Universitat de Girona
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CONTROL OF CARDIOEMBOLIC STROKE PREVENTION IN PATIENTS WITH PRE-EXISTING EMBOLIC CARDIOPATHY.

Final Research Project of the Medical Degree

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ABBREVIATIONS

AF: Atrial Fibrillation

AMI: Acute myocardial infarction

ASA: Acetylsalicylic Acid

CVA: Cerebrovascular accident

CES: Cardioembolic stroke

INR: International normalized ratio

IS: Ischemic stroke

OAC: Oral anticoagulant

TTR: Percent time in therapeutic INR range

ABSTRACT

TITLE

Control of cardioembolic stroke prevention in patients with pre-existing embolic cardiopathy.

BACKGROUND:

Cardioembolic stroke accounts for about 23% of all ischemic strokes and is strongly associated with a higher mortality rate and worse outcomes, though it is largely avoidable with appropriate prevention measures and strict control of the causative embolic cardiopathies.

Atrial fibrillation is the main cause of cardioembolic stroke, followed by ischemic cardiopathies and heart valve disease (rheumatic and prosthetic valves). Although recent literature thoroughly outlines several well-evidenced preventative treatments, the incidence of stroke is not decreasing. Many studies show that this fact could be associated with poor control and administration of these stroke prevention measures.

This study is designed to determine the proportion of cardioembolic stroke patients with a pre-existing embolic cardiopathy who are not receiving an optimal preventive treatment. Patient's clinical profile, associated risk factors, mortality rate, length of hospital stays and socioeconomically impact are also analyzed in order to provide up-dated data of the importance of this problem. Finally, this study aims to identify the probable deficiencies in primary and secondary prevention in order to determinate the elements that would help to improve the preventive programs.

OBJECTIVE:

To study the adequacy of treatment calculating the proportion of patients with cardioembolic stroke and pre-existing embolic cardiopathies whose preventive treatment was not appropriate, and to identify their clinical profile, the mortality rate and the grade of disability due to stroke, and the healthcare impact.

METHODS:

Medical records of 250 patients admitted to Doctor Josep Trueta University Hospital and Santa Caterina Hospital from Girona between 2010 and 2015 with a discharge diagnosis of cardioembolic stroke and a known history of a cardiac embolic source are reviewed in order to describe stroke patient's profile, to analyze their risk of stroke based in the CHA_2DS_2VASC score and the risk of major bleeding with the HAS-BLED score, and to qualify their stroke preventive treatment employed before having the cardioembolic infarction. According to the indications of the most recently validated guidelines, patients are divided in two groups: 1. Patients with adequate preventive treatment. 2. Patients with non-optimal preventive treatment. If patients were treated with *vitamin K antagonists*, the values of the international normalized ratio (INR) of 6 months prior to stroke are also collected in order to calculate the therapeutic time in range and quantify the level of anticoagulation control. Finally the mortality rate, the disability grade based on Rankin score, the length of stays at the hospital and the economical health-care impact are also determined.

KEYWORDS:

Cardioembolic stroke. Cerebrovascular accident. Embolic cardiopathies. Preventive treatment. Anticoagulation.

INTRODUCTION

BACKGROUND

CEREBROVASCULAR DISEASES OVERVIEW

The term **Stroke**, also named cerebrovascular accident, refers to an interruption of the cerebral blood flow that results in a transient or permanent dysfunction of one or more regions of the brain [1].

The World Health Organization and many Guidelines, uses the definition of stroke as a clinical syndrome, with a presumable or no apparent cause other than vascular origin, characterized by the rapidly development of clinical symptoms and/or neurological signs of focal or global cerebral disturbance lasting more than 24 hours (less than 1h-24h for transient ischemic attack) or leading to surgery or death [2-3].

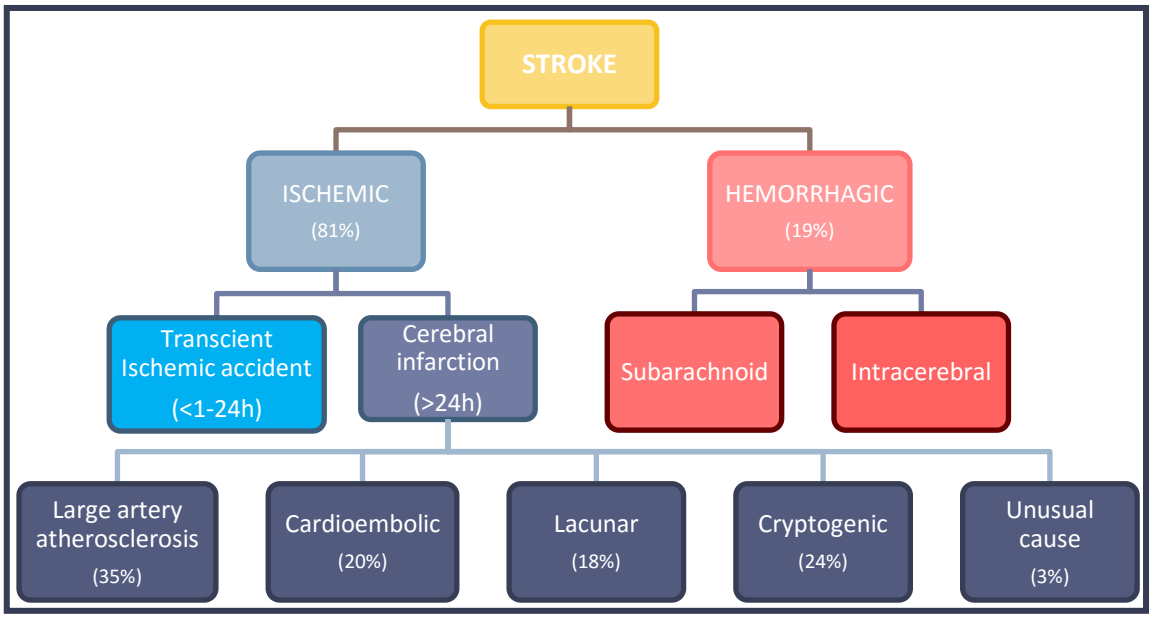
Depending on the nature of lesion, strokes can be classified as **ischemic** (81%) or **hemorrhagic** (19%)[4]. Either subtypes produce neurological deficits for more than 24h or show neuroimaging evidence of recent brain lesion.

Ischemic stroke is produced by a disruption of blood supply given to a brain region, whereas **hemorrhagic stroke** is due to a spontaneous rupture of a cerebral blood vessel or aneurysm that leads to an extravasation of blood into the vascular bed. This last type includes intracerebral hemorrhage (ICH), a collection of blood within the brain parenchyma caused by spontaneous, non-traumatic vascular rupture, and subarachnoid hemorrhage (SAH), defined as bleeding within the subarachnoid space.

There are different etiological and pathogenic subtypes of ischemic stroke based on the TOAST classification [5, 6]. The set of criteria used in this classification allows identifying the most probable cause that leads to vessel occlusion and, indeed, what is the best treatment strategy to perform:

- Large artery atherosclerosis due to embolus or thrombosis (35%)
- **Cardioembolism** (20%)
- Lacunar stroke due to small vessel occlusion (18%)
- Stroke of other unusual causes such as hematological diseases, arterial dissection, systemic diseases, etc. (3%)
- Stroke of undetermined cause or cryptogenic, what includes two or more causes identified, negative evaluation or incomplete evaluation. (24%).

Figure 1: Stroke Subtypes:



Addapted of Classification of CVA depending on its nature [3].

Among the several differences, the risks factors such as atrial fibrillation or hypertension, and the causative mechanisms (including embolism, thrombosis, lipohylainosis and hemodynamic) are very important to be correctly identified in order to choose the adequate preventive therapy and appropriate treatment

It is relevant to know that cerebrovascular disease is, after ischemic heart disease, the second cause of death and a major cause long-term disability with important socioeconomic consequences. According to WHO, stroke represents **9%** of all deaths around the world and consumes about 2-4% of total health-care costs (more than 4% in industrialized countries).

