which part of the brain is injured and how severely it is affected. A very serious stroke can cause sudden death. (6)

Stroke is a medical emergency that requires immediate diagnostic and therapeutic intervention. Ischemic damage can take several hours to develop and this time, consider as a therapeutic window, it is an opportunity to avoid or minimize brain damage. (4)

## 2.2. ETIOLOGY:

An ischemic stroke occurs when there is an interruption of blood supply to a focal area of brain parenchyma. This interruption is usually caused by the occlusion of an artery, but it could also be caused less often by other unusual mechanisms.

The etiological causes of stroke are divided in five types:

- Atherothrombotic: Atherosclerosis of large vessels clinically generalized.
- Cardioembolic
- Lacunar infarction: Occlusive disease of small arterial vessel (<2cm of diameter).
- Uncommon cause: Discarded the 3 previous causes. Caused by an artery disease different from atherosclerosis (Arteritis, Takayasu, arterial dissection, venous thrombosis) or systemic disorders.
- Indeterminate origin: After an exhaustive study, the previous causes have been discarded or more than one coexist.

In addition, we have 3 mechanisms: Thrombotic, embolic and hemodynamic. (3,4)

As we mention before, 80% are of ischemic origin, with carotid atherosclerosis in 20-30% of cases, being one of the main risk factors for ischemic stroke and TIA (6-8). Stroke caused by carotid stenosis can be produced by two main ways:

- The most common, as consequence of embolization of carotid artery bifurcation plaque to the intracranial vessels, usually to the middle cerebral artery (MCA) in the anterior circulation. *(This cause will be the center of our study).*
- As consequence of low flow (hemodynamic).
- Can also be caused as a result from lesions in CCA or in the distal or intracranial portion of ICA. (6,9)

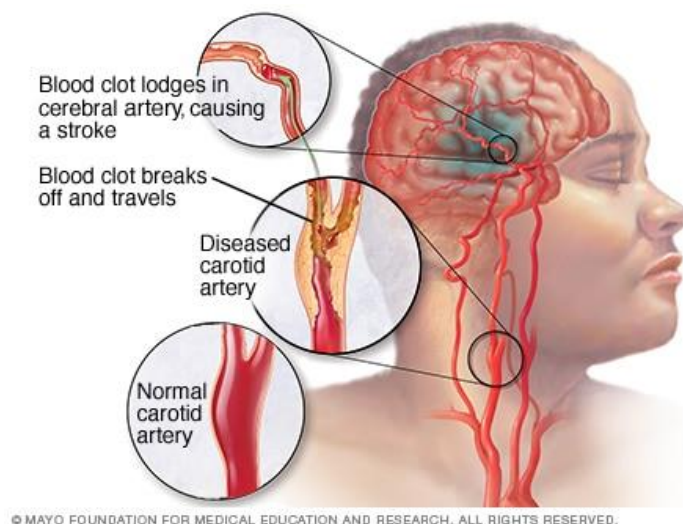


FIGURE 1: Pathophysiology of stroke caused by an embolus of atheromatous plaque of the CA. (9)



### 2.3. RISK FACTORS:

The etiology of stroke, as well as myocardial infarction and peripheral arterial disease, is multifactorial. Cardiovascular risk factors (CVRF) can be classified as modifiable, potentially modifiable and non-modifiable. In any case, whether they are modifiable or not, the association of CVRF increases the risk of stroke and its detection requires a more strict preventive control. The actions on the risk factors, mainly in secondary prevention, decrease not only the risk of suffering a stroke, but the rest of the vascular episodes. (3,4)

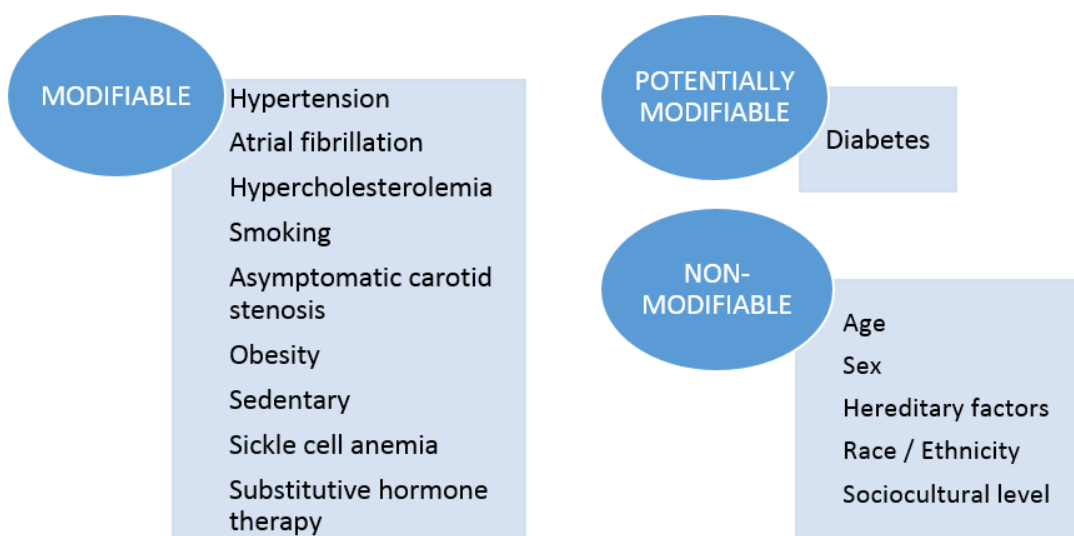


FIGURE 2: Stroke's risk factors by American Heart and Stroke Association (AHA/ASA) guides. (10)

Age is the main non-modifiable risk factor for stroke. The incidence of stroke doubles every decade after 55 years. The presence of a family history stroke, heart attack or transient ischemic attack are associated with an elevated risk of stroke. (1,2)

Sex: Males have a higher risk of stroke than females. Females are usually older when they have strokes, and they're more likely to die of strokes than are males. (9)

High blood pressure, after age, is the most important stroke risk factor given its high prevalence and its high risk potential in both ischemic and hemorrhagic. This is the only associated factor in a manner consistent with all types of stroke (RR = 2 to 4). (3,4)

Overall, about 10-15% of all strokes follow thromboembolism from a previously asymptomatic ICA stenosis >50%. (2)

Smoking causes an increase in viscosity blood and platelet aggregation favoring the thrombosis. The more dose and duration of the habit, the more risk. (11)

## 2.4. CAROTID ESTENOSIS:

### 2.4.1. PATHOGENIA: ATHEROSCLEROTIC PROCESS.

Atherosclerosis is considered a systemic chronic disease. Atherosclerosis plaque is formed by a nucleus lipid mainly of cholesterol that is deposited in the intimal layer of the artery. In addition, calcium deposits can be added to the primary lipid core generating different degrees of calcification. The lesion process consist of:

1. Deposition of lipids in the endothelium of medium and large arteries producing oxidative modifications.
2. This fact produces an activation and recruitment of macrophages forming foam cells (macrophages with massive amounts of cholesterol esters). They interact with T cells establishing a chronic inflammatory process.
3. Smooth muscle cells migrate from the medial to the intimal lamina of the artery wall and synthesize extracellular matrix proteins forming a fibrous plaque. The thrombosis potential increases because of the necrosis of macrophages and smooth muscle cells that leads to the formation of a necrotic core.
4. Macrophage segregate proteolytic enzymes that act degrading extracellular matrix proteins. Together with neovascularization they contribute to a weakening of the fibrous plaque.
5. Plaque rupture exposes plaque lipids and tissue factor to blood components, initiating coagulation, platelet adherence and the formation of thrombus. Evolution of advanced plaques involves repetitive cycles of micro hemorrhage and thrombosis that can cause occlusive arterial disease. (12,13)

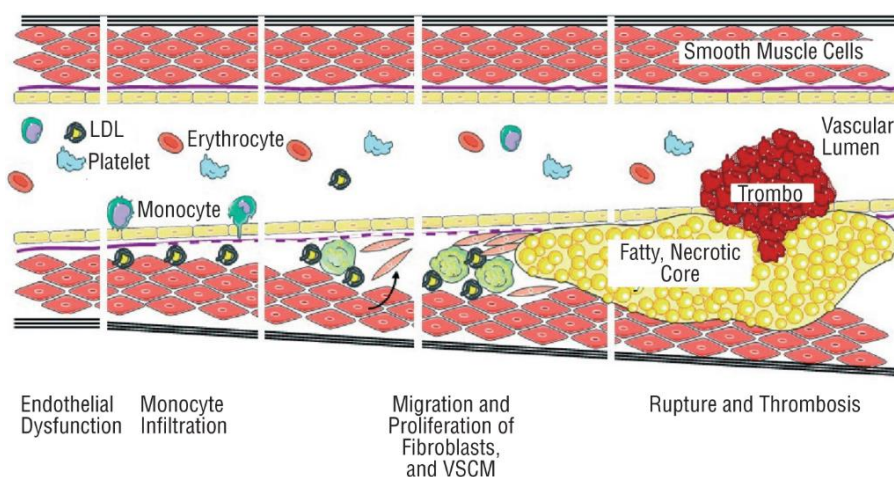


FIGURE 3: Different phases of atherosclerotic process.(13)

#### 2.4.2. CLINIC:

Stenosis of the internal carotid artery may occur asymptomatic (especially in stenosis <50%) or generate clinical symptoms in the form of TIA or cerebral infarction.

A characteristic clinical sign is the retinal TIA also known as amaurosis fugax, which consists of a transient monocular blindness homolateral to stenosis. It occurs because the optic nerve and the retina are innervated by the ophthalmic artery, branch of ICA, so if an embolus occurs it can clog this artery.

The clinical manifestations of TIA or stroke by this cause will be motor or sensory deficit in the hemibody contralateral to the pathological carotid and which usually affects the upper limb more frequently. It can be accompanied by another stroke clinic.

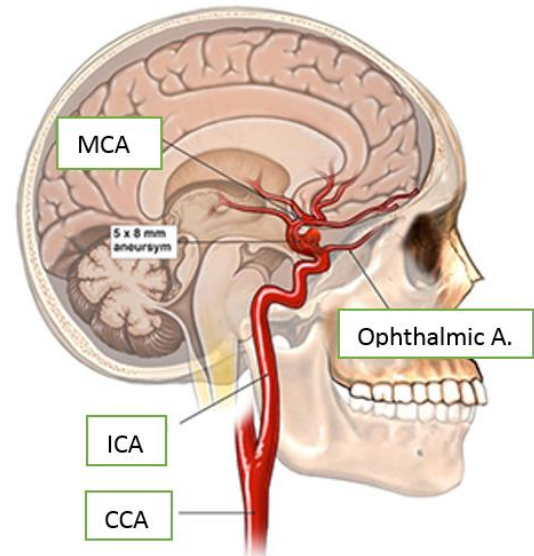


FIGURE 4: CA and branches. (14)

#### 2.4.3. DIAGNOSIS:

As we said before, carotid stenosis is a modifiable risk factor for ischemic stroke. (3,4,6,10) However, population screening is a controversial theme. For now, it's not recommended because it is difficult to identify those asymptomatic patients who would benefit from carotid plaque removal. (10,15)

The diagnosis of carotid stenosis is made so much by clinic as by imaging tests. In asymptomatic patients it is usually detected by the presence of a carotid murmur or by the casual finding of stenosis by duplex ultrasound (DUE). (16)

Duplex ultrasound of supra-aortic trunks is the most important non-invasive test for the diagnosis of carotid stenosis and provides both anatomical and hemodynamic information. It also allows us to assess plate characteristics such as morphology, echogenicity and surface. Due to this, together with its low cost and accessibility, make it the first line imaging modality. For stenosis greater than 70% have sensitivities between 80% and 100% and specificities between 68 and 99%. (2,15)

