Universitat de Girona
Facultat de Medicina

A COMPARATIVE STUDY ON THE EFFICACY OF THE COX-MAZE IV PROCEDURE VERSUS PULMONARY VEIN ABLATION FOR ATRIAL FIBRILLATION IN CONCOMITANTLY CARDIAC SURGERY

A multicenter, randomized and controlled clinical trial

FINAL DEGREE PROJECT

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This project would have not been possible without all people who have been helping me throughout this time.

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1. ABSTRACT

BACKGROUND:

Atrial fibrillation is the most prevalent arrhythmia which has consequences that have an impact on the morbidity and mortality of the elderly people. The worst associated prognosis is the generation of strokes and other thromboembolic events.

For the management of this pathology there are several options such as pharmacology therapy, ablation, cardioversion or surgery. The main limitation is the ineffectiveness of these procedures. However, surgery is the one that has seen less recurrence of fibrillation.

Thus, a technique called Cox-Maze IV has appeared, which is like an ablation of pulmonary veins but more complex and with more ablative lines, and therefore, with a greater capacity of success.

OBJECTIVE:

The main objective of this study is to evaluate whether is it more effective the Cox-Maze IV procedure in order to reduce the atrial fibrillation recurrence at 1 year compared with an isolated pulmonary vein ablation in concomitant surgeries with patients who, apart from this arrhythmia, suffer from valve disease or myocardial ischemia.

Other secondary objectives are the investigation of the same outcome regardless the type of atrial fibrillation, including paroxysmal, persistent, long-standing persistent and permanent, and assess if the effectiveness could last both in a short time (6 months) and in a long time (5 years). Finally, the last aim is evaluating if exist a reduction of stroke risk associated, along with mortality.

METHODS:

This protocol is designed as a multicenter, longitudinal, prospective, single blinded, randomized and controlled clinical trial. The study will be carried out in Hospital Universitari Dr. Josep Trueta, Hospital Clínic i Provincial de Barcelona and Hospital General Universitario Gregorio Marañón.

Patients will be randomly assigned into 2 groups with a ratio 1:1. Both groups will undergo cardiac surgery with the difference of the intervention for AF: the control group will take an isolated pulmonary vein ablation and, the group experimental will be undergoing a Cox-Maze IV. The recruitment of patients will last 12 months with a subsequent follow-up of 5 years.

KEYWORDS:

Atrial Fibrillation, arrhythmia, Cox-Maze IV, Pulmonary Vein Ablation

2. ABBREVIATIONS

ACC American College of Cardiology

AF Atrial Fibrillation

AHA American Heart Association

AVB Atrioventricular Block

AVN Atrioventricular node

BSE British Society of Echocardiography

CEC Cardiac Extracorporal Circulation

CEIC Comitè Ètic d'Investigació Clínica

CHA_2DS_2-VASc Congestive heart failure; Hypertension; Age>75; Diabetes mellitus, Stroke, vascular disease, Age 65-74, Sex category female.

CI Confidence Interval

COPD Chronic Obstructive Pulmonary Disease

DALYs Disability Adjusted Life Years

DM Diabetes Mellitus

EACTS European Association for Cardio-Thoracic Surgery

ECG Electrocardiogram

EHRA European Heart Rhythm Association

ESC European Society of Cardiology

HAS-BLEED Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly.

HRS Heart Rhythm Society

HTA Hypertension

HUJT Hospital Universitari Dr. Josep Trueta

LAA Left Atrial Appendage

LV Left Ventricular

LVEF Left Ventricular Ejection Fraction

MRI Magnetic Resonance Imaging

NOAC Non-vitamin K Antagonist Oral Anticoagulant

OAC Oral Anticoagulant

OR Odds Ratio

PV Pulmonary Veins

PVI Pulmonary Vein Isolation

QoL Quality of Life

RF Radiofrequency

SAN Sinoatrial node

SPSS Statistical Package for Social Sciences software

TE Thromboembolism

TIA Transient Ischemic Attach

VKA Vitamin K antagonist

3. INTRODUCTION

3.1. ATRIAL FIBRILLATION

3.1.1. Epidemiology of Atrial Fibrillation

Atrial fibrillation (AF) continues to be the most common **arrhythmia** worldwide (1,2). The prevalence is ranging from 0,1% among persons younger than 55 to 9.0% when the age is above 80 years, and it is expected to increase nearly 3 million individuals 80 years or older by the 2050 (3). In 2021, a Lippi's article (4) concluded that there has been an increase over the past 20 years, and it will continue for the next 30. Furthermore, Colilla et al. (5) estimates both age-adjusted incidence and prevalence have been grown up annually 4,6% and 4,3% respectively.

3.1.2. Risk factors and etiology

Therefore, although the advancing **age** is the principal factor of developing AF (3,6–10), there are other implications that contributes to increase the risk of getting it. Other demographic indicators are the **sex**, which the prevalence is greater in men than in women overall and in every age group (2,3,8–11), specifically the Framingham Heart Study (7) shows a 1,5 more risk for male than female, and the **race**. About the ethnicity, black patients appeared to be affected less likely than white (3), even though nearly all studies are based on data from caucasian population, such as the Rotterdam Study (9), which estimated the lifetime risk of atrial fibrillation in men (23,8%) and women (22,2%) in the age of 55 years. This value remains the same until the age of 75, after that, the percentage it is superior.

The modificable risk factors includes **hypertension**, both types of **Diabetes Mellitus** and heart diseases as **congestive heart failure**, **valve disease** or **myocardial infarction**, which indicators of damage are significant heart murmur or left ventricular hypertrophy. Other comorbidities are **vascular disease** and **asthma bronchiale** (11). These pathologies are significantly associated with both sexes except for myocardial infarction, which is more prevalent in men, and valve heart disease in women (7). Further, this cardiac comorbidity is also important to predict the risk to the young population (8). A Report from the Euro Heart Survey on atrial fibrillation (12) points out that female gender are older, with a lower quality

of life and more frequently with risk factors associated (hypertension, valve heart disease, diabetes and hyperthyroidism).

As a heart condition, the **obesity**, **smoking** and **alcohol** consumption, **dyslipidemia** and **sedentary** lifestyle are important exposures of predisposing AF.
The hazard has been decreasing in the past years with a similar trend in both sexes, excluding for smoking, that only has reduced in men. On the other hand, obesity and DM are growing up (6).

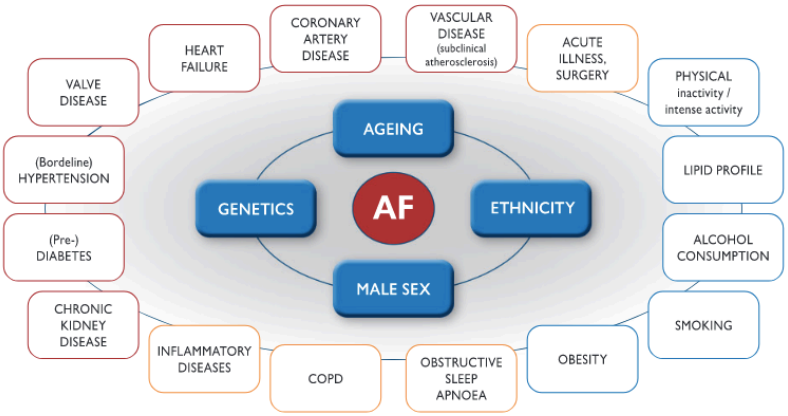

FIGURE 1. SUMMARY OF RISK FACTORS FOR INCIDENT AF (13).

The pathogenesis of AF is multifactorial. Inflammation is known to be involved in changes such degeneration, apoptosis and atrial fibrosis, which cause remodeling. This entire situation promotes the reentry of circuits, that along with shortening of the action potential duration and atrial refractoriness abbreviation are responsible of this abnormal and excessive activity (14).

Consequently, an ectopic focus activation behaves as an atrial trigger. The vast majority of atrial premature beats are originated in the **pulmonary veins** (15). However, exist another regions with capacity to initiate these episodes of AF: left atrial posterior wall, coronary sinus, inferior vena cava, superior vena cava, crista terminalis, vein of Marshall, interatrial septum, and mitral and tricuspid annuli (16–18). Santangeli et al. (19) cited by Gianni et al. (17) remarked the data of non-pulmonary vein triggers can be observed in up to 60% of patients with AF, being prevalent in those that are persistent. In addition, it's more common in female gender, with obesity, sleep apnea, older age, low left ventricular ejection fraction, severe left atrial scarring, hypertrophic cardiomyopathy and mechanical mitral valve.

3.1.3. Diagnosis, clinical features and classification of AF

The 2020 ESC Guidelines (13) introduced the concept of using a **ECG** to establish the diagnosis (class IB) and it is cited as:

"A **standard 12-lead ECG** recording or a **single-lead ECG** tracing of equal or more **30 seconds** showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired)".

The characteristic pattern includes "f" waves and the frequency is between 240-540 bpm.
The ECG demonstrate its ability for diagnose arrhythmias. Nonetheless, there is a need to characterize abnormal atrial substrate as well as triggered activity (20). Due to improve awareness of the individual anatomy, there is an electrophysiological technique called mapping technology, which is able to identify drivers and complex substrate (13,21). Despite of its effectiveness, more studies are needed to confirm the same results to be significant and useful in the clinical practice. Another advanced test could be cardiac MRI, an imaging test that it is capable of visualizing the cardiac anatomy, and therefore, of the atrium. It is useful to see if there are dilations or alterations related to atrial fibrillation.