Stroke prevalence, what refers to the burden of patients who survive to CVA, is approximately **500 people per 100.000 populations**[7]. In Spain, as it was analyzed in the NEDICES study, the prevalence in elderly population (65 or older) adjusted to the European population is **4.9%** [8].

In addition, a recent study (the IBERICTUS study), showed that the incident cases of stroke in subjects older than 18 years standardized to the European population is **187 cases per 100.000** inhabitants per year. Either stroke or TIA, the incidence was higher in men than woman and exponentially increases with the age. However, even is thought to be a disease of the elderly, 25% of strokes occurs in patients who are under age 65 [9].

CVA represents the **11'3%** of in-hospital global mortality and **23%** of the deaths are due to cardioembolic strokes, which is the most common cause compared with the other subtypes [10].

CARDIOEMBOLIC STROKE

DEFINITION:

Cardioembolic stroke is defined as medium or large infarction of the brain cortex due to a cerebral artery occlusion secondary to cardiogenic embolism what produces a brain dysfunction and therefore a sudden development of focal or global neurological symptoms in patients with absence of other causes of cerebrovascular accidents [11,12].

EPIDEMIOLOGY:

As it was mentioned before when describing the results of the IBERICTUS study, cardioembolic infarction accounts for an estimated 23% of all ischemic strokes. The incidence of this subtype increases with age, reaching 36% or even the 46%. Moreover, many strokes labeled as cryptogenic, which represent 23-26%, have clinical features and brain imaging findings compatible with embolism of cardiac origin in the absence of clearly identifiable sources [13, 14].

The death rate due to cardioembolic stroke in a month, in a year and in 5 years is approximately 33%, 50%, and 80%, respectively, and the in-hospital mortality rate is around 30%, which is the highest in comparison with atherothrombotic infarction (20%) and lacunar stroke (1%)[15].

In addition, CES is also related with a high risk of embolic recurrence, which triplicate the risk of death, and significant functional limitations at the time of hospital discharge, which may be related to the greater size of the lesion [16, 17].

In this respect, it should be taken into account that cardioembolic stroke not only represents a large proportion of all stroke subtypes, but it is also the main stroke-related cause of neurological dysfunction, disability, dementia and mortality. However, there has been a substantial progress in the knowledge of this disease and nowadays it is largely preventable if efforts at primary prevention are warranted.

PATHOFISIOLOGY: Mechanisms and Potential Cardioembolic Sources

A CES occurs when an emboli from the heart travels to the brain circulation resulting in the occlusion of a brain vessel, a compromise of vascular supply and consequently damage to the brain tissue [18].

The mechanisms that contribute to the formation of cardiac emboli can be divided in four groups [19, 20] .

- Blood stasis and thrombus formation in an enlarged or affected left cardiac chamber. This mechanism is often produced in patients with arrhythmias, including atrial fibrillation, sick-sinus syndrome or sustained atrial flutter, dilated cardiomyopathy, hypokinetic and akinetic ventricular regions, septal defects and atrial and ventricular aneurysms.
- Release of material from an abnormal valve surface, such as rheumatic mitral and aortic valve diseases, prosthetic valves and bacterial endocarditis.

- Tumor fragmentation, superimposed thrombus formation or infection are the mechanisms associated with heart tumors such as atrial myxomas or papillary fibroblastomas.
- Abnormal passage from the venous to the arterial circulation (paradoxical embolism) due to patent foramen oval.
- NOTE: It is important to mention that, atheromathosis of the aortic arch should be evaluated in the context of atherothrombotic and not thromboembolic mechanism [21].

The etiologies associated with risk of systemic thromboembolism and stroke, are called "embolic cardiopathies". However, due to the difficulty of making the correct etiological diagnosis of cardioembolic stroke, the cardiac diseases proposed as the causes of CES are known as "potential cardioembolic sources". Atrial Fibrillation would explain approximately 50% of all cardioembolic strokes, followed by ischemic cardiopathies (25%) and valve heart diseases, including rheumatic and prosthetic valves (20%). The remaining 5% would be attributed to less frequent potential cardiopathies such as myxomas and endocarditis, and to less frequent but with questionable power of embolization sources (patent foramen ovale, mitral valve prolapsed, mitral annulus calcification…) [22].

The risk of initial and recurrent embolism is not the same for all cardioembolic conditions and the preventive therapy vary according to it. The SSS-TOAST classification divides them into major sources or minor sources based on the evidence of their relative propensities for embolism [23–25].

Table 1: Risk of Cardioembolic Sources (Adapted SSS-TOAST classification) [26].

MAJOR CARDIOEMBOLIC SOURCES **(> 2% annual primary risk of infarction)**	- Atrial fibrillation - Sustained atrial flutter - Mechanical and Bioprosthetic valve prostheses - Recent acute myocardial infarction (<4weeks) - Earlier myocardial infarction (>4 weeks) with EF<28% - Left atrial or ventricular thrombus - Atrial myxoma, papillary fibrolastoma or other cardiac tumors - Endocarditis (infectious or marantic) - Dilated cardiomyopathy - Symptomatic congestive heart failure with EF <30% - Sick sinus syndrome - Rheumatic mitral or aortic valve disease
Minor cardioembolic sources **(<2% annual risk of infarction)**	- Patent foramen ovale - Artrial septal aneurysm - Left ventricular aneurysms without thrombus - Spontaneous echo contrast (witout AF or mitral stenosis) - Mitral annulus calcification - *Mitral valve propalsed (it is controverted)*

CLINICAL AND PAHTOLOGICAL DIAGNOSIS:

Clinical data

The classically clinical presentation of stroke is a neurological deficit of more than 24h of duration.

Some clinical findings of CES are similar to those of large-artery atherosclerosis, so it is very difficult to make an accurate diagnosis only based in the clinical presentation. Despite this fact, there are certain signs and symptoms that are more common presented in a CES presentation and may suggest its diagnosis [27]. These clinical features associated to cardioembolic stroke include:

1. Sudden maximum neurological deficit at onset (in less than 5 minutes) (80% CES, 40% lacunar, 46% atherothrombotic)
2. Transient decreased level of consciousness and or seizures at onset.
3. Rapid regression of symptoms (shrinking deficit syndromes) (5-12%)
4. Valsalva maneuver or provoking activities such as coughing, sneezing, bending… at the time of stroke onset.
5. Visual flied abnormalities, neglect and Wernicke's or global aphasia without hemiparesis.
6. Previous or simultaneous cerebral infarctions or TIA in different vascular territories.
7. History or co-ocurrence of systemic embolic
8. Headache and onset during activity are also associated but not specific of CES.

In addition, a clinical study has shown that atrial fibrillation and sudden onset of symptoms were significantly associated with cardioembolic stroke.

Imaging features

Neuroimaging findings that support cardioembolic stroke are:

- Infarction greater than 1.5cm, usually cortical.
- Simultaneous or sequential strokes in different arterial territories: bihemispheric combined anterior and posterior circulation or bilateral or multilevel posterior circulation.
- Carotid and middle cerebral artery distribution.
- Absence of atherosclerotic disease with transient or isolated arterial occlusions on cerebral angiography with evidence of intraluminal filling defects that disappear on subsequent injections in proximal portions of an artery with no atherosclerotic changes.
- Hemorrhagic transformation of an ischemic infarct (71% of CES)
- Early recanalization of an occluded intracranial vessel.

ETIOLOGICAL DIAGNOSIS:

After ruling out significant presence of atheromatous lesions and other possible etiologies, cardiac work-up studies such as, thoracic Rx, initial and serial ECG and 24h-Holter or prolonged cardiac monitoring are necessary to identify potential sources of embolism including myocardial infarction or atrial fibrillation.