Despite the great benefits of DUE, we must not forget that it is an explorer-dependent test. That is why we also count on other imaging techniques: Arteriography, computed tomographic angiography (CTA) and Magnetic resonance angiography (MRA). The advantage of these test is the ability to simultaneously image the aortic arch, supra-aortic trunks, carotid bifurcation, distal ICA, and the intracranial circulation. (2)

Arteriography is considered the reference test and provides an excellent information about anatomy from the aortic arch to the intracranial circulation. The problem is that it is an invasive test that can cause allergic reactions, arterial injuries, contrast nephropathy and risk of stroke (1.2%). That is why it has been relegated by TCA and MRA. (17)

In Health Technology Assessment (HTA) meta-analysis, DUS, MRA, and CTA were equivalent for detecting significant ICA stenosis. The recommendations for their use are in Table1. (2,18)

RECOMMENDATION	CLASS	LEVEL
DUE (as first-line), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenosis.	I	A
When carotid endarterectomy is being considered, it is recommended that DUE stenosis estimation be corroborated by CTA or MRA, or by a repeat DUE performed by a second operator.	I	A
When carotid stenting is being considered, it is recommended that any DUE study be followed by CTA or MRA which will provide additional information on the aortic arch, as well as the extra and intracranial circulation.	I	A
Intra-arterial digital subtraction angiography should not be performed in patients being considered for revascularization, unless there are significant discrepancies on non-invasive imaging	III	A

TABLE 1: Images test recommended in the diagnosis of CA stenosis by HTA meta-analysis. (18)

To classify the degree of severity of carotid stenosis, we take as a reference the percentages of NASCET: moderate stenosis is defined as <70% of the luminal diameter and sever stenosis is defined as 70-99% of the luminal diameter. (17)

When ECST/NASCET were randomizing patients, everyone underwent intra-arterial angiography. This has now been abandoned because of angiography-related stroke. Because of this, a table has been drawn correlating the stenosis percentages of the NASCET with DUS criteria for defining stenosis, using peak systolic velocity (PSV), end-diastolic velocity (EDV) and their ratios in the ICA and CCA. (20)

#### 2.4.4. MANAGEMENT:

MEDICAL TREATMENT: Recommendations for all patients for both, primary and secondary prevention of stroke.

- Healthy lifestyle: A healthy diet, smoking cessation, and physical activity and weight loss in case of obesity.
- Antiplatelet agents: Acetylsalicylic acid at low doses or clopidogrel.
- Antihypertensives: It's recommended to keep the pressure below 140/90 mmHg.
- Statins: Stabilize atherosclerotic plaque and reduce the incidence of coronary events. Its effect is beneficial even in patients with normal serum cholesterol levels.
- Glycaemia control: To keep glycosylated hemoglobin below 7% in diabetic patients.
- Anticoagulation: Only in patients with predisposing heart disease. (10)

SURGICAL TREATMENT: Consists of carotid endarterectomy or carotid stenting. (2,21)

Where possible, decisions regarding carotid interventions should involve a multidisciplinary team including neurologists/stroke physicians, vascular surgeons, and interventional radiologists. Multidisciplinary assessment is recommended to achieve consensus regarding the indication and optimal treatment of patients above all, taking the decision between by CEA or stent. (2,22)

The indications for surgical treatment in patients with symptomatic carotid stenosis arise from the two large randomized clinical trials: NASCET and ECST, according to degree of stenosis. (2,19)

But, since the increasingly frequent introduction of endovascular therapy in daily clinical practice, great controversy has arisen regarding the choice of the most appropriate treatment in patients with carotid stenosis. Since then, numerous studies have been carried out to determine which of the two techniques is most beneficial according to the characteristics of the patient, but today, there is still no study that shows a significant difference between the two of them. (23)

In this context, a set of the most important societies in this field published a guide of recommendations about the most appropriate treatment that is summarized in Table 2. (21).

CLASS I	LEVEL
Patients at average or low surgical risk who experience nondisabling ischemic stroke or TIA symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral internal carotid artery is reduced more than 70% as documented by noninvasive imaging ( <i>Level A</i> ) or more than 50% as documented by catheter angiography ( <i>Level B</i> ) and the anticipated rate of perioperative stroke or mortality is less than 6%.	A
	B
CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%.	B
Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences.	C
CLASS IIa	LEVEL
It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the ICA if the risk of perioperative stroke, MI, and death is low.	A
It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular.	B
It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.	C
When revascularization is indicated for patients with TIA or stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery.	B
CLASS IIb	LEVEL
Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by DUS), but its effectiveness compared with medical therapy alone in this situation is not well established.	B
In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities, the effectiveness of revascularization versus medical therapy alone is not well established	B
CLASS III: No benefit	LEVEL
Except in extraordinary circumstances, carotid revascularization by either CEA or CAS is not recommended when atherosclerosis narrows the lumen by less than 50%.	A
Carotid revascularization is not recommended for patients with chronic total occlusion of the targeted carotid artery.	C
Carotid revascularization is not recommended for patients with severe disability caused by cerebral infarction that precludes preservation of useful function.	C

TABLE 2: Recommendations for selection of patients for carotid revascularization. (21)

## 2.5. ENDARTERECTOMY:

The first carotid endarterectomy (CEA) was performed in 1954 to treat a 66-year-old female with 33 previous episodes of TIA after surgery the symptoms disappeared completely. Since then, this technique has become one of the most frequent interventions in vascular surgery services. (6,7)

As we mention before, CEA is consider as the first option in the treatment of carotid stenosis. It is recommended to perform it as soon as possible after the last ischemic event, ideally in the first 2 weeks. (2–4,19)

Its fundamental objective is the prevention, primary and secondary, of stroke. It has shown its usefulness compared with pharmacological treatment both in patients with previous neurological symptoms and in asymptomatic patients as long as the surgical risk is acceptable. Its superiority versus medical treatment lies in maintaining morbi-mortality rates of less than 6% in symptomatic patients and 3% in asymptomatic patients. (2,6,7,19,21).

Nowadays, CEA is a large field of study and research in vascular surgery, because there are many unknowns regarding its approach. There are many studies that have been done, and are being done, trying to find out what is the best approach. The main facts at issue are:

- Shunting: routine, never or selective during clamping.
- Primary arterial closure or closure with patch.
- Types of anesthesia: local or general anesthesia.
- Conventional or eversion technique.
- Transverse or longitudinal incision.
- Antegrade versus retrojugular exposure.
- Staged or synchronomous bilateral carotid intervention.

All of them are still being debated. There is not enough evidence, or significant results that indicate the benefit of some over others so, at the moment, the choice of what to do is left to the surgical team's discretion.

Management decisions must be made on an individual patient basis, based on patient comorbidities, anatomical features, and the experience practitioners locally. (2)



### 2.5.1. CONVENTIONAL CAROTID ENDARTERECTOMY (c-CEA):

During this technique, the incision in the artery is made longitudinally from the CCA to the ICA, extending it sufficiently to allow the evacuation of the damaged intima. After this, the atheromatous plaque is removed. Once finished, we can make a primary closure of the artery or close with a patch. The entire process is explained in section 6.6 (Interventions).

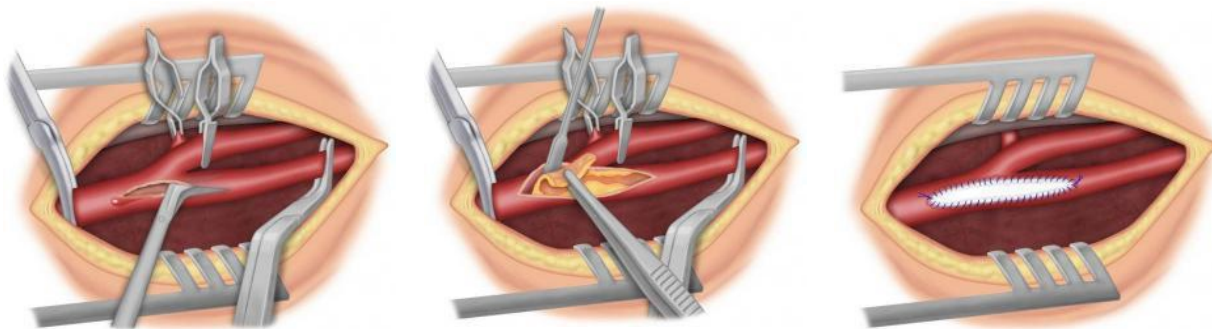


FIGURE 5: Conventional carotid endarterectomy process. (24)

### 2.5.2. EVERSION CAROTID ENDARTERECTOMY (e-CEA):

During this technique, the ICA is transected obliquely at its origin and a cylinder of atheroma is "expelled" via eversion of the outer media and adventitia. The distal intimal step is examined for residual flaps, which are then excised. The ICA is shortened (as required) and anastomosed to the CCA. The complete process is explained in section 6.6 (Interventions).

Advantages include: no risk of prosthetic infection (No patch for closure is used), it's quicker than patched c-CEA, bifurcation geometry is preserved and it's possible to shorten the distal ICA where necessary.

Disadvantages are that shunt cannot be inserted until eversion is completed and there may be problems accessing the upper ICA (if distal disease has been underestimated). (2)

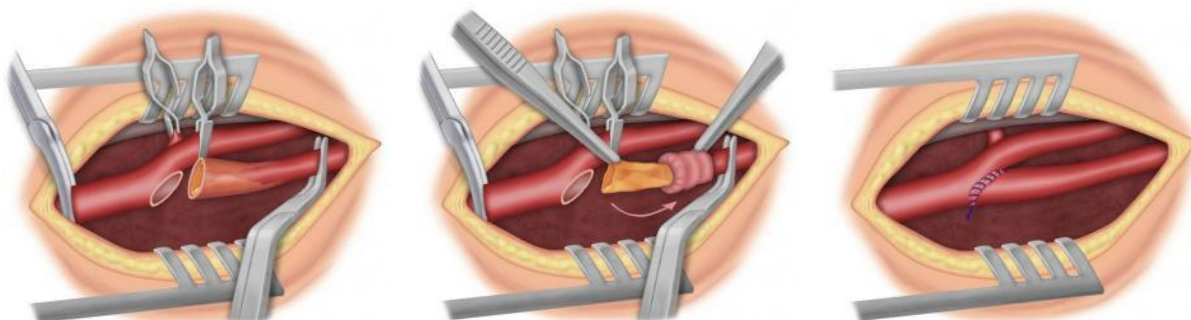


FIGURE 6: Eversion carotid endarterectomy process. (24)



### 2.5.3. EVERSION VERSUS CONVENTIONAL CEA:

A meta-analysis has reported that e-CEA was associated with a significantly higher incidence of post-CEA hypertension compared with c-CEA. By contrast, c-CEA was associated with a significantly higher incidence of perioperative hypotension. (25)

In a meta-analysis of 21 randomised and non-randomised studies comparing c-CEA with e-CEA, e-CEA was associated with significant reductions in perioperative stroke, perioperative death and a significant reduction in late carotid occlusion. (26)

However, in a Cochrane review there were no statistically significant differences regarding 30-day death/stroke, perioperative thrombosis, and late stroke. However, patients randomised to e-CEA had a double reduction in late restenosis >50% (2.5%), compared with patients undergoing c-CEA (5.2%). (27)

When the meta-analysis compared e-CEA with patched CEA, however, there were no differences in late restenosis. These data would, therefore, suggest that e-CEA provides equivalent outcomes to c-CEA, provided the arteriotomy is closed with a patch. (27)

In conclusion, the only real evidence shown so far in this field is the following:

RECOMMENDATION	CLASS	LEVEL
Eversion endarterectomy is recommended over routine primary arteriotomy closure.	I	A
The choice between eversion or patched endarterectomy should be left to the discretion of the operating surgeon.	I	A

TABLE 3: Recommendations for selection of e-CEA vs c-CEA. (27)