Evaluation diagnostic includes complete medical history, laboratory tests (thyroid and kidney function, serum electrolytes and full blood count), ECG and transthoracic echocardiography (LV size and function) (13).
Regarding early detection, electronic devices such watches or smartphones apps among others are used more and more for prevention, replacing pulse taking (22,23), that it is still recommended in the guideline 2020 like a test screening in patients above 65 years of age (13).

This supraventricular tachyarrhythmia is characterized with uncoordinated atrial electrical activation which causes an ineffective contraction, and because of that, patients without cardiopathy usually tend to be asymptomatic. Boriani et al. (24) found that 40% of patients do not manifest signs. On the contrary, if they have underlying pathology, symptoms are related to hypotension, low cardiac output and syncope. 15 years ago, Kirchhof et al (25) noticed the discrepancy between clinical relevance and treatment decisions, fact that cause the **EHRA classification** to relates the specific time when patient feels to be in arrhythmia.

mEHRA score	Symptoms	Description
1	None	
2a	Mild	Normal daily activity not affected, symptoms not troublesome to patient
2b	Moderate	Normal daily activity not affected but patient troubled by symptoms
3	Severe	Normal daily activity affected
4	Disabling	Normal daily activity discontinued

FIGURE 2. EHRA SCORE FOR AF (26)

Although the presence of symptoms may guide to an early diagnosis, Gibbs et al. (27) compared 13,235 asymptomatic and 38,797 symptomatic in a GARFIELD-AF-registered patients to observed no significant differences (adjusted hazard ratios, 95% confidence interval) in stroke dates (1.19, 0.97-1.45) or mortality (1.06, 0.94-1.20) over 2 years. Another systematic review and meta-analysis from Sgreccia et al. (28) supported this conclusion giving results as risk of death (OR 1.03, 95% CI 0.81-1.32) and risk of stroke (OR 1.22, 95% CI 0.77-1.93).

Moreover, AF presentation could be distinguished in some subgroups. In 2003, James L Cox (29) defined the concepts of continuous or intermittent AF, depending on its duration. In the same year, Europace (30) publish an International Consensus on nomenclature and classification of AF giving the following definitions:

"If the patient has had 2 episodes or more, AF is said to be recurrent. Episodes of paroxysmal AF usually self-terminate within 48 hours and, by definition, in fewer than 7 days. When an episode of AF has lasted longer than 7 days, AF is designated as persistent. […] When AF has been present for some time and fails to terminate using cardioversion or is terminated but relapses within 24 hours, it is said to be established or permanent."

At present, the classification that has been used since 2020 by health professionals is the one that is remarked in the guide, which categories in **paroxysmal**, **persistent**, **long-standing persistent** and **permanent** (13).

Val-FAAP study (10), a two-phase, cross-sectional and multicenter study where the focus was patients assisted in primary care, revealed a permanent pattern as the most frequently type of presentation (45,3%), followed by first episodic of AF (24,8%). Subsequential, in 2021, a prospective observational study (31) had the same proportions (25,5% paroxysmal, 52,5% persistent and 22% first detected).

Otherwise, paroxysmal AF has risk to progress into permanent form. According to Nguyen et al. (32) the conclusion was a 5,5% / year of progression. In the Journal of the American College of Cardiology, De Vos et al. (33) emphasized one article corroborating nearly 15% of the patients with paroxysmal AF progressed to persistent or permanent after 1 year of follow-up. It was the largest study evaluating clinical correlates related with progression, and the result was a developing risk stratification score named "the HATCH". It is based on parameters such heart failure, age, previous stroke or TIA, hypertension or COPD, which are independent predictors of progression of this arrhythmia.

In the bargain, the last guideline proposed a new structured characterization of AF known as **4S-AF** that provided prognostic information, but also clinical utility and prognostic value. In other words, it became useful to streamline the assessment at different healthcare levels, inform treatment decision-making, and facilitate optimal management. The 4S refer to stroke risk, symptom severity (EHRA score *(figure 2)*), severity of burden and substrate severity, and the class of recommendation and level of evidence is IIa and C respectively (13).

3.1.4. Management of atrial Fibrillation

3.1.4.1. ABC pathway

The treatment of atrial fibrillation requires a patient-individualized decision agreed with some healthcare professionals to achieve a multidisciplinary and integrated management. The 2020 guideline pointed out the patient's preferences, values and goals as an important features in deciding treatment (13). Further, new concepts have been introduced in this new guide in respect to the 2019 guide made by AHA/ACC/HRS (34). It is based on an integrated ABC Pathway (35):

The **"A"** section refers to **avoiding stroke** with anticoagulation therapy, since several studies indicated that AF is associated with high-risk thromboembolic complications (2,36–39). The **CHA_2DS_2-VASc score** *(figure 3)* classify stroke-risk and **HAS-BLEED score** (40) *(figure 4)* classify the risk of bleeding. Once at-risk patients are identified, those who have a low-risk with a minimum score of 1 in male or 2 in female in CHA_2DS_2-VASc *(figure 3)* are treated with NOAC. In case that the patient has a prosthetic mechanical heart valves or a moderate-severe mitral stenosis the prevention therapy is with vitamin K antagonist. In those with contraindication for long-term anticoagulation, left atrial appendage occluding could be an alternative.

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 y	1
Sex **c**ategory (ie female gender)	1

FIGURE 3. THE 2009 BIRMINGHAM SCHEMA EXPRESSED AS A POINT-BASED SCORING SYSTEM, WITH THE ACRONYM CHA2DS2VAS (41)

Letter	Clinical Characteristic[a]	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2

FIGURE 4. CLINICAL CHARACTERISTICS COMPOSING THE HAS-BLED BLEEDING RISK SCORE (42)

The **"B"** is about improve symptoms by **controlling rate** with drugs (beta-blockers, digoxin, diltiazem, and verapamil, or combination of them). When the medication fails, ablation of the atrioventricular node and pacemaker implantation could be the alternative. However, if the patient is unstable, urgent cardioversion should be considered immediately as a best treatment choice.
Also, another parameter of control is the **rhythm**, meaning maintain sinus rhythm either by **antiarrhythmic** medication, **cardioversion**, **catheter ablation** or **surgery**. The benefits are reducing symptoms and improving QoL, and there are some factors that guide to choose the best technique in each case: younger age, first episode, tachycardia-mediated cardiomyopathy, heart disease, ineffective with medication or patient's choice among others.

Electrical cardioversion it's not only recommended in hemodynamically unstable patients but is also the preferred strategy when the AF duration is prolonged, but it's necessary to use sedation. Instead, the pharmacological cardioversion (flecainide, amaiodarone or vernakalant) in stable patients it's easier and recommended in recent onset AF. Both procedures could be suitable options to perform if the episode was less than 12 hours ago; if it's not or unknown, there are two options: expectant conduction during 3 weeks with OAC or doing a transoesophageal echocardiography to exclude thrombus. To add, a recent fact that has been emphasized in the new guideline, and also appears in other studies (43), is the "wait-and-watch" approach, since there are many chances to convert spontaneously within 48 hours.

There is a variety of different pharmacological treatment. The choice of the drug is based on the characteristics of the patient, underlying pathology and efficacy (44). An important factor influencing this decision is the severity and type of associated heart disease.
The class IC are proarrhythmic and their use is limited to patients without structural heart disease, either to maintenance or to convert AF. On the other hand, the class III agents are used to maintenance of normal sinus rhythm. One example of this group is the amiodarone, which has been considered the most effective compared with other antiarrhythmic.

Therefore, the follow *(table 1)* and *(figure 5)* are representations of how the decision could be make and the different drugs that are used in AF's conversion.