If the etiology is unclear, transthoracic echocardiography with or without a following transeophageal echocardiography would be required in order to detect embolic cardiopathies such as heart valve diseases, cardiomyopathies, patent foramen ovale, etc. (see table one)

TREATMENT: Hyperactue and acute phase

The hiperacute treatment of any stroke consists in the admission in stroke units, monitoring of vital signs and application of general measures and recanalization therapies if it is possible.

After 48h of the occurrence of stroke, administration of aspirin reduces de mortality and the recurrences rates. Early anticoagulation is only administrated in certain situations such as suspected ischemic stroke of cardioembolic origin with high risk for reembolization (artificial valves, atrial fibrillation and acute myocardial infarction with wall thrombus).

PREVENTIVE TREATMENT

Primary preventive treatment, which will be further explained it in the next section, consists briefly in the following treatment:

- Anticoagulation is indicated in atrial fibrillation, mural thrombi, prosthetic valves, high risk patients with acute myocardial infarction and marantic endocarditis. Antibiotics are indicated for infectious endocarditis.
- Antiplatelets are recommended in dilated cardiomyopathy, patent foramen ovale, mitral annular calcification and mitral valve prolapsed.
- Cardiac tumors require surgery.

Oral anticoagulation with an international normalized ratio of 2-3 is the secondary prevention treatment in most patients with CES and without contraindication such as gastrointestinal bleeding, falls, poor compliance or uncontrolled epilepsy [28].

PREVENTION OF STROKE

Implementation of stroke prevention strategies is needed to avoid cerebrovascular accidents and recurrences events and to steadily reduce the outcomes and mortality of stroke.

The last Guidelines for the Primary Prevention of Stroke published in Stroke, Journal of the American Heart Association (2014) and Guidelines for the preventive treatment of ischemic stroke and TIA (2011) present evidence-based recommendations for the treatment and control of embolic cardiopathies [28,29]. According to these guidelines the primary preventive therapy of CES that should be employed is the following:

1. **Atrial Fibrillation**: AF predisposes to thrombus formation, especially in the left atrial appendage, due to the blood stagnation caused by the incorrect contraction of the left atrium. This frequent arrhythmia is the cause of approximately 50% of all CES and it increases 3 to 4 times the risk of having an ischemic stroke, being 17 times higher in cases with rheumatic valve heart disease. There are many factors that, together with atrial fibrillation, increase the risk of embolism, and for that reason IS risk stratification systems have been designed for patients with AF, being the **CHA_2DS_2-VASC** score the most recently validated one. This method uses a point-based scoring system to determinate the risk of embolism whereby scores of 0 = low, 1 = intermediate and ≥ 2 = high risk (see the following table for more definition).

Table 2: Risk Stratification to predict thromboembolism in Atrial Fibrillation

RISK FACTOR		SCORE
C	**C**ongestive Heart failure /LV dysfunction	1
H	**H**ypertension	1
A_2	**A**ge ≥ 75	2
D	**D**iabetes mellitus	1
S_2	**S**troke/ TIA /TE	2
V	**V**ascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	**A**ge 65-75	1
Sc	**S**ex **c**ategory (female gender)	1
	Total: 0 = low; 1 = intermediate; ≥ 2 = high risk	

LV = left ventricular; TIA = transcient isquemic accident, TE = thromboembolism.
Adapted table from Lip et al.

The preventive treatment consists in long-term oral anticoagulation therapy with **warfarin (Sintron)** at a target INR of 2-3 for patients with CHA_2DS_2-VASC score of ≥2 and acceptable low risk for hemorrhagic. In patients with nonvalvular AF (AF not associated with rheumatic valve disease) other oral anticoagulants such as **dabigatran**, **apixaban** and **rivaroxaban** are also indicated. In patients with intermediate risk of stroke (CHA_2DS_2-VASC score of 1), preferably **oral anticoagulation** or **aspirin (ASA)** may be indicated. If the stroke risk is low, preferably **no treatment** or **aspirin** is recommended. The combination of **ASA and clopidogrel** may be used in patients with contraindications for oral anticoagulants.

2. **Prosthetic valves:** Mechanical mitral or aortic valve prostheses significantly increase the risk of having a cardioembolic stroke. For patients with bioprosthetic mitral valves, the risk of embolic events without anticoagulation is 2% to 4% per year. The preventive treatment in patients with mechanical valve replacements includes oral anticoagulation with **warfarin/sintron** with an INR of 2-3 or 2'5-3'5 (see the table below). In patients with bioprosthetic aortic or mitral valve replacement, the recommendation is oral anticoagulation during the first 3 months achieving an INR of 2.0 to 3.0, followed by low-dose aspirin.

3. **Mitral stenosis:** Rheumatic mitral valve disease is the source of 9-14% systemic embolism, which 80% are cerebral. **Anticoagulation** is indicated in patients with mitral stenosis and one of the following conditions: atrial fibrillation, a prior embolic event, evidence of a left atrial thrombus and left atrial dimension ≥55 mm by echocardiography.

4. **Prolapsed mitral valve:** It is controverted if mitral valve prolapsed lone is a potential source of cardioembolism. However, guidelines recommend aspirin in patients <65years old with prolapsed mitral valve and anticoagulation with a INR target of 2-3 in >65 years old patients with AF, mitral regurgitation or heart failure.

5. **Dilated Cardiomyopathy:** Approximately 0-30% transthoracical echocardiographies show thrombi in dilated cardiomyopathy and 2-4% embolize. The primary preventive treatment consists in **aspirin** and **prophylactic anticoagulation** if there is a documented left ventricular thrombus or atrial fibrillation.

6. **Acute Myocardial Infarction:** Acute myocardial infarction is frequently associated with a left thrombus formation and because 20-50% are silent, AMI should be excluded in patients with stroke. Approximately 50% of all strokes occur in the first 5 days and 2.5% during the first following 4 weeks. Moreover 8-11% patients will have an ischemic stroke within the next 6 years. At the early onset of AMI, **heparin** should be the first treatment, followed by oral anticoagulation. Preventive treatment for high-risk patients (anterior AMI with thrombus detected) consists in **anticoagulation with vitamin K antagonists (sintron)** aiming an INR of 2.0 to 3.0 during 3-6 months and **aspirin** afterwards. **Long-term anticoagulation** should be considered in patients with decreased left ventricular ejection fraction, asymptomatic left ventricular mural thrombi, anterior apical akinesis or dyskinesis or ventricular aneurysm.

7. **Infective endocarditis:** There is a 25% higher risk of stroke for patients with endocarditis and vegetations. However, the risk of cerebral embolization decreases with effective antibiotic treatment under guidance of blood cultivars results, what is the main preventive treatment. Only surgery to prevent embolism would be needed if specific echocardiographic features are seen is persistent vegetation.

8. **Heart failure:** The annual rate of stroke in patients with congestive heart failure is 2% per year, and the risk of stroke, which is correlated with the severity of left ventricular dysfunction, is 4.1 times higher. **Anticoagulants**, as first option, **or antiplatelet agents** are reasonable for patients with heart failure who do not have AF or a previous thrommboembolic event.

9. **Cardiac tumors:** Arround 35% of heart tumors tend to produce embolus that travel to systemic circulation, 80% of overall to the brain. Surgical intervention is the main treatment of all tumors; however, if there are contraindications, anticoagulation would be indicated.

10. **Patent Foramen Ovale:** The non closed remnant of fetal circulation has been founded in up to 40% of younger patients with cryptogenic stroke. Many studies show that there is a probable association with increased risk of ischemic stroke, especially combined with atrial septal aneurysm and deep venous thrombus. However, due to the controversial studies, there is not primary preventive treatment indicated. Only in case of secondary prevention, anticoagulant therapy followed by aspirin is recommended and in case of recurrence, PFO closure would be indicated in individualized cases.