#### 2.5.4. GENERAL COMPLICATIONS:

##### EARLY COMPLICATIONS:

- Central neurological lesions: Postoperative stroke (1-5%) and death (0.5-1.8%).
- Local lesions:
  - o Wound hematoma: very common.
  - o Lesions of the cranial nerves: (2-17%) They can be temporary and disabling injuries are less than 0.5%.
    - Hypoglossal and recurrent laryngeal nerve are the most frequent injured.
    - Can also be affected: Vague, glossopharyngeal and spinal accessory nerves (uncommon), cutaneous sensory nerves (fraternal auricular and transverse cervical nerves).
- General complications:
  - o Myocardial infarction: most important cause of early perioperative mortality.
  - o Hypertension (19%) or hypotension (5%): many times it returns to normal in 24-48 hours.
  - o Hyperperfusion syndrome (2-3%): Characterized by unilateral headache, epileptic seizures and intracerebral hemorrhage; happening at 2-7 days.
  - o Surgical wound infection
  - o Bleeding

##### LATE COMPLICATIONS:

- Recurrent carotid stenosis: (1-20%) is the most common late complication caused by intimal hyperplasia because inflammatory response. Usually develops within 2 years.
- CEA's reintervention: (1-3%) presents additional challenges with dissection and reconstruction that can increase the risk of that association with a primary closure.
- Pseudoaneurysms
- Long term stroke: In the follow-up of a successful carotid endarterectomy, the stroke rate at 2 years in the NASCET was 1.6%, compared with 12.2% in the medically managed patients. (6,19,28)

## 2.6. CAROTID STENOSIS IN FEMALES:

### 2.6.1. BASIS OF SEX DIFFERENCES IN CAROTID DISEASE.

The traditional risk predictors for stroke in carotid disease have been assumed to be dependent on degree and severity of vessel stenosis, but other factors such as plaque size, composition, intraplaque hemorrhage, ulceration and overall plaque stability should be considered when determining risk of stroke.

Newer pathological and imaging studies highlight that carotid plaque constitution may play a role in defining risk of stroke. Differences in plaque morphology and composition could help explain why females benefit less from carotid revascularization and more from medical therapy than males. (29,30)

For example, males have larger-volume carotid plaque than females do, and plaque volume is a strong predictor of ischemic events.(31) Histologically, females have less inflammatory, more stable carotid plaque, with more smooth-muscle infiltration and fewer thin, fibrous caps and lipid-rich necrotic cores (which tend to rupture and embolize). (32,33)

Such differences may explain the comparatively shorter high-risk period after stroke in females who have carotid stenosis. (2,19) The higher procedural risk in females may be partially related to their smaller carotid arteries (34) and their tendency to present later in life with more comorbidities. (35)

In the future, advanced imaging modalities could aid in patient selection for carotid revascularization by helping to determine who is at high risk of stroke based on plaque characteristics, instead of simply basing decision on degree of stenosis. (29)

### 2.6.2. ASINTOMATIC DISEASE

The medical treatment of the patient with carotid disease has improved in the last 20 years: the treatment with statins, the aggressive control of the BP and the focus on the modification of the lifestyle. It is important to keep in mind that, although the studies have been updated, the management of carotid stenosis continues to take as reference the NASCET and EVCS studies, carried out in 1991. For this reason, the treatment of the disease is a subject of persistent debate. (29)

Clinical trials performed in asymptomatic patients, ACAS (36) and ACST (37), demonstrated that from 60% stenosis there was more benefit of CEA over only medical treatment. However, in reviews, in long term it was observed that females did not obtain so much benefit and that they had more surgical risk and more risk of stroke and death in 5 years. (38,39). In addition, other studies have shown that this risk was greater if the revascularization was done with a stent. (40,41)

However, statistical power for subgroup analysis by sex in all these studies may have been limited by low number of females enrolled (ACAS and ACST only 34%), not having reliable evidence of benefit for females with asymptomatic carotid disease. (29)

Given that more recent studies showed a decrease per year annual rate of stroke in asymptomatic patients overall because of medical treatment, and given the inconsistencies in benefit of CEA or stent in asymptomatic females, it is reasonable to consider medical therapy for females. But for now, having not strong evidence of this fact, it's recommend using all available risk reduction strategies in these patients, especially in light of the fact that carotid disease, even if asymptomatic, can be a marker of increased risk for peripheral arterial disease and myocardial infarction. (11,29)

### 2.6.3. SINTOMATIC DISEASE

In contrast, symptomatic females who underwent CEA for high grade stenosis (70%–99%) had significant overall stroke prevention. In a pooled analysis of NASCET and ECST, these females had a 41.7% absolute risk reduction over 5 years.

However, with 50–69% stenosis, CEA was not beneficial in females but was in male. Females treated with medical therapy had a low risk of stroke. They only benefitted from surgery if they had additional risk factors (age >70, severe hypertension, history of myocardial infarction or hemispheric event). (2,19)

Again, optimal medical therapy wasn't developed yet. Also, we have to keep in main that NASCET enrolled 30% females and ECST enrolled 28%, and that the technique used was conventional-CEA. (29,30)

#### 2.6.4. FEMALES REPRESENTATIVITY IN STUDIES.

Representation of females in stroke clinical trials remains an issue. The fact that females have been underrepresented in carotid stenosis trials has led to uncertainty about the optimal treatment for them.

In conclusion, major clinical attention should focus on this problem. Clinical trials focused on females are needed to evaluate the efficacy and selection of modern procedural interventions. This is a potential solution for this clinical problem and deserves serious consideration.

Finally, if these trials are designed with relatively few exclusion criteria, then a broader range of females can be enrolled, including greater representation of patients age 80 years and above. Inclusion of elderly patients is especially important considering the ageing of the population in most developed countries. (29,30)

### 3. JUSTIFICATION

The stroke is public health problem of the first order, being the second cause of mortality and the first cause of long term morbidities in the western world, causing a huge socioeconomic impact. In our country is the leading cause of death in females over 65, and incidence and prevalence are increasing due to the aging of the population. Carotid artery stenosis is considered to be the main risk factor to develop ischemic stroke. (2–5)

Therefore, the current guidelines, based on multicenter, prospective and randomized studies, consider carotid endarterectomy as the first option in the treatment of carotid stenosis. (2–4,19).

But this leads us to a conflict, which is that the large studies on which these guidelines are based have a very poor presence of females: NASCET 30%, ECTS 28%, ACAS and ACST 34%. This is because, being stroke most frequent in males, in most studies females are underrepresented. But the fact is that we are extrapolating results and indications to half of the population without having real evidence that this is the best approach. (2,19,29,30,36,37)

And it is necessary to understand that the approach to carotid stenosis and its study must be individualized by sex, since it has been shown that there are different anatomopathological characteristics in the atheroma plaques and in the size and diameter of the arteries. These characteristics have already been shown to influence the risk of stroke, but they could also explain why the treatments proposed so far do not benefit females as much as males. In addition, females usually present stroke at more advanced ages, accompanied by an increased operative risk and morbidities. (2,19,31–35)

The numbers show it, and here is the issue: How a disease more prevalent and high-risk in males is actually causing more deaths in females? Are we doing it right?

Frankly, today we do not have enough evidence to tell us which is the most appropriate treatment on carotid stenosis and prevention of stroke in females. (29,30)

Therefore, although in the largest meta-analysis comparing eversion with conventional endarterectomy do not show significant differences, as females are not well represented we cannot discard in them the idea that e-CEA may have advantages over conventional, for the anatomical and plaque characteristics of the females.

Our trial consist of compare two different techniques of endarterectomy, eversion versus conventional technique, to evidence if really, in females with severe carotid stenosis after a stroke episode, it could show benefits one over the other as a secondary prevention of it.

Our main objective is to demonstrate that, in females, the number of postoperative ischemic strokes within the first 30 days is lower after eversion carotid endarterectomy.

Secondary objectives also support that eversion could have better results than conventional endarterectomy: the number of long term ischemic strokes, mortality within the first 30 days, time of procedure, restenosis and development of pseudoaneurysms could be lower.

In addition, changes in post-surgery blood pressure are higher in the c-CEA, because it would produce more commonly hypotension; while the e-CEA, although some studies have said that could increase the BP, we believe that in females is not the case.

With this project we wish to achieve more information about the indication of eversion technique as endarterectomy of first choice in females. Several trials have demonstrated the safety and the efficacy of this technique and have shown some benefits for patients comparing to conventional. However, most studies conclude that more information is needed and much more are needed just in females.

In summary, we hope that this study will provide more information about this field. In addition, we also hope to encourage more studies like this to be carried out to increase the evidence on stroke and carotid stenosis in females, and this way, get more evidence about their best possible management.

## 4. HYPOTHESIS

### 4.1. PRIMARY HYPOTHESIS:

The proportion of postoperative ischemic strokes within the first 30 days will be lower in eversion carotid endarterectomy group than in conventional carotid endarterectomy group, in females as secondary prevention of an ischemic stroke caused by carotid stenosis.

### 4.2. SECONDARY HYPOTHESIS:

*In females:*

Eversion group will have a less number of restenosis and long-term ischemic stroke.

The number of cases with onset arterial tension changes after surgery will be lower in eversion group. Onset hypotension will be higher in conventional endarterectomy group.

Also, the total procedure time will be shorter in eversion group, compare to conventional endarterectomy group.

Mortality in the first month after surgery will be lower in eversion group.



## 5. OBJECTIVE

### 5.1. PRIMARY OBJECTIVE:

We want to know if there is a decrease in the proportion of postoperative ischemic strokes within the first 30 days, at the time of performing an eversion carotid endarterectomy versus conventional carotid endarterectomy, in females as secondary prevention of an ischemic stroke caused by carotid stenosis.

### 5.2. SECONDARY OBJECTIVES:

*To evaluate and compare:*

- The restenosis of the carotid artery.
- The occurrence of long-term ischemic stroke.
- The onset of hypertension/hypotension after surgery.
- The production of a carotid pseudoaneurysm.
- The total procedure time.
- The mortality within the first 30 days post-surgery.

## 6. METHODS

### 6.1 STUDY DESIGN:

A prospective, consecutive, comparative, control interventional and single-blind with external blind review clinical trial with randomized sample distribution: eversion or conventional technique for carotid endarterectomy.

#### 6.1.1. RANDOMIZATION METHODS:

We will use a computer generated randomization with the SPSS software (Statistical Package for the Social Sciences). The purpose of randomization is to ensure that the only difference between the two groups is the intervention we are comparing.

The investigators will not have access to the randomization sequence and will not be aware of which technique will be taking place in order to avoid selection bias.

The vascular surgeon will not have access to information of the type of surgery for each patient up to 24 hours before surgery to minimize any selection bias.

#### 6.1.2. DEGREE OF BLINDING:

This will be a single-blind trial with external blind review:

- Patients will not be aware of the type of intervention they receive.
- Vascular surgeons must know which technique they will apply, so it is not possible to preserve the surgeon's blinding.
- To get the external blind review, the evaluator in charge of the patient follow-up will be a vascular surgeon who has not been present throughout the surgery, and therefore, doesn't know what technique has been used.

## 6.2 STUDY POPULATION:

In our study we will include females with an indication of endarterectomy as secondary prevention after suffer an ischemic stroke caused by carotid stenosis.

### 6.2.1. INCLUSION CRITERIA:

- Females at least 18 years old.
- Patients that have suffer an ischemic stroke in the last 14 days.
- Demonstration of an atheromatous plaque in one of the carotid arteries with duplex ultrasound of supra-aortic trunks and a CTA or MRA, depending on the characteristics of the patient and the availability of the hospital.
- The carotid lumen obstruction is between 70-99%, or between 50-69% if, despite an adequate medical treatment, the patient presents recurrent ischemic events.
- Patients have to understand and sign informed consent form.