Antiarrhythmic drug	Administration and doses to convert AF	Acute success rate and expected time to sinus rhythm	Adverse effects and contraindications
FLECAINIDE	Oral: 200-300 mg Intravenous: 2 mg/kg over 10 minutes	51% at 3 hours, 72% at 8 hours	- Should not be used in ischemic heart disease or significant structural heart disease.
PROPAFENONE	Oral: 450-600 mg Intravenous: 1,5-2 mg/kg over 10 minutes	Oral: 45-55% at 3 hours, 69-89% at 8 hours Intravenous: 43-89% up to 6 hours	• Adverse effects: hypotension, mild QRS complex widening
VERNAKALANT	Intravenous. 3 mg/kg over 10 minutes **further dosing 10-15 minutes after the initial dose: 2 mg/kg over 10 minutes*	50% conversion within 10 minutes	• Should not be used in patients with arterial hypotension, recent ACS, NYHA III or IV heart failure, prolonged QT, or aortic stenosis • Adverse effects: hypotension, QT prolongation, QRS widening, ventricular tachycardia
AMIODARONE	Intravenous: 5-7 mg/kg over 1-2 hours **further dosing: 50 mg/h (maximum 1.2 g for 24 hours)*	44% (8-12 hours to several days)	• Adverse effects: phlebitis, hypotension, bradycardia/atrioventricular block, QT prolongation • Only if no other options in patients with hyperthyroidism
IBUTILIDE	Intravenous: 1 mg over 10 minutes **0.01 mg/kg if body weight is less than 60 kg* **further dosing 10-20 minutes after the initial dose: 1 mg over 10 minutes*	31-51% AF at 1 hour	• Should not be used in patients with prolonged QT, severe left ventricular hypertrophy, or low LVEF • Adverse effects: QT prolongation, polymorphic ventricular tachycardia (torsade de pointes) • ECG monitoring for at least 4 hours after administration

TABLE 1. ANTIARRHYTHMIC TREATMENT. (OWN CREATION BASED ON REFERENCES (13,44))

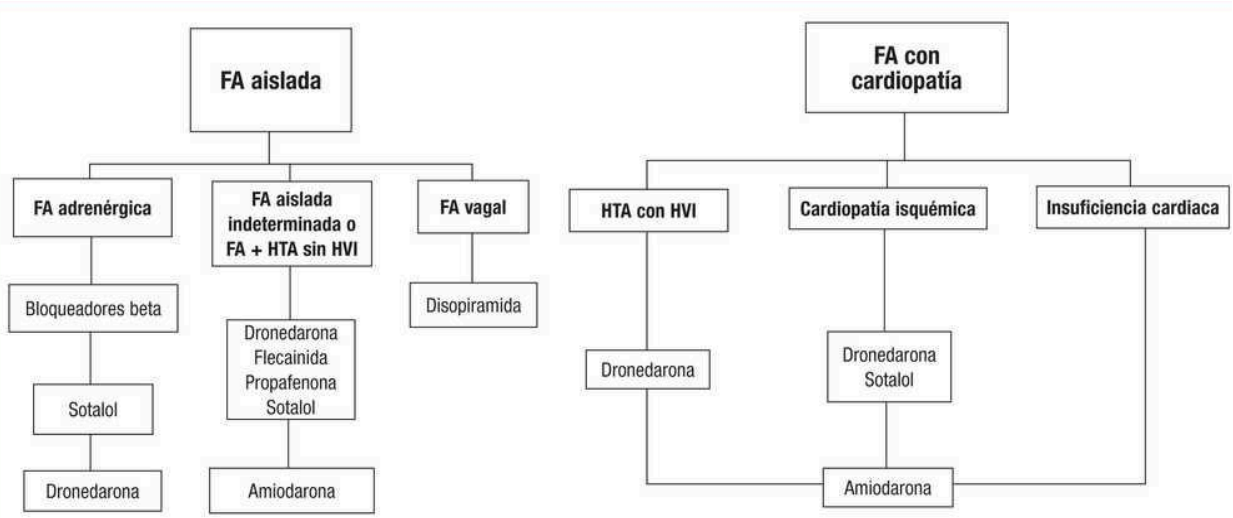

FIGURE 5. ALGORITHM IN THE PHARMACOLOGICAL TREATMENT OF AF (44)

The **catheter ablation** it's indicated for recurrence. The main technique is the isolation of pulmonary veins by linear lesions around their antrum which are done using radiofrequency. This method has been developing and improving over the years.

Another way to restore the rhythm is **surgery**.

And finally, the **"C"** refers to interventions to **reduce cardiovascular risk factors** and concomitant diseases. A lifestyle improves are control obesity and weight loss, reduce alcohol and caffeine habit, physical activity and follow-up comorbidities that could increase the cardiovascular risk or aggravate the prognostic, such as hypertension, sleep apnoea, DM and heart diseases.

3.1.4.2. History of surgeries

In the past, have been existed many different techniques for atrial fibrillation, but they have some limitations (45,46). Over the years, those procedures have been involving and modifying to find the best efficiency (47).

The first of all was in 1980 with a **left atrial isolation procedure**, which confined the abnormal fibrillation in left atria, so, the other part of the heart remained with normal sinus rhythm. Despite of this, the embolic risk was still constant. This procedure used the cut and sew technique to create the isolation of the left atrium, and so the AF, leaving a scar with no-conduction (45,48).

FIGURE 6. ISOLATED PULMONARY VEIN ABLATION (49)

Then, appeared the **transvenous catheter ablation of His bundle** in 1982. It became a standard procedure who require non-pharmacologic therapy (50), but it required an implantation of a pacemaker (45,48).

In 1985, **Guiraudon** et al. (45,51) described the **corridor procedure**, based on an isolation of both atria from their respective ventricles, but patients still were at risk of thromboembolism because the atria continued fibrillating. It was due because the corridor technique permitted the conduction between both SAN and AVN directly to the ventricles but not through both atria. Although patients didn't need the implantation of a pacemaker, it didn't solve the asincrony between atria and ventricles neither the vulnerability to suffer a thromboembolism. In his project, Guiraudon (51) commented the preference of using an alternative as a treatment, like the His-bundle ablation. Also, he highlighted the recently occurrence of a Maze surgery.

In 1987, **James L Cox** (45,52) developed a procedure that accomplished to solve the limitations of the previous techniques: stop the macro-reentrant circuit allowing the restoration of atrioventricular synchrony. The started experimentation was performed with live animals, specifically canins, with a procedure called **"atrial transection"**, based on multiple and complex incisions that where isolating the electrical paths: the pulmonary triggers and also the "marcroentries".

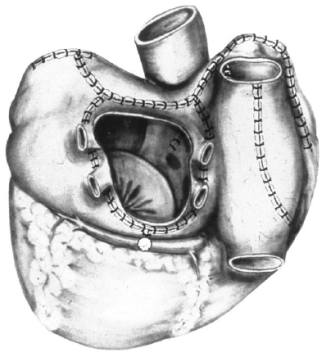

FIGURE 7. COX-MAZE I PROCEDURE (52)

Years later, although the original maze was effective, it caused lack of ability to generate tachycardia in exercise, and occasional left dysfunction on left atrial. In an effort to overcome these problems, the original technique was modified twice. The **Maze II** procedure, the incision across the dome of the left atrium was moved posteriorly to allow better intra-atria conduction, but it was really complex. In the **Maze III** procedure, by placing septal incision posterior to the orifice of the superior vena cava, was an improvement of the left atrium exposure. It's also names as **"cut and sew"**, and was a treatment less demanding than either Maze-I or Maze-II, with a benefits as improved long-term sinus node function, fewer pacemaker implantation and less recurrence of arrhythmia (53). On the other hand, there was a higher risk of hemorrhage or long time in OR with CEC and cardiac arrest, apart from the need of professionals with experience due to its complexity. One data is that less than 10% of cardiac surgeons did it.

3.1.4.3. Cox-Maze IV procedure

The **Cox-Maze IV** replicates the procedure of Cox-Maze III but, instead of incisions of the "cut-and-sew", it is used by bipolar **RF energy** and **cryoablation**. As a consequence, there are less time in OR and lowering complications. The performance starts with a sternotomy, although in some situations could be a minimally invasive right minithoracotomy. The next step is a bicaval cannulation followed by normothermic cardiopulmonary bypass. After that,

both sets of pulmonary veins are dissected, mobilized and encircled. In the right atrial, the patient is cooled to 34º and the lesions are performed from the free wall to the aortic side on the right atrial appendage by **RF ablation**. Also, it is used RF to ablate a vertical atriotomy line and both vena cava. The **cryotherapy** creates an ablation line from superior atria down onto the tricuspid annulus (performed 3 minutes at a temperature below -60/70º). Next step is arrest the heart after aortic cross-clamping in order to make the lesions on the left atrium: occlusion of the appendage and the ablation of all of the atrium with RF clamp. One more time, to complete the isthmus it's required cryoblation to create an epicardial lesions over the coronary sinus (45,46,54).

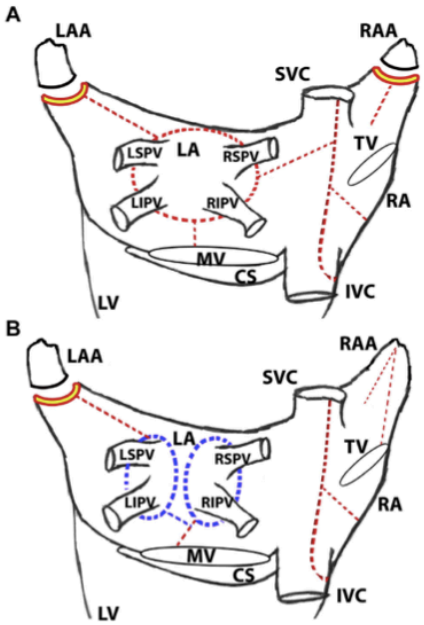

FIGURE 8. BIATRIAL LESIONS SET (46)

The next page there are some illustrations *(figure 9-10-11)* about where the lesions are performed in the Cox-Maze IV procedure, and how they are made.