11. **Atrial septal aneurysms** (with or without PFO): Atrial septal aneurysm (ASA) is a discrete protrusion (>10 mm) of a portion of the atrial septum into either atrial chamber. The prevalence is 2'2% and is present about 3 or 4 times more in stroke patients. About 55-70% of cases is associated with PFO and both mechanisms contribute to produce stroke (In situ thrombus formation and embolism through the PFO to the brain). In addition, the association of ASA and PFO carries a greater risk of stroke than PFO alone. The therapeutic approach is similar to that of patients with PFO alone but transcatheter closure is contraindicated.

12. **Mitral annulus calcification:** It is a chronic degenerative process characterized by calcium and lipid deposition in the fibrous support of the mitral valve. Many studies including the Framingham Study and the Strong Heart study showed that MAC could be an independent risk factor of stroke. Despite this fact, antithrombotic treatments should be only considered as a secondary prevention therapy.

13. **Isolated spontaneous echo constrast:** Spontaneous echocontrast (SEC) is a dynamic smoke-like echodensities due to interactions of blood cells under stagnant blood flow located in a cardiac chamber, usually the left atrium. It is an independent predisposing factor to left atrial thrombus formation and increases the risk of CES up to 3-4 times. It is associated with AF (50%), mitral stenosis, prosthetic valves, severe left ventricular dysfunction. However, indications of preventive treatment are being evaluated.

The Secondary prevention of CES includes oral anticoagulation with INR target of 2-3 and if OAC is contraindicated, aspirin 100-300mg/day would be the recommended treatment. In cases with mitral valve prolapsed, ruling out other possible causes is crucial, and if there are no other indentified, antiplatelet drugs is recommended.

Table 3: Recommendations For Cardioembolic Stroke Prevention.

EMBOLIC CARDIOPATHIES			PRIMARY PREVENTION	SECONDARY PREVENTION
Atrial fibrillation	>65 years old or CHA_2DS_2-VASC score of <1		ASA 300mg/day or Non treatment	OAC target INR: 2-3 ± ASA 300mg/day
	CHA_2DS_2-VASC score = 1		OAC INR: 2-3 or ASA 300mg/day	
	<65 years old, CHA_2DS_2-VASC score of ≥2, or rheumatic valve		OAC INR: 2-3 ASA 300mg/day + clopidogrel	
Prosthetic valves	Mechanic	First 3 months, mitral or multiple, ± FA	OAC INR: 2'5-3'5	
		After 3 months, aortic	OAC INR: 2-3	
	Biological		OAC INR: 2'5 3'5/3months ASA 300mg/day	
Mitral stenosis	+ AF, a prior embolic event, left atrial thrombus or enlarged left atrial		OAC INR: 2-3	
Prolapsed mitral valve	<65 years + TTE sever signs		ASA 100-300mg/day	
	>65 years + FA, mitral regurgitation or heart falliure		OAC INR: 2-3	
Acute Myocardial Infarction	High risk patients:		OAC INR 2-3 6months and ASA 300mg/day after	
	low EF, left ventricular thrombi or aneurysm, akinesis or dyskinesis		OAC INR: 2-3	
Dilated Cardiomyopathy	Non risk factors		ASA 300mg/day	
	+ FA, systemic emboli		OAC INR: 2-3	
Infective endocarditis	Non risk factors		Antibiotic	
	Vegetation + TTE signs		Surgery	
Heart failure			Consider AAS or OAC.	
Tumors	Non risk factors		Surgery	
	Surgery contraindication		OAC INR: 2-3	
Patent foramen ovale/atrial septal aneurysm			ASA 300mg/day	If recurrent stroke: transcatheter closure (not in ASA)
Mitral annulus calcification:			Non preventive treatment evaluated/studied	OAC target INR: 2-3 ± ASA 300mg/day
Isolated spontaneous echo contrast				-

ANTICOAGULATION CONTROL IN STROKE PREVENTION

Vitamin K antagonists including warfarin or acenocoumarol (Sintrom), are the anticoagulant drugs that have been showed successfully results in reducing the risk of stroke and it is the standard treatment for many embolic cardiopathies.

However, this therapy needs constant monitoring and appropriated modification of treatment in order maintain a determinate anticoagulation levels and therefore achieve maximal protection against stroke and minimum bleeding complications [30]. The therapeutic range of anticoagulation is measured via the international normalized ratio (INR) and its values should be between 2.0 to 3.0 for most of embolic cardiopathies. A subtherapeutic treatment (INR <2.0) could lead to a high stroke risk, and an excessive anticoagulation (INR >4.0) could result to higher rates of major bleeding [31].

A way of summarizing the INR control over time is using the time spent with the therapeutic range (TTR), what means the percentage time in which patient INR values are between 2.0 and 3.0. The TTR has been used in many clinical trials and it can be calculated employing different metrics, within the direct/traditional method and the Roosendaal method being the most recommended and used ones (according to the last National Conference of Anticoagulation Therapy, 2007):

- Traditional or Direct Method: This metric calculates the TTR counting up the number of tests within range and divide them by the total number of tests. For example, if the patient has 6 tests with an INR between 2.0 and 3.0 out of 8 visits, then the patient is considered in range 75% of the time.

- Roosendaal method (linear interpolation method): This is a complex method that looks at the amount of time between visits to determinate how long the patient might have been within their therapeutic range. For instance, if a patient has an INR at 2.5 on May 1st, and then an INR at 3.5 on May 31st, we can determinate the length of days in range with a linear interpolation method: since there are 30 days between tests, it is assumed that the patient slowly moved from 2.5 to 3.5 over those 30 days, so around May 15th the patient was probably over 3.0, and therefore was out of range. Consequently, it can be estimated that 15 days were in range, and 15 days were out of range, which means that the patient was within a range 50% of the time.

Using these methods, it is considered that anticoagulation treatment is inefficient when TTR is below 60%.

JUSTIFICATION OF THE STUDY

Cerebrovascular disease is one of the leading causes of mortality, disability and dementia in the world and constitutes an important healthcare and socioeconomic problem.

Cardioembolic stroke is frequent (around 30 cases per 100.000 inhabitants per year will have a CES) and it is associated with higher early and late mortality and greater disability than non-cardioembolic strokes, although it can be potentially avoidable with an appropriate preventive therapy and strict control of the causative embolic cardiopathies [33].

Embolism of cardiac origin accounts around one in four of all ischemic infarctions and **embolic heart disease** increases at least five times the incidence of having **stroke** [34]. Embolic cardiopathies can be known before presenting the cerebral infarction, or can be discovered through the firs-acute ischemic stroke.

However, CES occur most commonly in patients with known cardioembolic sources, with about 50% of all cardioembolic strokes being attributable to these factors (according to the table 2 and 3 presented in the Hanket et al. 2006 study). Approximately half of cardioembolic strokes are related to **atrial fibrillation**, followed by **myocardial infarction**, **valve heart disease, intraventricular thrombus**, and many other embolic heart diseases. All that embolic cardiopathies have evidence-based treatment to reduce the risk of having stroke and for that reason, primary and secondary stroke prevention is well described in recognized guidelines and should be correctly employed in order to avoid stroke.

Nevertheless, many studies showed that some of these preventive measures are not applied or well controlled. For instance, the Gladstone et al. study shows that patients with known atrial fibrillation presenting to the hospital with a first-ever acute ischemic stroke, only 40% were taking OAC before the admission, and 30% were not taking any antithrombotic prophylaxis [35]. In addition, of those taking oral anticoagulation, 75% had a subtherapeutic INR at admission. Another study (Leyden et al. 2009) showed that of 109 cardioembolic strokes, 92 were attributed to AF with 57 of them having a known diagnosed of AF before the event. Of these, 11 were subtherapeutically anticoagulated and 16 were not anticoagulated even not having any contraindication to warfarin [36].