### 6.2.2. EXCLUSION CRITERIA:

- Inaccessible stenosis for open surgery.
- Post-radiation stenosis.
- Restenosis post endarterectomy.
- Acute or evolving cerebral infarction.
- Established stroke with great motor sequelae.
- Allergy to any of the devices used in the interventions.
- Anatomical Contraindications: Existence of a cervical stoma, history of neck radiotherapy with resultant local fibrotic changes of the skin and soft tissues, and previous ablative neck surgery, such as radical neck dissection and laryngectomy.
- Coagulopathy or bleeding disorder.
- Connective tissue disease.
- Active systemic or localized neck infection.
- Medical contraindications: Grade 3, 4 COPD (GOLD scale); Grade 3, 4 cardiac failure (NYHA scale); renal insufficiency grade 3-5.
- Life expectancy <2 year.

## 6.3 SAMPLING

### 6.3.1. PATIENT SELECTION

We will use a non-probabilistic, consecutive and proportional to the number of admission sampling in a period of one and a half year.

We know that for our study we will need a large sample, so it will be focused as a multicenter study, performed in different hospitals at the same time.

These hospitals must have an adequate vascular surgery team according to the study. Surgeons have to be well trained in both techniques, and must have the necessary equipment to perform them. Also, remember that endarterectomies can only be performed in centers that have shown a risk of complications (stroke or death) less than 6%.

In the *Hospital Universitari Dr. Josep Trueta*, with a reference population of 156.000 people, an average of 80 endarterectomies are performed each year. We estimate that the number of patients who meet the inclusion and none exclusion criteria will be approximately 20 (25%). Taking into account these numbers, based on the reference populations of the hospitals of Barcelona that participate in our study, it has been estimated that we need 7 centers in total to reach the necessary number of 396 patients for complete the recruitment in one and a half year. Selected hospitals are mentioned in the section 11.1 (Research team).

Patients who meet all the inclusion criteria and none of the exclusion criteria will receive an information document describing the study (ANNEX 1). Patients must be informed that to participate is entirely voluntary and their decision will not condition the treatment they will receive. If finally, the patient is interested to participate, we will provide them the informed consent form (ANNEX 2) that must be signed.

### 6.3.2. SAMPLE SIZE

In a bilateral contrast, assuming an alpha risk ( $\alpha$ ) of 0.05 and a beta risk ( $\beta$ ) of 0.2 and having a value or statistical power ( $1 - \beta$ ) of 0.8, assuming a moderate effect and a rate of drop out of 1% (mortality rate shown by the literature (19,28)) it's needed a sample of 198 people per arm, being a total of 396 patients.

Sample size has been calculated with the Professor Marc Sáez' software based on the library 'pwr' of the free statistical environment R (version 3.5.1).

## 6.4 VARIABLES

### 6.4.1. INDEPENDENT VARIABLE

The independent variable in this study is the eversion CEA versus conventional CEA for the secondary prevention of ischemic stroke. It is a nominal dichotomous qualitative variable.

### 6.4.2. DEPENDENT VARIABLE

The onset of an ischemic stroke within the first 30 days, which is defined as a rapid development of signs of focal neurological involvement (sometimes global) that last more than 24 hours or lead to death.

We will measure it according to two possibilities:

- 30 days post intervention we perform a cranial MR study with a possible infarction study protocol and brain damage is demonstrated.
- The patient is admitted with a stroke code, and after performing the imaging tests, brain damage is demonstrated.

### 6.4.3. SECONDARY DEPENDENT VARIABLES

- Restenosis of the carotid artery (yes/no)

It is defined as the presence of the occlusion of arterial lumen measured with duplex ultrasound. It is a dichotomous qualitative variable.

- Occurrence of long-term ischemic stroke (yes/no)

The proportion of postoperative ischemic stroke after the first 30 days from surgery.

We will measure it as the patient is admitted with a stroke code, and after performing the imaging tests, brain damage is demonstrated. It is a dichotomous qualitative variable.

- Onset of hypertension (yes/no)

It is defined as a sustained systolic pressure  $\geq 140$  mmHg or sustained diastolic pressure  $\geq 90$  mmHg. This is a dichotomous qualitative variable.

We will consider the hypertension diagnosis when the elevation of the blood pressure is persistent: when the average of two determinations by tensiometer performed at each visit, in total of three visits, is always above these numbers, in the postoperative follow-up.

- Onset of hypotension (yes/no)

It is defined as a sustained systolic pressure  $\leq 90$  mmHg or sustained diastolic pressure  $\leq 60$  mmHg. This is a dichotomous qualitative variable.

We will consider the hypotension diagnosis when the decrease of the blood pressure is persistent: when the average of two determinations performed by tensiometer at each visit, in total of three visits, is always lower these numbers, in the postoperative follow-up.

- Production of a carotid pseudoaneurysm (yes/no)

It is defined as the demonstration of a pseudoaneurysm neck with periodic flow signal by the duplex ultrasound. It is a dichotomous qualitative variable. It is a dichotomous qualitative variable.

- Total procedure time (min)

It is defined as time between the skin incision until the skin closure in the intervention. It will be measured in minutes by the nurse. It is a continuous quantitative variable.

- Mortality (yes/no)

It is defined as the death of the patient in the first 30 days after surgery. It is a nominal dichotomous qualitative variable.

#### 6.4.4. COVARIATES

Randomizing the sample is a way of controlling possible confusion. But, in multicenter studies, there is a risk of residual confusion. That is why, to avoid it, we will control the following covariates:

- Neck fat (mm)
- Plate size (mm)
- Age (years)
- Bilateral atherosclerotic pathology (yes/no, qualitative variable)
- Tobacco: smoker or ex-smoker / non-smoker (qualitative variable)
- Socioeconomic factors: proxied by education and occupation (qualitative variables)

## 6.5 DATA COLLECTION

### 6.5.1. FIRST VISIT:

Our patients will be referred by the neurology service, as they will be females who have just suffered an ischemic stroke and have already received the treatment. There are two ways to reach us:

- Through a neurology consultation while the patient is admitted in hospital.
- The patient is presented at the weekly session of vascular surgery and neurology services.

In both cases, the consultation will be made after the neurologist has done the necessary tests and has diagnosed the carotid stenosis with duplex ultrasound of supra-aortic trunks and a CTA or MRA. If at the time of the consultation any of them is missing, or they are not of good quality, they will be repeated.

Once we know the case, we will proceed to contact the patient to explain the indicated intervention, which will be scheduled before 14 days after the stroke. If the patient is a candidate to participate in our clinical trial, we will proceed at this time to explain what it is. We will provide the sheet information and if, once read and understood, the patient want to participate, we will give the informed consent form of participation and of intervention (ANNEX 3) to sign it. We will collect data in the participant data sheet (ANNEX 4).

At this time, the patient will be randomized for the type of surgery. The vascular surgeon will not know until 24 hours before surgery to avoid selection bias.

### 6.5.2. HOSPITALIZATION:

- o ADMISSION: Patients will be hospitalized 6-12 hours before the intervention, if they are not already admitted due to stroke. Patients will not eat nor drink anything 6-8 hours before surgery. Preoperative evaluation will consist of:
  - Measurement of blood pressure, heart rate and temperature by the nurse.
  - General blood analysis: hematocrit and coagulation function.
  - Electrocardiogram and chest plate.
  - Evaluation of the anesthetist.
  - Respiratory functional tests if the patient has basic lung pathology.
  - Withdrawal of anticoagulants (except Adiro) and potent antiplatelet agents.

- SURGICAL INTERVENTION: Surgical team will be formed by vascular surgeons, instrumentalist nurses, and anesthesiologist. Interventions will be performed in the operating room. E-CEA and c-CEA are explained at point 6.6 (Interventions). During the surgery, an operating room nurse will record the operating time.
- POSTOPERATIVE: After surgery, patients will join the post-surgical unit: REA (*Unidad de reanimación asistida*) to recover from anesthesia, and will return to the vascular surgery service after 6 hours (may be up to 48 hours depending on anesthesia and complications). Before discharge:
  - During the stay in the hospital the patient will receive low molecular weight heparin, 1 mg/kg each 24 hours until discharge.
  - The neck drainage will be removed at 24-48 hours (depending on bleeding).
  - A daily medical evaluation will be conducted until discharge it's indicated. Vascular surgeon will assess if any access related complications appear.
  - Duplex ultrasound of supra-aortic trunks and a CTA or MRA will be done before the patient leaves to check everything is fine.
  - All patients will receive antiplatelet therapy for life after the discharge: acetylsalicylic acid (ASA).

### 6.5.3. FOLLOW-UP:

Controls will be made in vascular surgery consults and will be performed by a different surgeon than the one who performed the surgery, to avoid bias. Postoperative follow-up will allow us to detect the short-term and late complications.

The controls will consist of:

- Clinical evaluation.
- Measurement of blood pressure twice.
- Duplex ultrasound of supra-aortic trunks with Philips Sparq ultrasound system.
- *Only the first month visit:* Cranial MR study with a possible infarction study protocol.

The checks will be carried out in one month, three months, six months, one year and two years post-intervention.

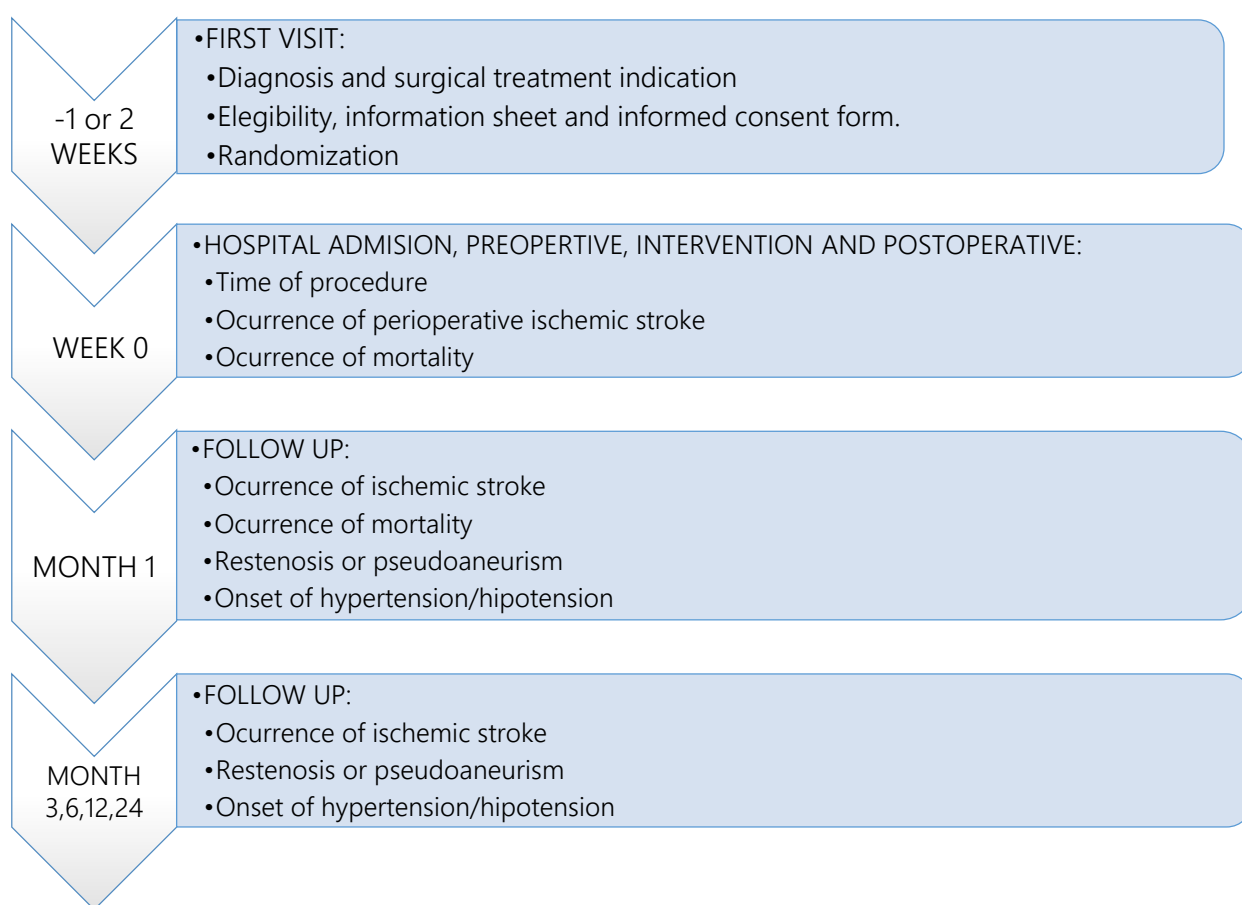
The participant data sheet will be filled by the physician as these data are collected.