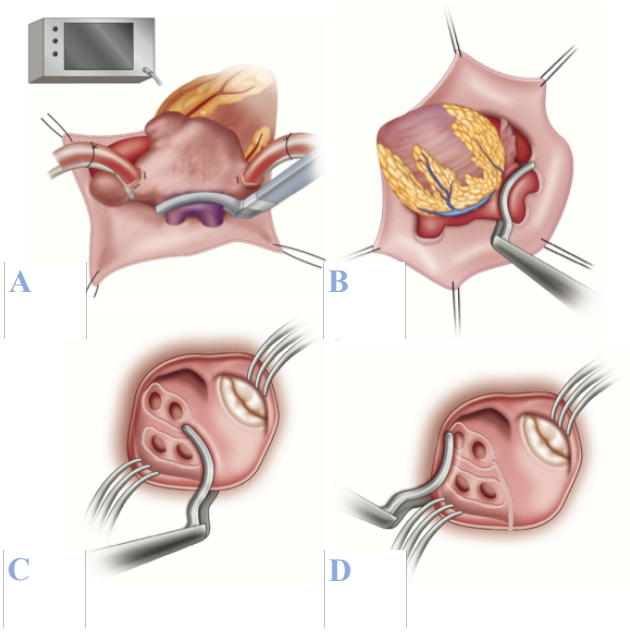

FIGURE 9. LESIONS IN LEFT ATRIUM (54)

A: ISOLATION OF RIGHT PULMONARY VEINS

B: ISOLATION OF LEFT PULMONARY VEINS

C: CONNECTION LESIONS BETWEEN INFERIOR PULMONARY VEINS

D: CONNECTION LESIONS BETWEEN SUPERIOR PULMONARY VEINS

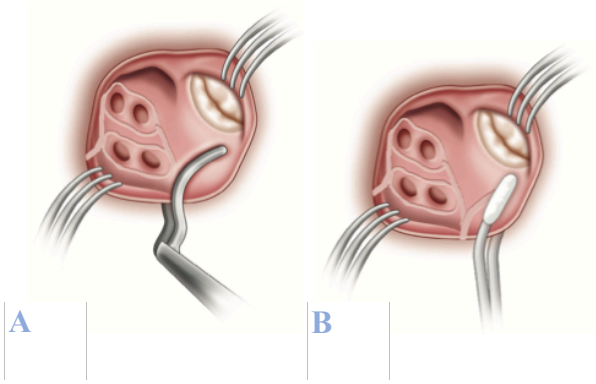

FIGURE 10. LEFT ATRIAL ISTHMUS LESION (54)

A: RADIOFREQUENCY

B: CRYOABLATION

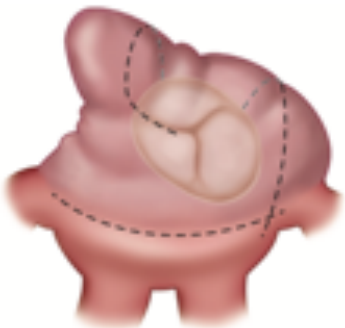

FIGURE 11. RIGHT ATRIAL LESIONS (54)

3.2. CURRENTS PROBLEMS IN ATRIAL FIBRILLATION

Nowadays, the increasingly advanced knowledge and technology provide the apparition of new treatment methods. Even so, the importance is emphasized in knowing if these new strategies are effective and improve respect to the previous ones. There have been several studies, either observational or experimental, to find out some aspects of the different procedures indicated in the management of atrial fibrillation: recurrence, limitations, benefit-risk and associations with comorbidities among others.

The principal failure of all the different techniques is the **recurrence** of episodes of AF. Multiple independent predictors have been identified such as age, persistent type, hypertension, hyperlipidemia and left atrial diameter. These recurrences are mainly due to re-conduction or non-PV foci. There are some authors that studied the p-waves (duration and morphology) and his role in become markers of failure (55).

3.2.1. Efficacy and recurrence of isolated ablation of pulmonary veins

The **indications** of catheter ablation are (13) :

- After failure of drug therapy, either if the fibrillation is paroxysmal or persistent (class I, level A).
- Intolerant to antiarrhythmic drugs.
- First-line therapy in patients with symptoms with paroxysmal episodes (class IIa, level B) or persistent with major risk factors of recurrence (class IIB, level C).
- Patient's choice.
- Highly probability of tachycardia-induced cardiomyopathy (class I, level B).

The CABANA Randomized Clinical Trial (56) was a multicenter experimental study which compared the catheter ablation with conventional medical therapy. The conclusion was no significantly to reduce death, stroke, bleeding or cardiac arrest. Another result was the AF

recurrence at 3 years of 50%, compared with 69% if the treatment was medical. Later, an important secondary objective of this trail was to define specifically the recurrence compared in both managements. In the 2020 report (57), an expanded analysis estimated a recurrence of 36,4% of the ablation patients and 59,2% of the drug-therapy patients at one year. Even so, catheter ablation was associated with a significant 50% approximately of reduction in first recurrence of AF.

Another randomized clinical trail, the CAPTAF (58), focused the study on the QoL depending if patients were treated with ablation or with antiarrhythmic. At twelve months, SF-36 General Health Score was more improved in the first group with a mean difference of 8,9 points (95% CI, 3.1-14.7; $p<0.003$). Other scale of quality, the European Heart Rhythm Association symptom score gave the same results, with a mean difference of -0.5 (95% CI, -0.9 to -0.2; $p<0.003$). Nonetheless, the recurrence of AF at a year was 25.3% in post-PVI and 29.7% in post-medication (it was no significant in the analysis).

Over the years, all studies have been showing the same results of exit and recurrence post-ablation of pulmonary veins. As Salah, Zhou, Liu and Yan (55), who analyzed how P-wave could predict the recurrence, gave a value of 30,3% of the sample who was still in fibrillation in a follow-up of 9 +/- 3 months post-PVI. Also, there are other conclusions that seems to support the outcome of better efficacy if the management is with catheter ablation contrasted with antiarrhythmic drug therapy. As one example is the *"Long-term outcomes and predictors of recurrence after pulmonary vein isolation with multiple electrode ablation catheter in patients with atrial fibrillation"* (59) published in Journal of Cardiovascular Medicine, that considered that PVI is safe and efficient method for treating paroxysmal, but with less benefits in persistent ones. At one year, 83% of patients in paroxysmal AF and 53% of persistent AF in the cohort were free from symptoms, and at two years, the data were 56% and 28% respectively.

An important limitation of catheter ablation and, obviously, the previous procedures, are the believing of pulmonary veins as the only trigger of AF. It is known that those focus have an important role in the pathophysiology, but also, a large percentage of patients require an additional ablation post-treatment. The meaning of this is the presence of **non-pulmonary veins focus**, outside the typical area. The proportion of non-PV is about 5 to 15%.

To add, a second limitation is the difference if the fibrillation is paroxysmal or persistent, since it seems that eliminate **persistent** by isolation it's more difficult and less effective, and it's recommended to ablate before AF paroxysmal progress to persistent (60).

3.2.2. Efficacy and recurrence of Cox-Maze IV. Indications of this procedure.

First of all, the **indications** recommended for surgical ablation of AF are (13) :

- Concomitant AF ablation in patients undergoing cardiac surgery (class IIa, level A).
- Episodes with symptoms which are refractory to antiarrhythmic therapy and have failed percutaneous or catheter ablation (class IIa, level B).
- Patient's choice to control rhythm after persistent AF with risk factors for recurrence despite at least one failed AAD (class IIb, level C).

One of the most recent studies called *"Mid-term outcomes of concomitant Cox-Maze IV: results from a multicenter prospective registry"* (61) in 2022 observed this technique undergoing concomitant surgery in different centers and surgeons. The result remarked the freedom from AF at 3 years remained high for the entire cohort at 84,7%.

This technique is superior than the others such as catheter ablation or other forms of surgical ablation. Further, it is categorize as the most **effective** treatment for AF, either at early-, mid- and long-term follow-up (62). One concept introduced by Philpott et al (63) in the *"The ABLATE Trial"* was the difference between the Cox-Maze III and the Cox-Maze IV, where the use of RF offers less complexity in surgery.

Also in 2022, there is a study with an exceptional results about the efficacy measured with the freedom of AF recurrence, which is 94%, 95%, 89%, 86% and 79% at 1, 3, 5, 7, and 10 years, respectively (64).
There are some other studies, where the results are always similar, even in two the Cox-Maze IV is evaluated as a stand-alone procedure and the benefits are the same (65,66), or another where this technique can be performed safely in patients with higher operative risk (67).

Finally, there has been some investigation about the indication of removing oral anticoagulation in patients after Cox-Maze IV procedure. The risk of stroke and bleeding is inferior than in the past, even though, more studies are still needed (68).

However, accordingly to MacGregor et al (69) the surgery is successful in restoring normal sinus rhythm in general population, but the results are less effective when the patient has more than 75 years old. Also, there was an increase of complications such mortality, implantation of pacemaker or heart failure.

3.2.3. Incidence of atrial fibrillation in patients with valve disease.

As it is said before, AF's incidence is greatly frequent. Further, patients with valve disease have an even higher prevalence.

This pathology is a common finding in a **mitral regurgitation** diagnose: it is present in about 30% of these patients (70). It is not only found in mitral insufficiency, since its incidence is high in any rheumatic disorder of the valve, adding **mitral stenosis** and tricuspid regurgitation in combination. The proportion of individuals with AF and mitral stenosis is approximately 29%, although it can rise to 54% when the diameter of the left atrium is greater than 4 cm (71).