According to the data of the mentioned studies and many others, these results would mean that approximately 46 to 63% of patients with cardioembolic stroke and a known embolic cardiopathy (atrial fibrillation) can receive a better control and treatment in order to prevent these cerebrovascular events [37, 38].

Despite these facts, these studies have some limitations such as the low sample and low precision. In addition, most of them only use Atrial Fibrillation as the only possible source of stroke and the indications for the preventive treatment are based in non-updated guidelines. So, a study with a higher sample and more precision, taking into account all potential embolic cardiopathies that may cause stroke should and using the recommendations of the most up-dated guidelines (from 2014) is needed to be performed.

Moreover, many studies used the $CHADS_2$ score to estimate the risk of stroke in patients with atrial fibrillation, which has been superseded by the CHA_2DS_2-VASC score on the 2010, and included in the 2012 European Society of Cardiology Guidelines for the management of atrial fibrillation. So, clinical characteristics and their risk of embolization calculated with the new score (CHA_2DS_2 -VASC) should also be studied in order to determinate other factors probably associated with a not adequate preventive treatment [36]. The HAS-BLED score is another tool that should be used to assess the risk of major bleeding in patients with AF, which is also calculated in our study to identify anticoagulant contraindications [39].

The CALIFA Study (2015), a prospective study, determined that almost half patients with Atrial Fibrillation and a high risk of thromboembolic events were not receiving an adequate anticoagulant treatment [40]. However, reviewing this study, it is not possible to know the number of non-optimal anticoagulated patients whose embolic cardiopathy was other than atrial fibrillation. In addition, it is not clear the proportion of patients who suffer a preventable outcome, such as cardioembolic stroke, due to the uncontrolled anticoagulation. So, knowing that cardioembolic stroke is one of the worst outcomes of non-treated atrial fibrillation and that other cardiopathies should also be adequately treated, it would be relevant to know the current proportion of patients with cardioembolic stroke whose preventive treatment is not optimal. Morover, there are no recently published articles of studies performed in Girona, or even in Spain, presenting this kind of information, which would be important to consider in order to improve and achieve correct stroke prevention.

For all these reasons, is fundamental to undertake a study with the purpose of describing the proportion and the clinical characteristics of patients with deficiencies in primary and secondary cardioembolic stroke prevention in our area, as well as to identify and quantify the outcomes and the socioeconomic impacts associated with cardioembolic stroke. This information would be is essential to provide specific results to educate both professionals and patients of the importance of a correct prevention therapy and to develop a proper and effective preventive program.

Box 1: WHAT THIS STUDY WOULD ANSWER?
• It is known that there is a high association between a non appropriate control of stroke prevention and the risk of suffering a stroke, but how big is this problem in our area? • How many patients have a cardioembolic stroke and did not receive a good control of preventive treatment even having an history of a cardioembolic source? • What are the profile and the risk of embolism of these? • What are the mortality and the disability of all this patients? • What are the length of stays and the cost of hospitalization of these patients? • What solutions can we provide and what are the elements to improve the preventive measures?
• How many patients have a good control of stroke prevention and still suffer it? • What is the profile of this patients and their risk of emboli? • What are the differences between both groups?

HYPOTHESES

There is an elevated and important number of patients who suffer cardioembolic strokes and have inadequacies in the control and care of their high risk embolic cardiopathies.

Specifically for those patients receiving vitamin K antagonist such as Acenocoumarol or Warfarin as a preventive treatment, the INR levels are not in the therapeutic range for more than half of time.

OBJECTIVES

MAIN OBJECTIVE

To describe the adequacy of treatment and the level of control in patients with cardioembolic stroke and a previously diagnosed embolic condition whose preventive treatment for the cerebrovascular event was not optimized.

SECONDARY OBJECTIVE

- To describe the clinical profile and the risk of embolism (based in CHA_2DS_2VASC) in patients with a cerebrovascular accident and a pre-existing embolic condition both with an optimized and non-optimized preventive treatment.
- To ascertain the mortality secondary attributable to the cardioembolic stroke.
- To assess the degree of disability/dependence due to the CES measured with the modified RANKIN scale.
- To estimate the length of hospital stays and inpatient cost for cardioembolic cerebrovascular events.
- To compare the characteristics of patients with an adequate preventive treatment and with a non-optimal preventive treatment.
- To compare the characteristics of patients with a poor, moderate and good control of the anticoagulation treatment.

METHODOLOGY

STUDY DESIGN

Observational and descriptive cross-sectional study with a retrospectively collected patient data to determinate the adequacy and the level of control in cardioembolic stroke prevention.

STUDY SUBJECTS

The last 250 patients with a discharge diagnosis of cardioembolic stroke with a prior known history of a cardioembolic condition admitted in the Doctor Josep Trueta University Hospital and Santa Caterina Hospital from Girona between 2010 and 2015.

INCLUSION CRITERIA

- Patients admitted at the hospital in last 5 years with the diagnosis of cardioembolic stroke.

  The diagnosis of cardioembolic stroke is based on the identification of a non-lacunar cerebral infarction secondary to emboli from the heart in a patient with a potential embolic cardiopathy and with the absence of other potential source of CVA, who present a sudden neurological deficit lasting more than 24h.

  The SSS-TOAST criteria is used to diagnose cardioembolic infraction, being all the essential criteria the ones needed to meet in order to confirm the diagnosis:

  Criteria for Cardioembolic Ischemic Stroke:

  Essential Criteria:

  - ✓ The presence of cardiogenic embolism.
  - ✓ The presence of significant cerebrovascular atheromatous lesions and other possible etiologies must be ruled out.
  - ✓ In the case of low-risk heart disease (see the list of cardioembolic sources), and having ruled out other causes of stroke, the condition will be classified as “possible” cardioembolic stroke.

- Patients with a known history of an embolic cardiopathy, including atrial fibrillation, prosthetic mechanical valve, acute MI 3 months prior CES, ischemic and nonischemic cardiomyopathy, valvular heart disease, infective endocarditis, cardiac tumors, patent foramen ovale and atrial septal aneurysms.

- Patients treated with vitamin K antagonists (acenocoumarol) whose INR values of the last 6 months before the stroke are available.

EXCLUSION CRITERIA

- Patients admitted with a stroke from any other origin.
- Patients with non embolic condition known before the stroke.
- Patients treated with acenocoumarol whose INR values are not available.
- Patients without medical records in SAP program or without required data for the study.

SAMPLE AND SAMPLING

A consecutive non-probabilistic sampling method is used.

The sample is recruited by identifying the last 250 patients admitted to our hospital with a diagnosis of cardioembolic stroke meeting the inclusion/exclusions criteria.

To have an idea of how the sample size was calculated and what is the power that it gives to our study, the following explanation may be useful:

There are around 550 stroke-related admissions in our hospital each year, within the 20-30% being CES, which is approximately 140 patients with CES each year. Around 70 patients each year out of 140 are expected to have a known embolic cardiopathy diagnosed before the stroke. So approximately a sample of 50 patients per year is expected to match the inclusion and exclusion criteria, what means 250 patients with CES and a pre-existing embolic cardiopathy admitted between 2010 and 2015.

If we use total sample of 250 patients, accepting an alfa-risk of 0'05 (95% of IC) and expecting a prevalence around 46% of patients with non adequate preventive therapy (according to the Gallagher et al. study) the precision of the our study would be 0'02.

STUDY VARIABLES

In this study, the main variables that answer the primary objective are the following:

- **Adequacy to preventive treatment**: This is a dichotomous categorical variable. The patients will be categorized as either *properly treated* or *non-optimal treated* depending on their indication for stroke preventive treatment according to the recommendations of the most up-dated guidelines (Guidelines by American Heart Association 2014 and Sociedad Española de Neurología 2011), which are summarized in the introduction of this paper.