The data about patient's admission and diagnosis of ischemic stroke will be collected from the patients' medical records and corroborated with the ICD-10 code regarding the diagnosis at discharge: I63-1 corresponding to "Cerebral infarction due to arterial embolism of precerebral arteries".

The data about patient's death and mortality because of ischemic stroke will be collected from the patients' medical records.

#### 6.5.4. SUMMARY:



## 6.6 INTERVENTIONS

Patients will be preoperatively examined by an anesthesiologist. General anesthesia will be used in every patient.

All procedures will be performed in a conventional operating room and will be monitored with continuous electrocardiographic and encephalographic control, blood pressure, oxygen saturation and pulse. Before starting, a transcranial duplex ultrasound will be done to check the pressure of the MCA and assess the possible need for shunt.

The interventions will always be performed by the same previously trained vascular surgeons in each hospital, who have completed the previous training with good results and have demonstrated their high ability for both interventions.

During the surgery, there are some common steps that we will follow in both interventions. We will use the different techniques object of this study when manipulating the carotid and the plaque.

At the end of surgery we will need to do an angiography. This means that the team in the operating room must wear a leaded uniform and the operating table must be radiolucent.

The step-by-step interventions are explained below:

### 6.6.1. COMMON BEGGINING OF THE INTERVENTION

1. General anesthesia.
2. Preparation and start intraoperative monitoring.
3. Administration of antibiotic prophylaxis: cefazolin 2g, or vancomycin if allergy.
4. Head slightly raised and lateralized 45° to the opposite side.
5. Oblique incision along the anterior border of the sternocleidomastoid muscle, centered on the carotid bifurcation.
6. Identify and dissect the common facial vein.
7. Avoid damage to the following nerves: mandibular ramus of the Facial, Hypoglossal, Vagus and upper Laryngeal.
8. Careful manipulation of the arteries to avoid cerebral embolism of the plates.
9. Dissect and release from all neighboring tissues the CCA, ECA and ICA.
10. Temporarily link the proximal branches of the ECA.

11. Infiltration of the carotid sinus with 0.25% Lidocaine to prevent large changes in blood pressure.
12. Systemic heparinization (intravenous sodium heparin bolus, 1 mg per kg).
13. Determination of the retrograde pressure of the ICA. We will obtain two determinations, pre and post-clamping the CCA. If there is no variation in pressure, we'll proceed the surgery. If there is a decrease of 40mmHg or below 50mmHg we must make a shunt that allows blood pass while the surgery, before continue.
14. Arterial clamping in the following order: ECA, CCA and finally the ICA.

#### 6.6.2. CONVENTIONAL CAROTID ENDARTERECTOMY

1. Linear arteriotomy from the CCA to the ICA beyond the extension of the plate.
2. Identify well a plane of cleavage between the unaffected middle layer and the plate.
3. Begin the resection of the plate by the CCA with a blunt instrument.
1. Continue the dissection of the plate inside the ECA and the ICA.
2. It is important to maintain a unique plane between the intimate layer and the middle in its circumferential dissection.
3. Arteriotomy should be closed with a 5/0, 6/0 polyester or prolene suture.
4. The arterial closure should be performed with suture around a prosthetic patch, with a space between the points of one millimeter, including in them the entire arterial wall, without causing stenosis of its light.

#### 6.6.3. EVERSION CAROTID ENDARTERECTOMY

1. Complete and transversal section of the carotid bulb.
2. Eversion performance of the segments of the tunica media and the adventitia of the native artery.
3. Simultaneously, extraction of the atheroma plaques with a blunt instrument through the plane of cleavage between the intima and the media in a circumferential manner: CCA, ECA, ICA.
4. Terminal-terminal circumferential primary closure, with a 5/0, 6/0 polyester or prolene suture.

#### 6.6.4. COMMON FINAL OF THE INTERVENTION

The common steps at the end are the following:

1. Before the final closure, the arterial blood serum should be filled to avoid gas embolism.
2. The order of removing the clamp is as follows: ECA, CCA and finally the ICA.
3. At this time we performed an angiography to assess the existence of complications of the intervention itself. With this test we can see the arterial light and evaluate the existence of dissection, narrowing of the vascular segment, aneurysmal dilation, intimal flap and presence of double lumen. We do it before closing the neck, in case there is a problem and the artery should be reoperated.
4. Arteriotomy should be covered with Surgicel.
5. Reverse Heparin with Protamine.
6. Absolute hemostasis and hermetic closure by planes, placing a drainage exteriorized by counter-opening.

Finally, once the surgery is over, we wait in the operating room for the patient to wake up from the anesthesia and perform a basic neurological examination to see if an ischemic event has occurred during the process. We check the tone, movement and symmetry of the contralateral hand and leg.

Once in the REA, past the effects of anesthesia completely, we will perform a thorough neurological exploration, making emphasis in the nerves' functions with surgical injury risk: mandibular ramus of the Facial, Hypoglossal, Vagus and upper Laryngeal.

The explanations of the interventions step by step have been adapted from the bibliography (6,7,42), together with the team of vascular surgeons of the H. U. Doctor Josep Trueta.

Images corresponding to the interventions are found in section 2.5 (endarterectomy).

## 7. STATISTICAL ANALYSIS

All statistical analysis will be carried out by the research team with the help of a statistical expert for data analysis. The program that will be used for it will be the Statistical Package for the Social Sciences (SPSS) for Windows®.

### DESCRIPTIVE ANALYSIS:

The qualitative variables (all the dependent ones except time of procedure; and the qualitative covariates) will be summarized using proportions, stratified by the groups of the independent variable (e-CEA and c-CEA).

The quantitative variables (time of procedure and quantitative covariates) will be summarized by means (standard deviations) and medians (interquartile range IQR). Again stratified by the groups of the independent variable.

### BIVARIATE INFERENCE:

The difference of proportions of the qualitative variables between the groups of the independent variable will be contrasted by chi-square, or Fisher's exact test when the expected frequencies are less than 5.

The difference of means between quantitative variables will be contrasted by Student's t.

The difference in medians will be contrasted by the Mann-Whitney U.

### MULTIVARIATE ANALYSIS

To assess the association between the independent variable and the dependent variables (with the exception of time of process) several logistic regressions (one for each dependent variable) will be estimated. We will adjust for the covariates explained above.

In the case of time of procedure a linear regression will be estimated. As above, the independent variable will be the intervention and the same covariates.

## 8. ETHICS

During the elaboration of the protocol and the focus of the trial, all the basic principles of ethics will be respected in accordance with the recommendations of the Declaration of Helsinki and the World Medical Association. The safety and viability of the two surgical techniques that belong to this clinical trial, have been tested in several studies, so that there is no ethical conflict in this regard. But, being a trial with invasive techniques, we will hire insurance for each participant that covers the damages that could be made.

Once the protocol is finished, this clinical trial will be presented for approval to the "Clinical Research Ethics Committee" (CEIC) of one of the hospitals within the study. Being multicenter, with the validation of a single CEIC is enough, since this is already valid for the rest of the centers. In addition, the CEIC will also assess the approval of the informed consent form and the information sheet of the trial for the patient. In this way, the protection of the rights, safety and well-being of the patients participating in the study is guaranteed.

In addition to the CEIC, the management of the centers that enter in the study will have to approve it as well. After this the trial will be registered in EudraCT and in ClinicalTrials.gov.

To participate in the study it is mandatory that patients read and understand the information sheet of this clinical trial, so they can be able to sign the informed consent form. This way, the principle of autonomy will be respected.

To ensure the confidentiality of the information regarding the identity of the subjects involved in this trial, the "*Ley Orgánica de Protección de Datos Personales y Garantía de los Derechos Digitales*" 3/2018 must be accomplished.

This clinical trial will follow the "*Ley de Investigación Biomédica*" 14/2017 which regulates invasive procedures.

Another ethical consideration is that e-CEA is more likely to improve our outcomes researched. As our hypothesis is not yet proven, patients receiving the c-CEA are not being predisposed to a worse intervention, so no ethical aspect is being violated in our study.

## 9. STUDY LIMITATIONS

- The first limitation in our study is the impossibility of making a double blinding. This is because the vascular surgeon must know if he/she has to perform a c-CEA or e-CEA. It is only possible to maintain the patients' blind; they will be informed that he can receive one or other technique. To overcome this limitation, the vascular surgeon in charge of follow up and statistician will be blind and will not be aware of which participant belongs to which group. Neither will the main researches know.
  
- Randomizing the sample is a way of controlling possible confusion. But, in multicenter studies, there is a risk of residual confusion. That is why, to avoid it, we will control the covariates mention in section 6.4.4. (Covariates).
  
- We must make sure that the surgeons are well trained in performing both techniques, and that the technical quality among all the surgeons in the study is homogeneous and of high quality. This is complicated to measure and therefore we must take into account that there will inevitably be differences between them. To limit this bias, the previous months to beginning the patients' recruitment, a training will be carried out to vascular service of each hospital included in the study, to ensure that the technique is correct. This training program is explained in section 10.3. (Vascular surgeons' training). The training will be in charge of a vascular surgeons specialized in these interventions.
  
- Despite the formation, variability between surgical experts is evident; that is the reason why we must emphasize the importance of making the procedures as homogenous as possible with training program, and data collection must be made as well in an uniform way between the different hospitals, what will be very well explained in the coordination phase, and both, coordinator and project manager, will be in charge of supervise it.
  
- It is important to highlight that being a multicenter study implies more coordination and stronger efforts for quality assurance referring to recruitment, treatment and follow-up. But, in the other side, sample's representation and team involved are higher than in an unicenter study, which gives more external validity.

- We must take into account the possible loss of patients follow-up. In our main variable we will only consider as “loss of follow-up” the patients who die in the first month (time when the main dependent variable is measured). Secondary variables will be collected during 2 years so maybe some patients may not come to visit or die in this time, so these results may be biased. Although we expect that not coming to visit is something unusual because most of the appointments take part in the standard post-operation control care, if a patient does not attend to the appointment, the hospital will attempt to contact via phone or e-mail.



## 10. WORK PLAN

INVESTIGATORS: M<sup>a</sup> Lucía Escabias Criado, Dra. Anna Presas Porcell.

COLLABORATORS: Vascular surgeons, anesthetists and nurse staff of hospitals where this trial is carried out. There will be a coordinator per hospital.

HIRED STAFF: Project manager (PM), statisticians and vascular surgeon trainer.

### 10.1. PROTOCOL DEVELOPMENT:

- Conducted by: Investigators
- Duration: 3 months

We will make the study protocol and errors will be corrected. For its approval it will be submitted to the CEIC review.

### 10.2. COORDINATION PHASE:

- Conducted by: Investigators, vascular surgeons, nursing staff, and anesthetists.
- Duration: 3 months

At the beginning of the trial, the chronogram will be performed and all investigators and coordinators from each hospital will meet face-to-face to define their participation at every stage of the study. This meeting will take place during a day in Barcelona. After it, every coordinator will have to transfer all the information to the hospital team involved.

Vascular surgeons must know in detail the protocol in order to perform a correct patient selection and data collection. They will also be informed of the type of training they will receive and when. All the information will be shared with the anesthetists and nurses.