Another part of this section is based on a recent study (2022), where Kim et al (72) evaluated the clinical benefits of Cox-Maze during mitral valve surgery with an observational cohort: the results showed us positive effects for mortality, bleeding and ischemic stroke, but not for hemorrhagic stroke. During the perioperative there is a 0.55 for mortality which is a low observed-to-expected ratio. As a consequence, it suggests that the addition of Cox-Maze to mitral valve procedures, even with a high complexity, **did not increase operative risk**.

The incidence is also high in **aortic** dysfunction such **stenosis** or **regurgitation**. Otherwise, as aortic stenosis is the more prevalent valve disease, the outcomes of treat the arrhythmia in these patients is relevant to prevent complications and morbidity. The percentage of aortic stenosis with AF is about 44%. As with mitral valve disease, the combination of aortic disease with atrial fibrillation worse the prognosis and mortality (73).

The revised recommendations in 2021 version of the *"Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the ESC and the EACTS"* (74) indicates:

- "For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKA_s in patients with aortic stenosis, aortic and mitral regurgitation (class I)".
- "**LAA occlusion** should be considered to reduce the thromboembolic risk in patients with AF and a $CHA_2DS_2VAS_C$ score equal or superior to 2 undergoing valve surgery (class IIa)".

Thus, the LAA occlusion decreases the stroke and mortality rate in patients with pre-existing AF. In addition, the closure should be considered an essential element in the surgical approach to arrhythmia, since 90% of the thrombi found in patients with non-valvular AF and 57% found in valvular AF are in the LAA.

3.2.4. Morbidity and association with stroke and thromboembolisms events

A very important complication, almost the one that affects the most, of having atrial fibrillation is the fact of the association with the **stroke**. So, if the treatment fails, the recurrence of the arrhythmia is a factor influencing patient's morbidity.

In 1992, the *"Oxfordshire community stroke project"* (37) determined the influence of AF in the first ever stroke by an observational cohort. They compared the average of annual risk in patients with sinus rhythm and patients with AF *(figure 12).*

TABLE V—*Absolute risks: average annual risk over five years (calculated from life tables) in patients who survived at least 30 days after first ever cerebral infarction*

	Annual risk (%)	95% Confidence interval
Recurrent stroke:		
Sinus rhythm	8·2	5·9 to 10·9
Atrial fibrillation	11·0	6·0 to 17·3
Difference*	2·8	−2·6 to 8·9
Recurrent stroke or vascular death:		
Sinus rhythm	11·8	9·2 to 14·8
Atrial fibrillation	15·8	9·9 to 24·1
Difference*	4·0	−2·3 to 11·7

*Not significant at $p<0.05$; adjustment for age and infarct type did not affect significance.

FIGURE 12. ANALYSIS OF THE AVERAGE ANNUAL RISK OF STROKE (37)

With the years, the incidence has been decreased thanks the warfarin to prevent these thromboembolic episodes. Even so, the number of cases is high and relevant to the population *(figure 13)* (36).

Year	All Patients With AF, n	Warfarin Use, n (%)	Stroke Rates Per 1000 Patient-Years		
			Ischemic	Hemorrhagic	Any
1992	39 329	9652 (24.5)	46.7	2.9	49.7
1993	42 052	13 027 (31.0)	43.1	2.4	45.5
1994	46 025	16 299 (35.4)	38.3	2.6	40.8
1995	48 922	19 280 (39.4)	36.7	2.6	39.3
1996	52 979	23 169 (43.7)	31.3	2.1	33.4
1997	56 020	26 363 (47.1)	29.4	2.5	31.9
1998	57 946	28 625 (49.4)	25.7	2.7	28.4
1999	59 803	30 584 (51.1)	25.4	1.6	27.1
2000	62 515	33 357 (53.4)	23.7	2.4	26.1
2001	65 944	36 064 (54.7)	22.1	2.1	24.1
2002	67 341	37 940 (56.3)	19.5	1.7	21.2

FIGURE 13. INCIDENCE OF STROKE BETWEEN 1992-2002 (36)

Nowadays, the attributable risk of stroke in patients with AF are 4.6% in individuals between 50-59 years and 7.9% in 60-69 years, but 11.6% between 70-79 and more than 20% in those aged 80-89 years old (75). Other studies (38,39) also allege that age is a factor that increases the occurrence of stroke in people with AF.

After studies that assess this association, it was determined that approximately **one-fifth** of all strokes is attributable to AF (38).

In the 2020 guideline (13) consider that 20-30% of all ischemic strokes and 10% of cryptogenic strokes appear in population with AF *(figure 14).*

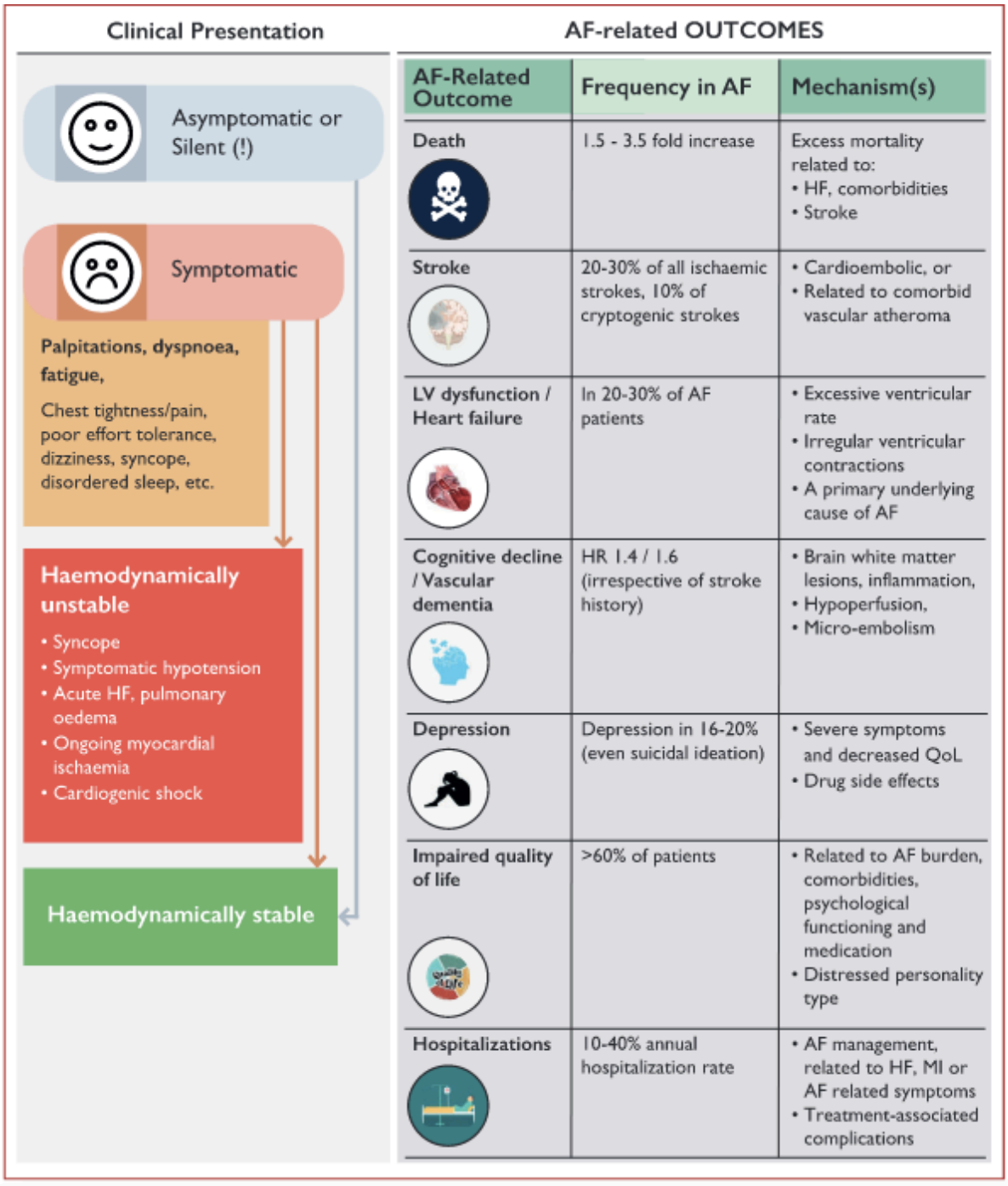

FIGURE 14. CLINICAL PRESENTATION OF AF AND AF-RELATED OUTCOMES (13)

Apart from the association between AF and stroke, especially in elderly population, the presence of an AF increases the 30-daymortality post-stroke. Also, at a year of follow-up, 63% of the AF subjects and 34% of the non-AF subjects has died. So, in conclusion, the stroke in patients with AF would be more severe, more recurrence, with higher **mortality** and poorer **functional status** (76).