- **Level of anticoagulation control**: This is a categorical variable. Patients treated with acenocoumarol are categorized in poorly controlled, moderately controlled and good controlled according to the anticoagulation control, which is assessed by measuring the percent time in therapeutic INR range (TTR).

Variables also important to collect and calculate in order to achieve the purposed objectives are the following:

- **Risk of stroke based in CHA_2DS_2VASC score**: This is a discrete numeric variable and will be expressed in points. The embolic risk is calculated by adding points for each risk factor depending on the patient's clinical aspects: Congestive heart failure (1 point), high blood pressure (1 point), diabetes mellitus (1 point), age > 75 years (2 points), history of cardiovascular disease or systemic embolism (2 points), vascular disease including prior AMI, peripheral artery disease and complex aortic plaque (1 point), female, age 65-75 (1 point) female (1 point). Low risk = 0; intermediate risk = 1, high risk ≥ 2. (This score is summarized in the introduction of the paper).

- **Risk of bleeding based in HASBLED score**: This is a discrete numeric variable and allows calculating the bleeding risk. The method is a scoring-based system similar to the previous one and measured in points: Hypertension (systolic blood pressure > 160mm Hg) (1 point), abnormal renal function (1 point), abnormal liver function (1 point), history of stroke (1 point), bleeding tendency/predisposition (1 point), labile INRs if on sintron (1 point), age > 65 (1 point), drugs (1 point), alcohol (1 point). Low bleeding risk = 0, moderate = 1-2, high ≥3.

- **INR values from 6 months previous to CVA in patients with Acenocoumarol**: the international normalized ratio (INR) provides a standardized measure of the VKA anticoagulant effect, which should be kept within a target of 2.0-3.0 to control the intensity of anticoagulation. It is a numeric continuous variable.

- **Therapeutic Time in range (TTR) calculated by direct method**: Is the proportion of the INR values during 6 months. Poor INR control is considered when percent time in therapeutic range is <60%. It is a continuous numeric variable expressed in percentage.

- **TTR calculated by the Roosendaal method**: incorporating the INR measurements of the 6 months prior to CES, INR specific person-time is calculated in %. Good control is considered if ≥70 % of the time INR is between 2 and 3, moderate control if it is 65-70%, and poor control if it is <65%. It is a continuous numeric variable expressed in percentage.

- **Embolic cardiopathies:** these are ordinal categorical variables and patients will be categorized depending on their kind of cardioembolic pathology. This data is useful in order to determine the treatment indications.
    - Atrial fibrillation
    - Cardiac valve disease (mitral or/and aortic stenosis, prolapsed mitral valve, mitral or/and aortic insufficiency, mitral calcification annulus).
    - Heart valve replacement (mechanic or biological mitral or/and aortic prosthetic valve)
    - Other Cardiac surgery
    - Dilated cardiomyopathy.
    - Congestive heart failure
    - Previous ischemic cardiopathy (AMI)
    - Septal or chamber heart defects (patent foramen oval, aneurisms…)
    - Isolated spontaneous contrast
    - Cardiac tumors
    - Infective endoarditis.

Variables considered as outcomes of suffering a cardioembolic event are the following:

- **Length of hospital stay**: number of days that patients spend in hospital due to CES. It is a discrete numeric variable.

- **Cost of hospitalization**: number of stays x price per bed in Euros. It is a continuous numeric variable.

- **Mortality**: It is a dichotomous categorical variable defined as: Yes/No.

- **Clinical evolution during admission by using the modified Rankin Scale (mRS):** The scale runs from 0-6 running from perfect health without symptoms to death (no symptoms = 0, no significant disability = 1, Slight disability = 2, Moderate disability = 3, moderately severe disability = 4, Severe disability = 5, dead = 6). It is a dichotomous categorical variable and is defined as: poor prognosis if there is a punctuation of >2 and good prognosis if there is a punctuation of ≤2 .

Other variables that are also important to collect (including covariates and confounding variables) are the following:

- **Sociodemographic variables**:
  - **Sex**: this is a dichotomous categorical variable and patients will be categorized either *male* or *female*.
  - **Age**: this is a continuous numeric variable and will be expressed in *year.*
  - **Provenance**: this is a nominal categorical variable and patients will be categorized by the *country of born.*

- **Medical and Surgery History and Personal habits:** these are dichotomous variables and will be expressed as *yes* or *not* depending if patients presented or not presented the following pathologies or procedures:
  - Diabetes Mellitus
  - High blood pressure
  - Percutaneous revascularization
  - Peacemaker or automated implantable cardioverter-desfibrillator
  - Previous stroke or systemic embolism
  - Peripheral vascular disease
  - Chronic obstructive pulmonary disease
  - Liver disease
  - Kidney disease
  - Smoking
  - Drug use
  - Alcohol habit

- **Treatment variables:** these are ordinal categorical variables and the following medicines used by the patients prior to stroke are collected.
  - Antiplatelet and/or anticoagulation therapy employed before the stroke: aspirin, acenocoumarol or warfarin, new anticoagulants.
  - Other treatments such as: beta-blockers, diltiazem, verapamil, digoxin, statins, antidiabetics.

- **Possible anticoagulation contraindications:** categorical variables
  - Repeated falls or unstable gait
  - Haemostatic disorders or uncorrected major bleeding disorders (thrombocytopenia, hemophilia, liver failure, renal failure)
  - Potential bleeding lesions (active peptic ulcer)
  - Uncooperative/unreliable patient (history of any mental disorder)

PROCEDURES

In this study, clinical histories and medical records of 250 patients with a discharge diagnosis for cardioembolic stroke admitted in the Doctor Josep Trueta University Hospital and Santa Caterina Hospital in Girona between 2010 and 2015 are reviewed and interpreted in order to record clinical and laboratory data onto a purpose-built database.

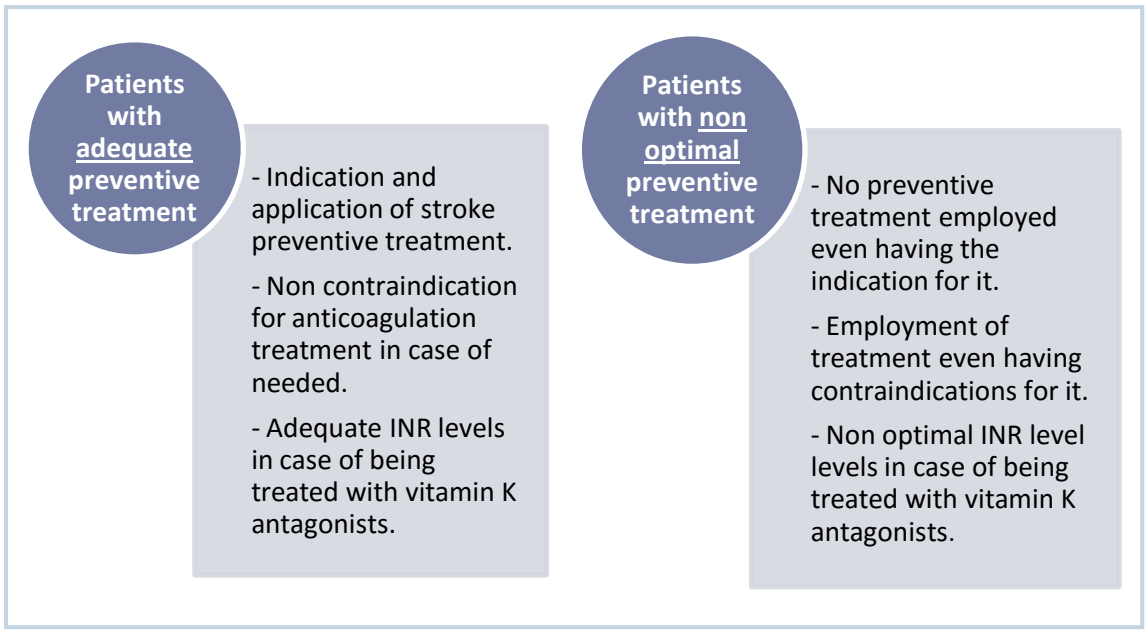
Only patients that meet inclusion/exclusions criteria participate in this study. The number of the excluded patients and the reason for its exclusion is also detailed.