A meeting every 3 months to clarify possible doubts and do an update will take place between the project manager and each hospital's collaborating team. These will be done face-to-face during 4 years.

If there is any change in the collaborators during the study, the new one will be informed in detail. In the case of vascular surgeon, it will have to past the formation program first.

### 10.3. VASCULAR SURGEONS' TRAINING:

- Conducted by: Training team
- Duration: 2 months

During this time the training programs will be carried out in each hospital. All the team involved in the surgery will participate in it, with greater emphasis on the surgeons who will carry it out.

The training program will assure us that all surgeons will do the interventions in the same way and follow the same technique. In this way we minimize the bias.

The training will have two parts:

- Face-to-face: it will last 1 day in each hospital, and will consist of 2 theoretical hours and 6 hours of practice, during 3 interventions (*it is estimated as necessary to acquire the eversion's ability*). The same surgeon trainer will visit each hospital, within the term of 10 days. 2 surgeons will be trained per hospital.
- Telematics: The trainer will be in continuous contact with the trained surgeons, who will have to perform half of the endarterectomies, during the next two months of training, in the conventional way; and half of them with eversion technique.

### 10.4. PATIENTS' SELECTION AND INTERVENTION:

- Conducted by: Investigators, vascular surgeons, anesthetists
- Duration: One year and a half

The patients' recruitment will take place in hospitals inside the trial. Patients will be referred by the neurology service, after having suffered an ischemic stroke and being diagnosed with carotid stenosis. Investigators and collaborators will evaluate if the patients meet all inclusion and exclusion criteria.

Patients will be informed about our trial and will receive an information sheet, if acceptance, the informed consent form must be signed. The participant data sheet will be filled by investigators and collaborators. After this, patients will be included in the study and will be randomised and assigned in one of the two arms.

Finally, the intervention will be carried out within a maximum period of 14 days after the stroke. In each hospital, interventions will always be held on the same two vascular surgeons, nursing staff and anesthetist.

#### 10.5. DATA COLLECTION & PROCESSING DATABASE:

- Conducted by: Investigators, vascular surgeons, nursing staff
- Duration: 3 years and a half

After discharge, patients will attend outpatient consultations for 2 years, follow-up by a different vascular surgeon from the one who performed the surgery (the surgeon in charge of follow-up cannot know what technique was performed).

During this time, the data will be collected simultaneously and recorded in the trial database. These data will be reviewed by the researchers.

#### 10.6. DATA ANALYSIS:

- Conducted by: Investigators and statistical consultant
- Duration: 3 months

A statistical expert will be hired to perform the analysis of the collected data, who will work with investigators.

#### 10.7. INTERPRETATION AND CONCLUSIONS:

- Conducted by: Investigators
- Duration: 4 months

At the end of the statistical analysis, the researchers will interpret and draw the final conclusions about the results obtained.

#### 10.8. DISSEMINATION PLAN:

- Conducted by: Investigators
- Duration: 3 months

Finally, the results and conclusions will be written and they will be sent to different journals for their publication. They will also be defended in different congresses.

The chronogram is available in the ANNEX 4.

## 11. FEASIBILITY

### 11.1 RESEARCH TEAM

The research team in this clinical trial is composed by the main investigators, vascular surgeons, nurses and anesthetists from the 7 hospitals included, who all of them will be well-trained and will work coordinately to fulfill the marked objectives. These hospitals are:

1. Hospital Clínic de Barcelona, Barcelona
2. Hospital Germans Trias i Pujol, Badalona
3. Hospital Universitari de Bellvitge, Hospitalet de Llobregat
4. Hospital Universitari Dr. Josep Trueta, Girona
5. Hospital Universitari Vall d'Hebron, Barcelona
6. Hospital del Mar, Barcelona
7. Hospital de la Santa Creu i Sant Pau, Barcelona

Necessary means such as personnel salaries, operation rooms, diagnostic devices and follow-ups will be provided by the hospital respectively.

We will hire a Project Manager to help the main investigators at coordinating and data quality control due to the fact that this multicenter study comprises many hospitals and there must be an extra effort or reinforcement on these aspects to avoid rectifiable errors than can reduce easily the value of the study.

We will hire a statistical analyzer as well to process the extensive statistical analysis.

We will hire a vascular surgeon trainer responsible for ensuring the correct procedure in both surgical techniques in the equipment of all hospitals.

### 11.2 MEANS AVAILABLE

The operation room's availability depends on the hospital's characteristics. Some of them sometimes don't have an exclusive one for vascular surgery and they are being shared with other departments but, if it is being scheduled correctly and well-coordinated between departments this will not be an obstacle. Also, all surgical devices for endarterectomy are available in these hospitals.

After surgery, patients will have to rest in hospital for 3 days approximately, so it is important to have available beds after the surgery.

For diagnosing and patient's follow up we need blood pressure cuffs, DUS, CTA, MRA, and angiography. All of these means are available in these hospitals.

The material required for this trial is the standard material used in endarterectomy intervention.

### 11.3 PATIENTS

Taking as a reference patients undergoing an endarterectomy in 2018 in the HUDJT and its population, we approximate that there is circa 80 endarterectomies per year every 156.000 population. We estimate that the number of patients who meet the inclusion and exclusion criteria will be approximately 20 (25%).

Taking into account these numbers, based on the reference populations of the hospitals of Barcelona that participate in our study (that are higher than Girona), it has been estimated that we need 7 centers in total to reach the necessary number of 396 patients for complete the recruitment in one and a half year.

The evaluation of the outcomes will be done during 2 years after the intervention, thus 3 years and a half will be necessary to obtain the sample size and to evaluate the results in every patient.

## 12. BUDGET

### 12.1. STAFF COST:

The research team is employed by the institutions and is not required to work overtime, so their services are not included in our budget.

The research team will carry out all the tasks related with recruitment of patients, interventions, data collection, interpretation of results and publications. However, the research team does not have enough knowledge to perform the statistical analysis. We will hire **statistics support** and the estimated budget is 1400€ (35€/hour, assuming 40h).

Due to the great size and complexity of this project, we have considered necessary the hiring of a **project manager**, who from the coordination phase to finish the data collection, will be in charge of supervising, coordinating and directing the project, being its main task to fulfill the work objectives in each center within the study, be in touch with coordinators in every hospital, and do the visits and meetings established. In addition, he will also be responsible for respecting the dates to comply with the work plan. In this way, he will be hired part-time for 4 years, with an annual salary of 15.000€, which will be left in a total of 60.000€.

### 12.2. COORDINATION MEETING

At the beginning of the coordination phase there will be a meeting in Barcelona which will be attended by a project coordinator of each hospital, project manager and main investigators. It will be held in one of the study hospitals, and will last one day.

For this, we must take charge of diets of that day and the transportation of people coming from Girona. Attend 10 people in total, so the budget will be 325€ (250€ for diets plus 75€ for the transport of 3 people from Girona).

### 12.3. FORMATION

The formation program will consist in 8 hours for each hospital, distributed as follows: Two theory hours and six practical in vivo hours. The price per hour will be 40€, so the price for each hospital will be 320€. As we have 7 hospitals in our study, the final cost is 2.240€.

As the trainer lives in Barcelona, we have also taken into account the transport of the trainer to Girona, estimated at 50€ between train and diets.

#### 12.4. SUPERVISION

The Project Manager will have meetings every 3 months with each hospital. As the PM lives in Barcelona, we have also taken into account the transport of the PM for every visit to Girona. 50€ will be budgeted for each visit between train and diets. These visits will take place during 4 years, so the total amount will be 800€.

#### 12.5. MATERIAL:

Other services include printing information sheets for patients, informed consent forms and participant data sheets (We estimate 0.30€ per patient, so it will be 118'80€).

#### 12.6. INSURANCE POLICY

As this is an invasive study, we will hire insurance that covers the damages that may be caused to the patient as a result of the interventions and also covers the civil liability of all professionals involved in the clinical trial. This insurance covers all damages that affect the patient's health after one year from the end of the trial. The estimated price is 50€ so, as every patient will have it, the cost will be 19.800€.

#### 12.7. SURGICAL MATERIAL AND STAY AT HOSPITAL:

For our project, there is no need for any surgical material or hospital stay longer than normal. As the cost of interventions and stay at hospital are already included within the budget of the hospital itself, being covered by social security, we will not need to allocate any budget to this section.

#### 12.8. POSTSURGERY CONTROL

Within the patient's follow-up, the only added act will be the ultrasound duplex of the third month. The estimated price is 53€ so, as every patient will have it, the cost will be 20.988€.

## 12.9. PUBLICATION AND PRESENTATION COST

Finally, it has been taken into account the costs of the dissemination plan. This study is expected to be published in scientific journals with open access. The budget is estimated to be around 2500 €.

The costs of attending to the International Symposium of Endovascular Surgery (*Sociedad Española de Angiología y Cirugía Vascular*) have been calculated. We budgeted 1500€, which includes inscription (1000€), transport, accommodation and diets (500€).

### SUMMARY:

	CONCEPT	AMOUNT	COST	SUBTOTAL
STAFF COST	Project manager	4 years	15.000€/year	60.000€
	Statistical expert for data analysis	40 hours	35€/h	1.400€
COORDINATION MEETING	Girona assistants' transport	3 trips	25€/trip	75€
	Diets	10 people	25€/person	250€
FORMATION	Vascular surgeons' training program	56 hours (8 per hospital)	40€/hour	2.240€
	Trainers' transport	1 trip	50€/trip	50€
SUPERVISION	Transport to Girona	16 trips	50€/trip	800€
MATERIAL	Printing and papers	396 units	0.30€	118,80€
INSURANCE	Insurance that covers damages	396€	50€/person	19.800€
POSTSURGERY CONTROL	Third month duplex ultrasound	396 units	53€	20.988€
PUBLICATION AND PRESENTATION COST	Publish in Journal of Vascular Surgery	x	x	2.500€
	International Symposium of Endovascular Surgery (people)	1	1	1.500€
<b>TOTAL COST</b>				<b>109.721,80€</b>



### 13. PROJECT IMPACT AND APPLICABILITY

As we exposed in section 3 (Justification), stroke is the leading cause of death in females over 65, and the trend of incidence and prevalence is increasing. Carotid artery stenosis is considered to be the main risk factor to develop ischemic stroke, which has a huge socioeconomic impact in the national healthcare as it is the first cause of long term morbidities in western world.

Today there are very few studies on stroke and carotid stenosis in females and their most appropriate treatment. This is because, being stroke most frequent in male, in most studies females are underrepresented. In addition, if we observe studies on endarterectomies, the representation is lower, since below the stenosis of 70% there are very few indications for intervention in females. Therefore, although in the largest meta-analysis comparing eversion with conventional endarterectomy do not show significant differences, as females are not well represented we cannot discard in them the idea that e-CEA may have advantages over conventional, for the anatomical and plaque characteristics of the females.

With this project we wish to achieve more information about the indication of eversion technique as endarterectomy of first choice in females. Several trials have demonstrated the safety and the efficacy of this technique and have shown some benefits for patients comparing to conventional. However, most studies conclude that more information is needed and much more are needed just in females.

If we get the expected results, we will show that e-CEA has benefits for patients and the health system in comparison to c-CEA. With this technique, secondary prevention of ischemic stroke can be done with better results both short and long term reducing postoperative and long term ischemic strokes, restenosis, pseudoaneurysm, onset of hyper/hypotension and mortality. This way, patient's benefit will be increased. For the health system, the impact of the study lies in the reduction of the operating time, the decrease of use of the health system's resources due to less complications.

In summary, we hope that this study will provide more information so that this technique is widely used by vascular surgery services. In addition, we also hope to encourage more studies like this to be carried out to increase the evidence on stroke and carotid stenosis, and its better management in females.