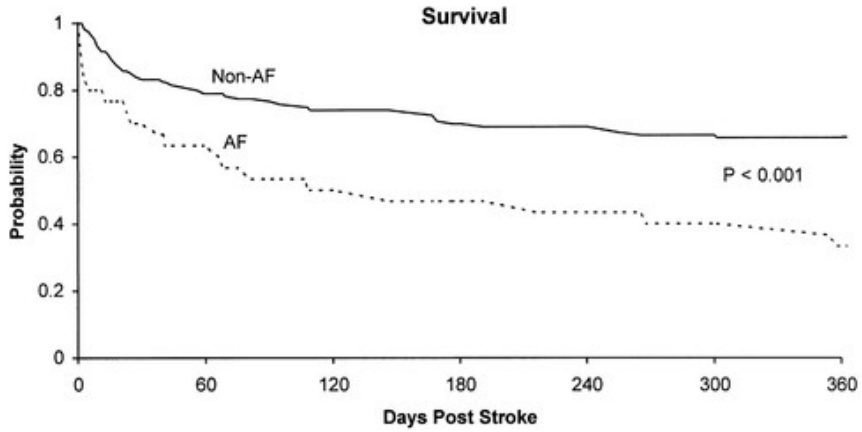

FIGURE 15. ONE-YEAR KAPLAN-MEIER SURVIVAL IN AF SUBJECTS AND NON-AF SUBJECTS (76)

Apart from embolic stroke, other complications associated are heart failure, myocardial infarction, dementia and chronic kidney disease.

3.2.5 Disease burden associated with AF

The **age-adjusted mortality rate** of this arrhythmia in 2010 was 1.6 for men and 1.7 for women. The association with risk factors such hypertension and obesity may be a cause since these have been increased over the years, just the same it has happened with the burden (77).

The worldwide burden of AF, in terms of **DALYs**, has been increased 85% during the past 20 years. Lippi's et al (4) demonstrated a Pearson's "r" correlation of 0.988. Also, extrapolating data they were able to estimate a theoretically value of 10.080 million DALYs and 0.427 million deaths by the year 2050 *(figure 16).*

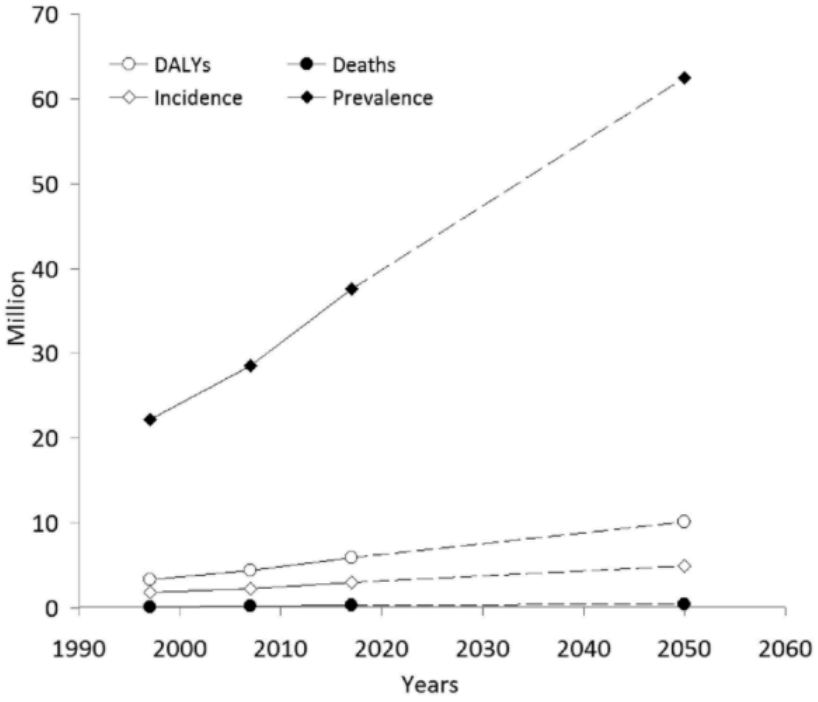

FIGURE 16. WORLDWIDE BURDEN OF AF (4)

3.2.6 Economic burden of AF

Either the diagnose as the management of this disease require several test and controls over the years due to its importance at a long-term risk of stroke and other comorbidities. So, in the context of costs, larger quantities of resources can be expected on its healthcare. And if, with all this add its great prevalence, the amount of money used in healthcare is very high. From an economic perspective, it has been estimated an annual cost of 2.315€ for patient in Spain (78).

Also, atrial fibrillation could be considered one of the major **public health burden worldwide** (2).

3.3. SUMMARISE OF THE INTRODUCTION

To summarise, atrial fibrillation has been considered the most **common arrhythmia** in the worldwide (1,2), along with one of the most major causes of **disease burden** and **economic burden**. Further, several studies have assumed conclusions that this number will increase (3,4). Even this disease is more prevalent in elderly people (3,6–10) , their consequences have such an impact on morbidity and mortality that early diagnosis and its multidisciplinary health care have been studied a long time. Also, it is associated with cardiovascular risk factors such hypertension, obesity, diabetes mellitus, valve disease and other types of cardiac dysfunction (11).

And finally, it must be taken into account that there is an association between this arrhythmia and the generation of **strokes** and **thromboembolic events**, since it has been mentioned the fact of one-fifth of the strokes are caused by AF (38).

The management of this arrhythmia is multidisciplinary with different kind of techniques which may be individualized for the patient. They exist from less invasive treatments such as pharmacological, to catheter ablation, to the most invasive, like surgery.

Patients who has other cardiac pathologies such valve disease have more prevalence to be diagnosed with an AF, and, if their management it's surgical, it could be considered to correct the arrhythmia once the patient is in the operating room. Over the years, new procedures have appeared and improved, ending with this new **Cox-Maze IV**, which it is a technique that utilizes radiofrequency and cryoablation to make the process simpler.

4. JUSTIFICATION

In front of a such **prevalent disease** (1,2) with a clear assumption of increasing during the following years due to the new technology and knowledge acquired over the time, adding the great **burden**, either evaluated with mortality rate, DALYs or economic cost, and even more, with the risk of **stroke** (38) associated with this arrhythmia, forces us to act in order to reduce the consequences and the **outcome impact of atrial fibrillation** in the public health.

So, the preceding information is the first reason of my justification, referring to the fact of its great importance as a such common disease in **elderly** people (3,6–10), who have been associated with several risk factors (hypertension, obesity, diabetes mellitus, valve disease and other types of cardiac dysfunction) (11).

The secondly argument is based on the management of AF (13), specifically in the difficulty of **controlling the rhythm**. There are several options such antiarrhythmic therapy, cardioversion, catheter ablation or surgery, but the main limitation of all of these is the adverse effect that their **recurrence** supposes.
Over the years, different conclusions have been arising in some researches, although the most common result seems to approve that the efficacy of pharmacological treatment and catheter ablation are low.

In the history of surgeries, it has been developed different techniques and, with each one that came out, it provided better efficacy. The most recent, the **Cox-Maze IV** procedure replicates the anterior technique but using radiofrequency and cryoablation (45,46,54).
Despite its great **success**, since it is a surgical procedure, it is indicated when the patient has to enter in the operating room, and it would be a mistake not to correct the fibrillation concomitantly if it exists according to observational studies, just like the closure of the left atrial appendage.
And even with many studies that show its great effectiveness compared to the others, surgeons do not usually use this method. Indeed, there are investigations which their result is the indication to perform since it does not increase the operational risk (67).

However, it is more frequent to perform other procedure which is simpler and requires less work named as **isolated pulmonary vein ablation**. But some authors assessed that its efficacy is limited because there exist ectopic focus outside the pulmonary veins (55,59). In general, it is good for paroxysmal disease since the anatomical substrate is more normal than in persistent disease, in which is altered with fibrotic tissue.

So, the results so far have shown effectiveness in both procedures, but they have never been compared between them in a clinical trial, which is a type of study that may arise more significant results, and cannot be compared with observational and cohort studies, that these have been published before. Besides, previous studies only compared antiarrhythmic drugs with ablation, or Coz-Maze with other non-surgical techniques.

As a consequence, this study projects aims to assess whether the **Cox-Maze IV** procedures will give more **control of the rate** and **less complications** in patients **undergoing cardiac surgery** compared with an **ablation of pulmonary veins**.

Consequently, this study will be a **clinical trial** comparing two surgical procedures because, even though their efficacy is better than the drug therapy, they are only used when the patient undergoes cardiac surgery since entering in the operation room carries its own risk.

Conclusively, my justification to realize this project is based on give a final objective **indication** since, nowadays, the best intervention developed so far is Cox-Maze IV, which is not being performed in a daily practice of cardiac surgery, and many times, the more uncomplicated, the ablation of pulmonary veins, are neither performed. In addition, it will allow us to give a clearer indication of how to proceed when a cardiac patient has valve disease or ischemia, along with atrial fibrillation, with the best treatment strategy, either in relation to the stay in the operating room, or to the results (recurrence and complications).

5. HYPOTHESIS

We postulate some premises that will be able to confirm or refute after the results of this clinical trial.

The **main hypothesis** is:

1. The **Cox-Maze IV** procedure is more effective in reducing atrial fibrillation **recurrence** at **1 year** in those patients who concomitantly undergo surgery for valve disease or myocardial revascularization compared with the **isolated pulmonary vein ablation**.

The **secondary hypothesis** are:

2. The studied intervention will be efficacious regardless of the **type** of atrial fibrillation: paroxysmal, persistent, long-standing persistent and permanent.
3. The studied intervention will be efficacious either at **short-term period** (6 months) to **long-term period** (5 years).
4. The application of Cox-Maze IV will reduce the **risk of stroke** and thromboembolic occurrences, as well as **mortality**.