The study is approved by the Ethic committee of Santa Caterina Hospital and Doctor Josep Trueta Universitary Hospital of Girona, and all memberships of research team signed the statement attesting to having read and approved the final protocol.

After having filled up the database with the required patient's information, a control of quality is performed, and afterwards the statistical analysis.

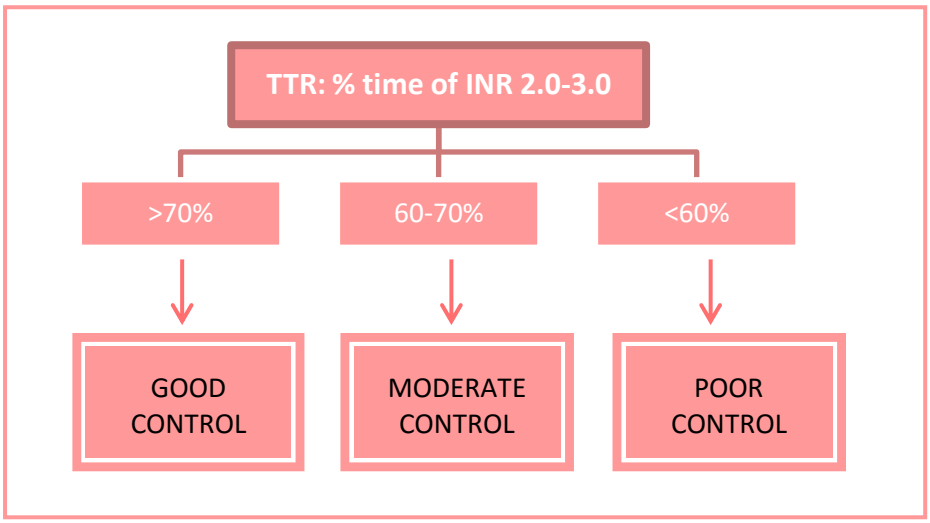
Patients included will be classified in 2 groups: 1) patients with a correct stroke preventive treatment and 2) patients with a non optimal preventive treatment. This classification is based according to stroke prevention therapy indications for each embolic cardiopathy described in the last American (2014) and Spanish (2011) up-date guidelines, which are summed up in the introduction of this paper. Also for that reason, the CHA_2DS_2-VASC and HAS-BLED score of every patient is calculated, which provide information to determine the indication and contraindications for atrial fibrillation anticoagulation treatment.

Figure 2: Classification of patients based on the adequacy of treatment:



In addition, patients receiving vitamin K antagonists (acenocoumarol) prior to the CES, are divided in three groups according to the level of TTR control, calculated by the direct and Rosendaal method using the INR measurements of the 6 months prior to stroke (metrics explained in the introduction of this protocol). It is considered a poor control of anticoagulation therapy if TTR is lower than 60%, a moderate control if the TTR is between 60 and 70% and a good anticoagulation control if the TTR is higher than 70%.

Figure 3: Classification of patients based on the level of anticoagulation control:



Both stratifications allow characterization of patients subsets associated with the different control levels.

Once having these groups, clinical characteristics of each one is described in order to identify the possible elements to improve the preventive treatment.

Finally, mortality rate after suffering stroke, level of disability and dependence after stroke calculated with the modified Rankin scale, length of stays in the hospital and its hospitalization costs is also determined.

STATISTICAL ANALYSIS

The statistical analysis is performed using the free R software (version 3.2.0), all tests will be considered statistically significant at a *p* value ≤0.05, and the methods that will be employed are following summarized:

1. All the patients meeting the inclusion and exclusion criteria will be include in the statistical analysis, and the reason for those who will not participate in the study will be specified.

2. Univariant analysis: The results obtained for categorical and quantitative variables will be described using standard descriptive statistics:
    a. Categorical variables: the absolute and relative frequency distribution will be presented and expressed as proportions.
    b. Quantitative variables: Measures of central tendency including the mean (±SD) in case of normal distribution, the median (quartiles) in case of non-normal distribution, the minimum and the maximum, and measures of statistical dispersion such as the standard deviation will be used in order to express quantitative variables. For all the quantitative variables, the confidence interval stated at the 95% will be expressed.

3. Bivariate analysis:
    a. The characteristics of patients with an adequate and non-optimal preventive treatment will be compared using the Chi Square test or Fisher's exact test for categorical variables, as well as for the contingence analysis tables and for the proportion comparison and/or frequencies distribution.
    b. To compare the quantitative variables of the groups, the *t* test will be used for the variables with normal distribution and the Mann-Whitney test for the variables with a no-normal distribution.
    c. Finally, to compare the groups according to the anticoagulation treatment (poor, moderate and good) with continuous variables the ANOVA/Kruskal-Wallis tests will be used.

4. Multivariate analysis:
    a. A logistic regression analysis will be used to analyze the association between mortality and grade of disability with all the following variables: age, sex, provenance, medical and surgery history and personal habits, treatment, anticoagulation contraindications, CHA_2DS_2VASC risk score of stroke and HASBLED risk score of bleeding.
    b. A generalized linear model will be used to analyze the association between length of hospital stays and the hospitalization costs with the mentioned confounding variables.

ETTHICAL ASPECTS

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

In addition, the processing of personal data required in this study, its communication, the personal data cession of all the patients and the confidentiality is in compliance with Spanish Law 15/1999 of December 13 on the Protection of Personal Data (LOPD) and with the Royal Decree 1720/2007 of December 21 of the Development of the Organic Law on Data Protection.

Patient data, including clinical history information, names and surnames, remain anonymous when introducing and processing this information into a database, which will also be handled according to the mentioned Law and exclusively used for the development of the study.

Moreover, in order to guarantee the confidentiality of the survey data, the access will be only restricted to the research team, the Ethical and Clinical Investigation Committee, the pertinent health authorities and those responsible for data analysis. The content of the database and the documents generated during the study will be protected from not permitted uses of alien persons, and therefore, considered strictly confidential and will not be disclosed to third parties except those already specified. For that reason, membership of the research team, the hospital and the collaborators participating in the study, must sign a statement attesting to having read and approved the final protocol, and agree with the national and international ethical aspects with the investigation (see annex).

Taking into account that this study has a retrospective design, there are no interventions (either diagnostic or therapeutic) applied to patients, so this study doesn't represent any risk for the participants.

Finally, the study is presented, evaluated and approved by the Ethical and Clinical Investigation Committee of the Santa Caterina Hospital and the Doctor Josep Trueta University Hospital.

STUDY LIMITATIONS

- Due to the fact that the patient data is retrospectively collected, some medical missing information is not available and cannot be collected. In addition, the tests and the established diagnoses of the included patients cannot be controlled. However, medical records are considered the best reliable source to obtain detailed data of determinate patients. Finally, because the information from medical records is introduced into a database, some data may not be adequately collected. For that reason, a control of quality before closing the database will be performed.

- Inter-observer variability: the INR values already recorded were measured by different nurses at different times.

- The design of the study also leads to a difficult control of possible confounding variables that could modify the prescription or not for the preventive treatment. In order to avoid this problem, all the data that was considered important to make a decision for employing either a treatment or another (such as the risk of embolism calculated with the CHADSVASC score, the risk of bleeding calculated with the HAS-BLED score, or other possible contraindications for anticoagulation) is collected.