## 14. ABBREVIATIONS

ACAS: Asymptomatic Carotid Atherosclerosis Study	GRANMO: <i>Grandària Mostral "calculator"</i>
ACST: Asymptomatic Carotid Surgery Trial	HTA: Health Technology Assessment
ASA: Acetylsalicylic Acid	ICA: Internal Carotid Artery
BP: Blood pressure	ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10 <sup>a</sup> edition.
CA: Carotid Artery	MCA: Middle Cerebral Artery
CAS: Carotid Artery Stenting	MR: Magnetic Resonance
CCA: Common Carotid Artery	MRA: Magnetic Resonance Angiography
CEA: Carotid Endarterectomy c-CEA: Conventional CEA e-CEA: Eversion CEA	NASCET: North American Symptomatic Carotid Endarterectomy Trial
CEIC: Clinical Research Ethics Committee	NYHA: New York Heart Association
COPD: Chronic obstructive pulmonary disease	PM: Project Manager
CTA: Computed Tomography Angiography	PSV: Peak Systolic Velocity
CVRF: Cardiovascular Risk Factors	REA: Unidad de Reanimación Asistida
DUE: Duplex Ultrasound	SPSS software: Statistical Package for the Social Sciences software
DWI: Diffusion-Weighted magnetic resonance Imaging	TIA: Transient Ischemic Attack
ECA: External Carotid Artery	
EDV: End-Diastolic Velocity	
GOLD: Global Initiative for Obstructive Lung Disease	

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## 16. ANNEXES

### 16.1 INFORMATION SHEET FOR PARTICIPANTS

#### HOJA DE INFORMACIÓN AL PACIENTE

Título del estudio: EVERSION CONTRA LA ENDARTERECTOMÍA CONVENCIONAL EN EL SEXO FEMENINO COMO PREVENCIÓN SECUNDARIA DE UN ICTUS CAUSADO POR ESTENOSIS CAROTIDEA: UN ENSAYO CLÍNICO ALEATORIZADO Y CONTROLADO.

Investigadoras: M<sup>a</sup> Lucía Escabias Criado, Dra. Anna Presas Porcell.

El ictus es una de las causas más importantes de muerte y discapacidad en nuestro medio. La estenosis de la arteria carótida por una placa de ateroma es una de las principales causas de ictus isquémico.

Hoy en día, endarterectomía carotídea (cirugía mediante la cual se corrige la estenosis) es una de las técnicas de elección para el tratamiento de la estenosis y prevención de nuevos episodios. Actualmente, existen dos posibles técnicas para llevarla a cabo: la eversión (corte transversal de la arteria) o la clásica (corte longitudinal). Ambas han demostrado seguridad y fiabilidad como tratamiento pero, pese a haberse comparado en numerosos estudios, aun no se ha demostrado que una de ellas sea mejor que la otra, de manera que a día de hoy se realiza según preferencia del cirujano.

Aun así, entre estos estudios, la mayoría de participantes eran del sexo masculino, de manera que son necesarios estudios hechos expresamente en el sexo femenino para determinar si hay mayor beneficio de una sobre la otra atendiendo a las características específicas, tanto anatómicas como de la propia estenosis, en el sexo femenino.

La invitamos a participar en un estudio de investigación sobre la comparación de la eversión y la endarterectomía convencional en el sexo femenino como prevención secundaria de un ictus causado por estenosis carotídea. Su duración será de dos años y se realizará en su hospital de referencia.

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 interesada 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 EL OBJETIVO DE ESTE ESTUDIO?

El objetivo de este estudio es comparar los resultados de dos técnicas quirúrgicas a la hora de hacer una endarterectomía carotídea (por eversión o convencional), para ver cuál de ellas es más beneficiosa en el sexo femenino como prevención secundaria del ictus isquémico. Nuestro objetivo principal es ver si se produce una disminución en la proporción de ictus isquémicos postoperatorios dentro de los primeros 30 días tras la cirugía.

Nuestros objetivos secundarios son la comparación de episodios de ictus isquémico a largo plazo, mortalidad en los primeros 30 días, porcentaje de reestenosis de la arteria, aparición de pseudoaneurismas, aparición de hiper o hipotensión, y comparación de tiempo de duración del procedimiento.

#### 2. ¿CÓMO SE DESARROLLARÁ?

Para llevar a cabo este estudio, dividiremos en 2 grupos a todas las personas candidatas, un total de 396 pacientes de 7 hospitales diferentes. Un grupo recibirá la endarterectomía por eversión y el otro grupo recibirá la endarterectomía clásica. Esto se efectuará durante 1 año y medio. El estudio tendrá una duración total de 4 años y medio.

Tras el alta, se hará un seguimiento al paciente al mes, 3-6-12-24 meses, con las pruebas clínicas necesarias para ver si los resultados han sido óptimos, y durante este tiempo todos los datos se irán recogiendo en una base de datos. Para evitar errores, las pacientes no sabrán que técnica han recibido, y tampoco lo sabrá la persona encargada del seguimiento de la paciente.



### 3. ¿POR QUÉ HE SIDO INVITADA A PARTICIPAR?

Ha sido invitada a participar pues usted ha sido diagnosticada de estenosis carotídea y su neurólogo/a le ha indicado una intervención quirúrgica para quitar la placa de ateroma que ocupa la luz de su arteria. Además, cumple con los criterios de inclusión y ninguno de los criterios de exclusión del estudio.

### 4. ¿TENGO QUE PARTICIPAR?

Tiene que saber que su participación en este estudio es VOLUNTARIA. Depende de usted participar o no, y es libre de retirarse en cualquier momento y sin ningún motivo. Si decide participar, le pediremos que firme un formulario de consentimiento. Su decisión no afectará la atención médica que recibe.

### 5. ¿EN QUÉ CONSISTIRÁ MI PARTICIPACIÓN?

Su participación en este estudio constará de varias partes:

- Para empezar, un cirujano/cirujana vascular del equipo de investigación le realizará una entrevista en la que recogerá datos de carácter personal y clínico. En esta misma visita se comprobará que todas las pruebas diagnósticas de la estenosis carotídea que le realizaron previamente los neurólogos están hechas correctamente. Si no es así, o faltara alguna, tendrán que repetirse.
- Firmando el consentimiento informado, accede a dejarnos utilizar sus datos obtenidos con estas pruebas y las que se le realicen durante el estudio.
- El mismo día de la intervención quirúrgica programada por su cirujano/a, se le realizará la preparación preoperatoria. Tras la intervención estará 3 días ingresada.
- Para terminar, se le hará un seguimiento al primer mes, 3<sup>o</sup>-6<sup>o</sup>-12<sup>o</sup> y 24 mes. En estas visitas se le hará una evaluación clínica y estudio de imagen con eco-doppler. Además, en la visita del primer mes también se le hará una resonancia magnética.
- Además, durante el proceso, se revisará su historia clínica para comprobar si sufre algún episodio de ictus isquémico o defunción. Todos los datos serán recogidos y analizados.

## 6. ¿MI PARTICIPACIÓN SERÁ CONFIDENCIAL?

La información recogida en este estudio será introducida en una base de datos para su posterior análisis. Los datos de carácter personal e información recogida en el estudio son **TOTALMENTE CONFIDENCIALES** y quedan protegidos de acuerdo con la legislación vigente sobre la protección de datos de carácter personal (Ley Orgánica de Protección de Datos Personales y Garantía de los Derechos Digitales del 3/2018). Los resultados de este estudio se utilizarán para su presentación en congresos médicos o la publicación en revistas científicas.

## 7. ¿CUÁLES SON LOS POSIBLES BENEFICIOS DE PARTICIPAR EN ESTE ESTUDIO?

Su condición de estenosis carotídea debe tratarse de todos modos. Si está en el grupo de endarterectomía clásica, recibirá la misma cirugía que si no participase en el estudio, pero si está en el grupo de endarterectomía por eversión, podría beneficiarse de menos riesgos y complicaciones quirúrgicas.

También es posible que usted no obtenga ningún beneficio directo por participar en el estudio; no obstante, se prevé que la información que se obtenga pueda beneficiar en un futuro a otras pacientes y pueda contribuir a un mejor conocimiento del efecto de las diferentes técnicas en el sexo femenino.

## 8. ¿CUÁLES SON LOS POSIBLES RIESGOS DE PARTICIPAR EN ESTE ESTUDIO?

No se prevén riesgos ni inconvenientes para participar en este estudio.

Los posibles eventos adversos son los mismos que cualquier endarterectomía. Una vez finalizado el estudio, usted recibirá la atención médica necesaria según su condición independientemente de su participación o no en éste.

Las participantes no recibirán una compensación económica por participar en el ensayo clínico, pues sesgaría la selección de los pacientes.

9. ¿PUEDO RETIRARME O CAMBIAR DE OPINIÓN UNA VEZ EMPEZADO EL ESTUDIO?

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

10. ¿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 contactar con la investigadora Sra. Escabias por teléfono 699 25 70 38 o email [luciaescabias@udg.edu](mailto:luciaescabias@udg.edu).

Gracias por leer esto.

Por favor guarde esta hoja de información.

Si está de acuerdo en participar en el estudio, por favor firme el consentimiento informado que se adjunta. Al firmarla, se compromete a cumplir con los procedimientos del estudio que se le ha expuesto.

## 16.2 INFORMED CONSENT FORM OF PARTICIPATION

### HOJA DE CONSENTIMIENTO INFORMADO

Título del estudio: EVERSION CONTRA LA ENDARTERECTOMÍA CONVENCIONAL EN EL SEXO FEMENINO COMO PREVENCIÓN SECUNDARIA DE UN ICTUS CAUSADO POR ESTENOSIS CAROTIDEA: UN ENSAYO CLÍNICO ALEATORIZADO Y CONTROLADO.

Yo (Nombre y apellidos): \_\_\_\_\_

Declaro bajo mi responsabilidad que:

- He leído detenidamente y he entendido toda la hoja de información que se me han entregado. Entiendo que podré conservar una copia.
- He recibido suficiente información sobre el estudio.
- El/la investigador/a 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 mi decisión, mi atención médica y mis derechos legales no se verán afectados.

Por lo tanto, acepto voluntariamente participar en este estudio de investigación y doy mi consentimiento para el acceso y utilización de mis datos siempre en conformidad con la Ley Orgánica de Protección de Datos Personales y garantía de los derechos digitales del 3/2018.

En \_\_\_\_\_, a \_\_\_\_ de \_\_\_\_\_ del 20\_\_\_\_

Firma paciente:

Firma investigador/a:

DNI:

DNI:

## 16.3 INFORMED CONSENT FORM OF INTERVENTION

### DOCUMENTOS DE CONSENTIMIENTO INFORMADO

#### DOCUMENTO DE CONSENTIMIENTO INFORMADO PARA ENDARTERECTOMÍA CAROTÍDEA

Nº HISTORIA .....

Don/Doña ..... de ..... años de edad.  
(Nombre y dos apellidos del paciente)

Con domicilio en ..... y D.N.I. nº .....

Don/Doña ..... de ..... años de edad.  
(Nombre y dos apellidos)

Con domicilio en ..... y D.N.I. nº .....