6. OBJECTIVES

The **primary objective** of this study is to determine whether it is more effective the **Cox-Maze IV** procedure in order to reduce the **atrial fibrillation recurrence at 1 year** compared with an **isolated pulmonary vein ablation** in concomitant surgeries with patients who, apart from atrial fibrillation, suffer from valve disease or myocardial ischemia.

As **secondary objectives**, it will assess if the studied intervention is efficacious regardless the type of atrial fibrillation: **paroxysmal**, **persistent**, **long-standing persistent** or even **permanent**. In addition, we will evaluate if the outcome is maintained both in a **short period of time** (6 months), as well as **long** (5 years).

Another objective of the study will evaluate if exist a **reduction of stroke risk** associated, thromboembolic episodes and **mortality**.

7. METHODOLOGY

7.1. STUDY DESIGN

The study will be a **multicenter**, **longitudinal**, **prospective**, **single blinded**, **randomized** and **controlled clinical trial**.

Patients will be randomly assigned into 2 groups with a ratio of 1:1. Both groups will have cardiac surgery based on two procedures: A specific treatment to cure valve disease or cardiac ischemia and the treatment for atrial fibrillation, which will be different depending on the group in order to achieve a conclusion. Thus, the part of the surgery based on correcting the arrhythmia is the study intervention.

- The **control group** will take part in a conventional technique that has been used over the years: an isolated pulmonary vein ablation.
- The **experimental group** will be undergoing a newest procedure called Cox-Maze IV.

The study will be carried out in 3 hospitals of Spain: Hospital Universitari Dr. Josep Trueta in Girona, Hospital Clínic i Provincial de Barcelona in Barcelona and Hospital General Universitario Gregorio Marañón in Madrid.

The recruitment of patients will last 12 months, with subsequent follow-up of each patient for 5 years in order to determine the incidence of recurrence of non-sinus rhythm, with all of the secondary variables and co-variables. The study will end after the statistical analysis and the final conclusion. As a consequence, the results will be published in an article, as well as the realization of congresses and conferences.

7.2. STUDY POPULATION

The selection of subjects will be based on those individuals who meet all the requirements in the **inclusion criteria** and none of the **exclusion criteria**, obviously apart from the fact that they want to participate and sign the prior informed consent.

Once the patient has signed the informed consent, they will be included in this study and become a participant.

Inclusion criteria:

- Patient with an age between **18** and **75** years old.
- To be diagnosed of **atrial fibrillation**.
- To have an indication of cardiac surgical treatment concomitantly:
    - **Aortic valve disease** with surgical indication.
    - **Mitral valve disease** with surgical indication.
    - **Myocardial revascularization** with surgical indication.
- Ability to follow-up time of **5 years** after the surgery, attending all posterior scheduled visits.

Exclusion criteria:

- Patients with **contraindication** to undergo surgery.
- **Previous** atrial fibrillation treatment: ablation, medical or cardioversion.
- **Emergency** situation.
    - It requires an immediately cardioversion.
- Non-availability of complete **clinical history**.
- Not being able to carry out an adequate post-treatment **follow-up**.

Withdrawal of subjects:

They will be withdrawn in any of the following cases:

- Patient no longer wants to participate in the study, whatever the reason is. They will have to sign the withdrawn document *(annex 5-6)*

- Excessive risk or **risk** with a demonstrated lack of benefits.

- Participant is **not following** the procedure.

- Participant may be deliberately providing **false information**.

- Delayed detection of a **violation** with the criteria of inclusion and exclusion.

7.3. SAMPLING

7.3.1. Sample selection

Sample recruitment will be obtained through a **consecutive method,** that is a non-probabilistic sampling technique.

In a medical consult for following-up of atrial fibrillation, valve disease or cardiac ischemia with those patients who meet all the inclusion criteria and none of the exclusion criteria will be invited to participate in the study. The patients will be recruited from the three centers where the study will be developed: **HUJT**, **Hospital Clínic i Provincial de Barcelona** and **Hospital General Universitario Gregorio Marañón**.

All candidates will receive an **information sheet** *(annex 1-2)* and each doctor will give them a contact number of the responsible of the study. Each hospital will have this person who is in charge to explain the role of the patient in the study, as well as its motivation, parts, benefits, risks and impacts. Any question that may arise it will be respond. An important task of the responsible is the capacity to communicate with understanding.

After all giving-information, the patient will be able to sign the **informed consent** *(annex 3-4)* if they want to participate. Once that occurs, the procedure will start with the inclusion of patients in the register, with the intention of verify the criteria and data of the possible subject. It will be also registered in the medical clinical history of the patient.

7.3.2. Enrollment rate assurance

From another band, in order to obtain a high enrollment rate, we are not going to advertise since our sampling method is consecutive. But we will give talks and **keep informed** the cardiology staff and those who are surrounded by patients with atrial fibrillation at work or at their consults. And if happens a case that believe one patient could be included, they will explain that there is a study about atrial fibrillation and give them the information sheet *(annex 1-2)* with our contact number.

7.3.3. Randomized stratification

Moreover, to improve the study and reduce any possible confounding factor we will add the **stratification technique** according to the pathology that caused the patient's admission to the operating room. It allows us to separate the patients if they have mitral valve pathology, aortic valve pathology or if they have ischemia. We do this since there is not the same prevalence of association with atrial fibrillation depending on the cause. Further, it let us to predict more specific results and corroborate the association.

7.3.4. Sample size

We used the program **GRANMO** free calculator available online to calculate the sample size of this clinical trial.

This study is designed with two groups with a ratio 1:1, with an acceptance of 0.05 of alpha risk and 0.2 of beta risk in a two-sided test. Moreover, we will assume a 10% of lost rate to avoid bias. Our objective is a 90% of effectiveness with the new procedure compared with 70% of the simpler one, that means a proportion of our variable (recurrence of atrial fibrillation) of 0.30 in the first group (control group) and 0.10 in the second group (experimental group).
So, **66 subjects** are necessary in both groups to recognize as **statistically significant.**
This data is justified due to several observational studies that have been published over the years.

Subjects withdrawn from the study will not be replaced.

7.3.5. Randomization and blinding methods

After the registration of the patients with accepted indication for inclusion in the study, the **randomization** will be performed by an investigator. Individual's data will be confidentially maintained and an **identification code** will be assigned to each patient, made thanks to the company's automatic software.

As a way to reduce the possible bias, we will use a **simple-blind** and **observer-blind** process. That is to say when the patient will not know what surgical technique is being performed, same as statistic's personal who are in charge of evaluating the masked results and the health personal who do the medical control visits. However, it's not possible for the professional surgeon be blinded, since it's the responsible for the surgical procedure.

7.3.6. Estimated time of recruitment

Based on the calculation of the sample size, for the study it will be needed to carry 66 patients in both groups in order to be able to start the process. So, in total we need **132 individuals.**

The data in reference of how many surgical procedures happened in a year it has been known for the surgeons in each hospital. At Hospital Universitari Dr. Josep Trueta there are a report of approximately **10** cases of Cox-Maze IV in one year. In Hospital Clínic i Provincial de Barcelona there are **50** cases per year, and in Madrid the number is twice or even more.
The ablation of pulmonary veins is more frequent in every hospital since its simplicity and comfort.
Also, it has to take into account the fact that some people may not want to participate.
Taking into account this information, the time of recruitment has to be, at least, **one year**, in order to achieve the minimum cases to continue the project.

7.4. STUDY VARIABLES

7.4.1. Independent variables

The independent variable is the additional surgical procedure that the medical research used to treat the atrial fibrillation in those patients with an indication to operate valve disease or ischemia. So, it is the intervention: the **isolated pulmonary vein ablation** and the **Cox-Maze IV technique**.
Further details on the study interventions procedures are detailed in section 7.5 *(Study intervention and follow-up).*

It is a **dichotomous nominal qualitative** variable, being one or other.

To justify the results, this independent variable will be performed by the same surgical team in each center, with a previous training, with the aim to standardize both procedure, avoiding bias in the intervention time.

7.4.2. Dependent variables

7.4.2.1. Of the main objective: Atrial Fibrillation recurrence at 1 year

The primary outcome is the **recurrence of atrial fibrillation** at 1 year. This dependent variable is defined as either the presence of the typical characteristics of this arrhythmia in the **ECG** or a **documentation** of a failure with an alternative treatment to amend.
The typical pattern seen on electrocardiographic testing include irregular R-R intervals, absence of distinct repeating P waves and irregular atrial activations. To diagnose AF the minimum duration of AF tracing is at least 30 seconds in a single-lead ECG, or entire 12-lead ECG (13).
The other criteria to diagnose the recurrence is the need to do cardioversion, using antiarrhythmic drugs or with the implantation of a pacemaker.

As I said before, the answers could be “the patient had a recurrence of AF” or “the patient didn’t have a recurrence of AF”. Therefore, it is a **dichotomous nominal qualitative** variable.

Measurements and instruments for the primary outcome variable

To measure the main variable, we will use a simple test which is a part of the scheduled medical visit to control follow-up.