- Another limitation is the non-multicenter design. However due to the fact that the sample takes into account only the patients admitted in a hospital center, this study will be performed, afterwards, as a multicenter study, with a national collaboration.

SCHEDULE, EXECUTION PLAN AND CRONOGRAM

Stage 1: Project Design

In the beginning of April 2015 the first meeting of the research team was performed in order to decide the main topic of the research study and to elaborate a working plan.

After one month of reading articles and reviewing some literature, the research team met again many times with the proposal of designing a protocol which would be presented to the Ethical and Clinical Investigation Committee of Santa Caterina Hospital (ECIC) for its evaluation.

On September 2015, ECIC approve the Study Research Protocol.

Stage 2: Data management

After ECIC approbation, the research team built the database that would be filled with the collected information from the medical records of the selected patients.

During September and October 2015, medical records of the patients with the discharge diagnosis of Cardioembolic Stroke admitted in the Doctor Josep Trueta University Hospital between 2010 and 2015 were reviewed in order to make the selection of the suitable patients for the study according to the inclusion and exclusions criteria. The list of patients diagnosed with a cardioembolic stroke was obtained from a previous database elaborated by the Neurology Service. In addition, while doing the patient selection, the needed information was also collected and introduced in the database.

Memberships of the research team worked together and had frequent meetings during these period in order to monitor the process, perform a correctly data collection and discuss the doubtful cases and possible problems.

Stage 3: Statistical analysis

A qualified person in statistics and the research team processed the data and analyzed the information. The preliminary results were obtained in November.

Stage 4: Results interpretation

Memberships of the team interpreted and discuss the obtained results and write the final conclusions of the study.

Stage 5: Presentation and publication of the results

The article showing the results and the final conclusions will be written during December 2015.

The results will be presented in national conferences and congresses and if it is possible to others. Publishing the article in a cardiology journal will also be attempted.

CRONOGRAM

PHASES and TASKS		April 2015	May 2015	June 2015	July 2015	August 2015	September 2015	October 2015	November 2015	From December 2015
Stage 1: Project design	First research team meeting: Topic decision and working plan									
	Bibliography research and literature review									
	Protocol design of the Study Research									
	Evaluation and approbation of the Study Research Protocol by Ethical and Clinical Investigation Committee of Santa Caterina Hospital									
Stage 2: Data management	Data base elaboration									
	Revision of medical records of patients with cardioembolic stroke and selection of patients suitable for the study according to the exclusion/inclusion criteria									
	Introducing the collected data of patients to the data base.									
	Control and quality of data collection.									
	Closing database.									
	Research team meetings									
Stage 3: Statistical analysis										
Stage 4: Interpretation of the results										
Stage 5: Presentation and publication of the results and scientific diffusion										

BUDGET

The budget is divided in four sections:

STAFF WORKING COSTS:

There is no cost for the staff working, because the memberships of the research team do all the literature revision and bibliography research, as well as searching in the computer database program of the hospital the last 250 patients with a discharge diagnosis of a cardioembolic stroke.

Research team also reviews all the medical records of the participants and identifies those patients who meet the inclusion and exclusion criteria required and specified in the protocol. In addition, the purpose database, collecting only the needed patient's information from the medical records and introducing it into the built database, is also performed by the memberships. All this process is done accurately and respecting the principles of confidentiality of patients.

STATISTICAL ANALYSIS COSTS:

Once having completed the database, a control of quality is performed in order to make sure that all the data is correctly collected. After closing the database, a Statistical expert is hired for the data analysis. This service needs extra cost, due to the fact that the research team doesn't have a qualified statistician in the team.

MATERIAL EXPENSES:

Articles and literature material for the bibliography research, as well as printing and paper packs, are the only material expenses that will be required.

No extra money is needed for this section.

RESULTS PRESENTATION AND SCIENTIFIC DIFUSSION:

Results are interpreted by the research team, as well as writing the conclusions.

The results of the study are presented in a National congress and in an International congress, what includes the inscription, the travelling, the accommodation and the diets for the memberships of the research team that will attend.

ARTICLE PUBLICATION

An article presenting the obtained results is written and it is sent and official published in the Revista de la Sociedad Española de Cardiologia. This process also requires publication expenses.

REQUESTED BUDGET

Study Budget	Quantity	Cost	Subtotal
Statistical analysis costs:			
- Qualified statistician……	90h	50€/h	4.500€
			Subtotal: 4.500€
Material expenses:			
- Articles and literature material……	5units	30€	150€
- Printing and paper packs……..	40units	3€	120€
			Subtotal: 270€
Presentation, travel and subsistence costs:			
- National conference attendance: Cardiovascular Diseases Congress by Sociedad Española de Cardiologia 2016:			
○ Inscription……	2 people	311€	622€
○ Travel costs……..	2 people	150€	300€
○ Accommodation and diets……	2 people	350€	700€
- International conference attendance: European Society of Cardiology Congress 2016:			
○ Inscription……..	2 people	310€	620€
○ Travel costs……..	2 people	200€	400€
○ Accommodation and diets……	2 people	350€	700€
			Subtotal: 3.342€
Publication costs:			
- Publication costs of the results in Revista de la Sociedad Española de Cardiología:			
○ Revising, editting, formatting, layout, graphic design, preparation of digital metadata……..	1 unit	1.000€	1.000€
			Subtotal: 1.000€
			TOTAL: 9.112€

EXPERIENCE OF THE RESEARCH TEAM

The research team includes multidisciplinary experts such as cardiologists, general practitioners and medical students, and it has a notable capacity to develop this scientific study.

This multidisciplinary group has more than 20 years of investigation experience in the cardiovascular diseases field including studies about hypertensive heart diseases, atrial fibrillation, stroke and coronary artery disease such as angina and myocardial infarction.

Nowadays, not only this study is being performed, but also *The ATOM* study, which is a metaregression of published clinical trials that evaluate the blood pressure-lowering effects of the antihypertensive drugs and combinations; the *Família Experta* study, whose main objective is to scientifically demonstrate that with a better health knowledge and a correctly employment of the guidelines by the carergivers could reduce the number of hospital readmissions and improve that the quality life of patients with cardiac failure and chronic obstructive pulmonary disease; and *the TRECE* study, which is a study to describe the treatment in patients with coronary heart disease.

In addition, the research team also collaborated in international studies such as *the Beautiful* study, a randomized trial designed to evaluate the effects of Ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction; and *the EUROPA* study, a multicentre trial which evaluated the efficacy of Perindopril in reduction of cardiovascular events among patients with stable coronary artery disease.

Finally, it is relevant to mention that the leadership of the research team, Dr. Marco Paz Bermejo, constantly attends to congresses and meetings of the cardiology area, and gives conferences and speeches in many centers. For instance, Dr. Paz has been participating as a speaker in the last National Cardiology Congress of Spain, performed in Bilbao the October, 2015.

IMPACT OF THE PROJECT ON THE NATIONAL HEALTH SYSTEM

Cardioembolic stroke is a disease with a high clinical impact although it is largely preventable with an adequate preventive treatment.

With this project, relevant and important information about the currently situation of stroke preventive measures is provided in order to identify the elements that should be modified and improved to achieve better cardioembolic stroke prevention.

Moreover, the study contributes to describe the clinical profile of those patients who suffer a cardioembolic stroke even having a known history of a cardioembolic source, which will help to generally identify the most vulnerable patients and the ones that should be strongly controlled.

In addition, anticoagulation therapy is also evaluated to determine if with the existing management patients are adequately anticoagulated or if more advances and efforts in the Cardiovascular and Stroke Research should be performed. Raising professional awareness of the importance of a proper control of anticoagulation to prevent cardioembolic stroke is also a potential benefit that this study provides.

Finally, the socioeconomical impact that cardioembolic stroke represents, is also provided expressing the mortality, the stroke outcomes and the length of stays and hospitalization cost in order to present reliable data of the importance of this problem.

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