En calidad de ..... de .....  
(Representante legal, familiar o allegado) (Nombre y dos apellidos del paciente)

#### DECLARO:

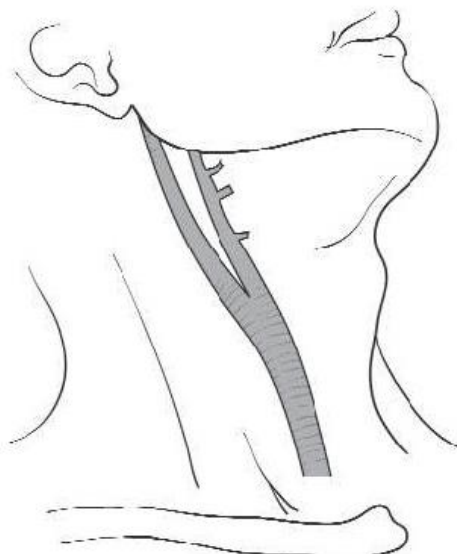
Que el doctor / a .....  
(Nombre y dos apellidos del facultativo que proporciona la información)

1.- Me ha explicado que en mi situación es conveniente realizar una ENDARTERECTOMÍA CAROTÍDEA

2.- Me ha informado que:

- La circulación del cerebro depende sobre todo de las arterias carótidas. Si se estrechan de forma importante (estenosis carotídea) disminuye la cantidad de sangre que llega al cerebro, y pueden producirse síntomas como pérdidas de fuerza, parálisis o dificultad para hablar o comprender. Si se cierra la arteria por completo lo habitual es una "trombosis cerebral", con secuelas importantes y en muchas ocasiones mortal.

- Esta intervención consiste en "limpiar" la arteria por dentro. Se realiza a través de una herida en la zona lateral del cuello. Una vez limpia, puede dejarse de su tamaño inicial o "ampliarla" con un parche de material sintético o con una vena. Si se utiliza la vena se necesita una herida en otra zona para conseguirla.



## DOCUMENTOS DE CONSENTIMIENTO INFORMADO EN ANGIOLOGÍA Y CIRUGÍA VASCULAR

- La anestesia puede ser general o local (regional), dependiendo del caso y la valoración de los anestesiistas. Ellos me explicarán las posibilidades, sus ventajas, sus riesgos y sus complicaciones.
- Es posible que durante o después de la operación necesite una transfusión de sangre o derivados. Me informarán desde el Banco de Sangre, pero es necesario decírselo a mi médico si tengo algún problema al respecto.
- Después de la operación lo normal es que pase las primeras horas en una unidad de vigilancia especial (UVI, Reanimación).

3.- Comprendo que aunque la técnica sea la adecuada y correcta su realización, pueden producirse complicaciones generales como en cualquier otra operación. Pueden ser inesperadas o relacionarse con mi situación general (diabetes, obesidad, hipertensión, cardiopatía, etc.): .....

Pueden producirse complicaciones específicas como:

- Que se produzca un infarto cerebral. ¿Por qué?
  - Para realizar esta intervención es necesario cerrar el paso de sangre al cerebro durante unos minutos (clampaje carotídeo), y aunque se utilizan distintas técnicas para proteger el cerebro, siempre es posible que se produzca un daño cerebral durante la intervención, con síntomas que pueden aparecer después de la operación o en las horas o días siguientes.
  - La zona que se limpia queda habitualmente "rugosa" y se pueden formar trombos en esa superficie que cierren la arteria (trombosis) y que se muevan hacia el cerebro (embolización).
- Que llegue "demasiada sangre" al cerebro (reperfusión). Aparecerá dolor de cabeza, adormecimiento o desorientación.
- Que se produzca una hemorragia o un hematoma en el cuello. Puede ser especialmente grave si dificulta la respiración y obligar a una operación urgente.
- Puede irritarse o lesionarse alguno de los nervios que pasan por el cuello, y aparecer ronquera, afonía, dificultad para mover la lengua o masticar, o acorchamiento del cuello, el labio o el lóbulo de la oreja. Suelen desaparecer, pero a veces se mantienen durante mucho tiempo.

Algunas de estas complicaciones pueden ser graves y necesitar una nueva operación de forma urgente.

También comprendo que a veces pueden aparecer complicaciones a nivel de las heridas (hematomas, líquido acumulado (linforragias, seromas) o infecciones).

4.- Entiendo que durante la operación pueden producirse situaciones o hallazgos que obliguen a modificar la estrategia que inicialmente me han explicado, o que hagan necesarias otras técnicas.

5.- He comprendido que las intervenciones sobre las arterias carótidas se hacen normalmente sólo para evitar que se obstruyan, y NO VA A HABER NINGÚN CAMBIO EN LOS SÍNTOMAS SI YA EXISTEN DEFECTOS NEUROLÓGICOS ESTABLECIDOS.

También comprendo que con el tiempo pueden volver a producirse estrechamientos en la misma arteria (reestenosis) que me produzcan los mismos problemas, y que incluso necesiten una nueva operación.

6.- Me ha informado que como alternativa para el tratamiento de estas lesiones en algunos casos se pueden realizar técnicas endovasculares (con catéteres por dentro de las arterias). En otras ocasiones se puede sustituir el segmento de carótida lesionado (bypass carotídeo).

También es posible NO actuar sobre la carótida y sólo hacer que la sangre esté más fluida con medicamentos (antiagregantes / anticoagulantes).



## DOCUMENTOS DE CONSENTIMIENTO INFORMADO

He comprendido las explicaciones que me ha dado mi médico en un lenguaje claro y sencillo, y he podido aclarar todas las dudas que se me han planteado.

Entiendo que puedo cambiar de opinión y decidir no operarme sin tener que dar ninguna explicación.

Estoy satisfecho con la información recibida y comprendo el tipo de tratamiento y sus riesgos.

Y en tales condiciones

**CONSENTO**

que se me realice un ENDARTERECTOMÍA CAROTÍDEA

En ..... (lugar y fecha).

Fdo.: El/la Médico

Fdo.: El Paciente

Fdo.: El representante legal,  
familiar o allegado

**REVOCACIÓN**

Don/Doña ..... de ..... años de edad.  
(Nombre y dos apellidos del paciente)

Con domicilio en ..... y D.N.I. nº .....

Don/Doña ..... de ..... años de edad.  
(Nombre y dos apellidos)

Con domicilio en ..... y D.N.I. nº .....

En calidad de .....  
(Representante legal, familiar o allegado)

de .....  
(Nombre y dos apellidos del paciente)

Revoco el consentimiento prestado en fecha ....., y no deseo proseguir el tratamiento, que doy con esta fecha por finalizado.

En .....  
(Lugar y fecha).

Fdo.: El/la Médico

Fdo.: El Paciente

Fdo.: El representante legal

## 16.4 PARTICIPANT DATA SHEET

### HOJA DE DATOS DE LA PARTICIPANTE

Número de la participante: \_\_\_\_\_

Nombre (Iniciales): \_\_\_\_\_

Apellidos (Iniciales): \_\_\_\_\_

Presencia de síntomas neurológicos:      Sí       No

En caso afirmativo, la estenosis que produce la clínica es:      Derecha       Izquierda

DATOS DE REFERENCIA:

CARACTERÍSTICAS SOCIODEMOGRÁFICAS:

○ Fecha de nacimiento: \_\_\_/\_\_\_/\_\_\_

CARACTERÍSTICAS CLÍNICAS:

○ Hábito tabáquico:      Fumadora       No fumadora       Exfumadora

○ Índice de masa corporal (IMC):      Peso normal       Sobrepeso       Obesidad

○ Hipertensión:      Sí       No

○ Diabetes Mellitus:      Sí       No

○ Dislipemia:      Sí       No

○ Enfermedad arterial coronaria:      Sí       No

○ Enfermedad arterial periférica:      Sí       No

○ Historia farmacológica (dosis y duración):

Antiagregantes: \_\_\_\_\_

Antihipertensivo: \_\_\_\_\_

Estatinas: \_\_\_\_\_

Agentes hipolipemiantes: \_\_\_\_\_

Antidiabéticos: \_\_\_\_\_

Otros: \_\_\_\_\_

Ninguno

Desconocido



## ESTUDIO VASCULAR:

## ESTUDIO VASCULAR DE LAS ARTERIAS CAROTIDAS:

Arteria Carótida izquierda:  Normal  
 <50% estenosis  
 50-69% estenosis  
 70-99% estenosis  
 Oclusión

Arteria Carótida derecha:  Normal  
 <50% estenosis  
 50-69% estenosis  
 70-99% estenosis  
 Oclusión

Lesiones en otras arterias supraaórticas: Sí  No

¿Cual?: \_\_\_\_\_

ESTUDIO TRANSCRANEAL VASCULAR:  Normal  
 Estenosis asintomática intracraneal  
 Estenosis sintomática intracraneal  
 Oclusión de arteria intracraneal  
 Microangiopatía

## PRUEBAS DE IMAGEN:

RESONANCIA MAGNÉTICA: Estudio cerebral multimodal  Presencia de daño cerebral  
 Ausencia de daño cerebral

## ESTUDIO DE PERFUSIÓN:

Técnica utilizada: AngioRM  AngioTAC

Estenosis de la ACI: Derecha  Izquierda

Grado de estenosis:  Normal  
 <50% estenosis  
 50-69% estenosis  
 70-99% estenosis  
 Oclusión



6º MES	Tensión arterial	1ª medición: ____/____ 2ª medición: ____/____
	Eco-doppler de troncos supraaórticos: Valoración arteria carótida interna.	<input type="checkbox"/> Normal <input type="checkbox"/> Reestenosis: <input type="checkbox"/> <50% <input type="checkbox"/> 50-69% <input type="checkbox"/> >70% <input type="checkbox"/> Pseudoaneurisma
	Resonancia magnética: Estudio cerebral multimodal	<input type="checkbox"/> Presencia de daño cerebral <input type="checkbox"/> Ausencia de daño cerebral
	Ictus isquémico	<input type="checkbox"/> Sí <input type="checkbox"/> No

12º MES	Tensión arterial	1ª medición: ____/____ 2ª medición: ____/____
	Eco-doppler de troncos supraaórticos: Valoración arteria carótida interna.	<input type="checkbox"/> Normal <input type="checkbox"/> Reestenosis: <input type="checkbox"/> <50% <input type="checkbox"/> 50-69% <input type="checkbox"/> >70% <input type="checkbox"/> Pseudoaneurisma
	Resonancia magnética: Estudio cerebral multimodal	<input type="checkbox"/> Presencia de daño cerebral <input type="checkbox"/> Ausencia de daño cerebral
	Ictus isquémico	<input type="checkbox"/> Sí <input type="checkbox"/> No

24º MES	Tensión arterial	1ª medición: ____/____ 2ª medición: ____/____
	Eco-doppler de troncos supraaórticos: Valoración arteria carótida interna.	<input type="checkbox"/> Normal <input type="checkbox"/> Reestenosis: <input type="checkbox"/> <50% <input type="checkbox"/> 50-69% <input type="checkbox"/> >70% <input type="checkbox"/> Pseudoaneurisma
	Resonancia magnética: Estudio cerebral multimodal	<input type="checkbox"/> Presencia de daño cerebral <input type="checkbox"/> Ausencia de daño cerebral
	Ictus isquémico	<input type="checkbox"/> Sí <input type="checkbox"/> No

## 16.6 CHRONOGRAM

	<b>Nov 2018</b>	<b>Feb 2019</b>	<b>May 2019</b>	<b>Jul 2019</b>	<b>Jan 2021</b>	<b>Jan 2023</b>	<b>Apr 2023</b>	<b>May 2023</b>	
<i>STARTING MONTH:</i>									
<i>ENDING MONTH:</i>	<b>Jan 2019</b>	<b>Apr 2019</b>	<b>Jun 2019</b>	<b>Dic 2020</b>	<b>Dic 2022</b>	<b>Mar 2023</b>	<b>Apr 2023</b>	<b>Jul 2023</b>	<i>RESPONSIBLES:</i>
<b>1. Protocol development</b>									Investigators
<b>2. Coordination phase</b>									Investigators, PM, vascular surgeons, nursing staff, anesthetists
<b>3. Vascular surgeons' training</b>									Training team
<b>4. Patients' selection and intervention</b>									Investigators, PM, vascular surgeons, anesthetists
<b>5. Data collection &amp; processing database</b>									Investigators, PM, vascular surgeons, nursing staff
<b>6. Data analysis</b>									Investigators and statistician
<b>7. Interpretation and conclusions</b>									Investigators
<b>8. Dissemination plan</b>									Investigators