We will quantify the rhythm by an electrocardiograph technique. This measure will be evaluated at one month, followed by 3, 6, 9 and 12 months. Later, one year-consult will be performed up to 5 years post-intervention. However, an ECG could be enough, we rather to use a **ECG-Holter 24 hours** to improve the sensibility since exist paroxysmal AF which it is characterize to course with episodes.

In addition, we will always take into account any suspicious data of atrial fibrillation recurrence that may appear during the follow-up visit, from the anamnesis focused on the characteristic symptoms of this arrhythmia (EHRA symptom scale *(figure 2)*) or the documentation of an alternative treatment to restore sinus rhythm. All data will be verified with the patient's medical history.

7.4.1.2. Secondary outcomes

Recurrence of atrial fibrillation depending of the type, and **recurrence of atrial fibrillation at short-term and a long-term**

Both secondary variables are the same of the main objective in an extended way. In this case we will want to found out if there will be differences if the fibrillation is **paroxysmal**, **persistent**, **long-standing persistent** or **permanent**, and if the efficacy of the procedure is maintained in a short-term, defined by **6 months** approximately, and in a long-term, meaning up to **5 years**.

The first variable is about knowing the effectiveness of all type of atrial fibrillation, since it is more frequent to be persistent, and the results of previous studies concluded a more recurrence in this patients with persistent fibrillation compared with patients with paroxysmal.
The argument for searching the second outcome is attributed to looking for the evidence that ensures whether the freedom of recurrence is permanent or, if only, it is lengthened compared

to previous values, but it will appear in the future. In other words, with this variable we will be able to confirm the real efficacy of the treatment over the years.

The way to measure is exactly the same as in the preceding one. There are 4 different arrhythmias, and in each type the answer could be "yes" or "no" recurrence, just like with the short- and long-time period of observation.

Incidence of a stroke /thromboembolism events

Another dependent variable of the secondary objectives is the incidence of a major thrombotic situation, specifically a high importance of a stroke because of the evident association with atrial fibrillation. All situations of thromboembolic events that could occurred and be measured are (41):

- **Ischemic stroke**
- **TIA**
- **Peripheral embolism**
- **Pulmonary embolism**

This is a **dichotomous nominal** qualitative being "yes" or "no" if happens any circumstance described as a thromboembolic during all along the study from the start of the post-intervention. So, the way to measure is based on the **clinical history** or self-recalled in the **anamnesis**.

Incidence of electrical cardioversion

This variable will appear in the case that the treatment, either ablation or maze procedure, **fails**. It consists to applicate of a selected amount of energy via two electrodes to revert the abnormal rhythm (46). Another indication that the patient may have to proceed with this is hemodynamic instability (13).

The **dichotomous nominal** variable is answered with **anamnesis**, apart from his **clinical history** that it will be documented.

Apart from its own meaning as a secondary variable, it also expresses the diagnosis of recurrence of this arrhythmia, which we mentioned before.

Management of antiarrhythmic treatment post-surgery

It's also a **dichotomous nominal** variable with a "yes" if the patient will require pharmacological therapy. We are going to obtain this data with the **interview** with the patient in every medical control and with the **history** of the clinical report.

In the introduction, and especially with *table 1* and *figure 5*, it is specified which drugs are used to convert atrial fibrillation. Likewise, if a patient receives a treatment with one of these after the procedure (either ablation of pulmonary veins or Cox-Maze IV), it will mean that the process has **failed**.

Requirement of an implantation of a pacemaker

It is also a **dichotomous nominal** variable as the previous ones. As it is said before, other alternative treatment to be used in case of failure and recurrence of AF. **Medical clinical history** and patient's **anamnesis** will be the form to know of the existence of this variable.

For the past years, the implantation of a rate-responsive ventricular pacemaker it has been indicated if the procedure to restore and maintain sinus rhythm has not been successful. Basically, it is a technique where the atrioventricular node is ablated, and because of that, a permanent conduction block appears (80). Despite of the benefits from controlling the rate, there are some disadvantages compared with the pharmacological treatment. Accordingly, the implantation of a pacemaker is indicated as an alternative in case of **failure**.

Complications post-surgery

Complications will be understood by any situation that is worsens the patient's situation. In the *table 2* we can see the different types of common complications, which could be distinguished by time in immediately, early or lately.

Those complications that have a relevant significance are excluded and defined as their own variables such recurrence of AF, stroke and mortality.

It is a **polytomous nominal** variable. Spite of the multiple type of complications that exist, we will name a list of few ones, with an option of "others".

Sepsis	Complete AVB	Neurological dysfunction
Wound infection	Other dysrhythmias	Respiratory insufficiency
Bleeding	HTA	Acute renal failure
Hemodynamic instability	Hypotension	Hemorrhagic shock
Electrolyte disturbances	Myocardial infarction	Cardiogenic shock
Atrial premature beats	Congestive heart failure	Others

TABLE 2. COMPLICATIONS OF CARDIAC SURGERY (OWN CREATION BASED IN (81))

Quality of life evaluation

This variable will be measured in every medical visit with the patient. We will assess it with a **quantitative discrete variable** with a score of **0 to 100**. We will use a questionnaire named as "The 36- Item Short Form Health Survey questionnaire" or "**SF-36**" *(annex 7).* It measures eight scales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. In general terms, this test analyses two distinct concepts: a physical dimension and a mental dimension.

So, the dependent variable will be the mean of these eight items since all of these aspects have a complete reference to patient's life. Before using the scale, it is necessary to homogenize the direction of the answer: for every item, the higher punctuation will significance the better health state. Then, the final score value will indicate the quality of life of the patient (79).

Mortality

This last variable is defined as the "**end of patient's life**", and it is a **dichotomous** variable with answers as "alive" or "death". We will know the data with the **clinical history** of the patient.

	Noun of the variable	Type of the variable	Measure of the variable	Possible results
INDEPENDENT	Surgical intervention	Dichotomous nominal qualitative	Group depending on the randomization	Group control: pulmonary veins ablation Group experimental: Cox-Maze IV
DEPENDENT	AF recurrence at 1 year	Dichotomous nominal qualitative	Anamnesis + EF + ECG-Holter 24 hours	Presence (yes) or Absence (no)
	AF recurrence depending the type	Dichotomous nominal qualitative	Anamnesis + EF + ECG-Holter 24 hours	Presence (yes) or Absence (no) in every type of AF
	AF recurrence at short-term and a long-term	Dichotomous nominal qualitative	Anamnesis + EF + ECG-Holter 24 hours	Presence (yes) or Absence (no)
	Incidence of stroke or thromboembolism events	Dichotomous nominal qualitative	Anamnesis + Clinical History	Presence (yes) or Absence (no)
	Incidence of electrical cardioversion	Dichotomous nominal qualitative	Anamnesis + Clinical History	Presence (yes) or Absence (no)
	Management of antiarrhythmic treatment post-surgery	Dichotomous nominal qualitative	Anamnesis + Clinical History	Presence (yes) or Absence (no)
	Requirement of an implantation of a pacemaker	Dichotomous nominal qualitative	Anamnesis + Clinical History	Presence (yes) or Absence (no)
	Complications post-surgery	Polytomous nominal qualitative	Anamnesis + EF + Clinical History	Any complication (noun)
	Quality of life	Discrete quantitative	Questionnaire SF-36	0-100
	Mortality	Dichotomous nominal qualitative	Clinical History	Death (yes) or Alive (no)

TABLE 3. INDEPENDENT AND DEPENDENT VARIABLES (OWN CREATION)

7.4.3. Co-variables

In every subject enrolled in the study, we will collect the following baseline characteristics in order to have a control data. Also, some will be useful to compare with the results. These variables are called co-variables because they have association with the both main variables (dependent and independent). So, to avoid the confusion factor, in every patient we will asked and measure these aspects, apart from consulting the register of their clinical history.

Age

It will be measured in **years**. So, it is a **discrete numerical or quantitative** variable (absolute number). This topic is important since the prevalence increases highly with the increase of age. Although the study allows patients over 18 years of age, we assume that the majority will be over 50 years due to the earlier studies carried out on prevalence.

Sex

It is a **categorical nominal** variable with answers like male or female. As seen on the introduction, the men are more predisposed to catch the arrhythmia.

Type of valve diseases

It is also a **categorical nominal** variable. There are different types of insufficiency or stenosis. Despite this, in our article we only have the following categories (they are part of the inclusion criteria):

- **Mitral regurgitation**
- **Mitral stenosis**
- **Aortic regurgitation**
- **Aortic stenosis**

- **Nothing** (in case of ischemia)

To classify which type we will use an **echocardiography** since this test is able to confirm the presence of stenosis or insufficiency, define the valve morphology, characterize the function of the left ventricle (LVEF) and discard other valve diseases.

Severity of the valve disease

It is an **ordinal qualitative** with mild, moderate or severe response. We will use an **doppler echocardiography** to measure.

In the insufficiency, the measure of severity is based on the **gradient** between valves considering that it is significant when the mean gradient is over or equal than 50 mmHg or the peak gradient is over or equal to 60 mmHg. Also, another way to measure is with the **valve area**.

On the other hand, when the patient has stenosis in the clinical practice we used the **valve area** with the **regurgitation flow** estimated by doppler. It's severe in case of less than $1cm^2$ in the valve orifice (74).

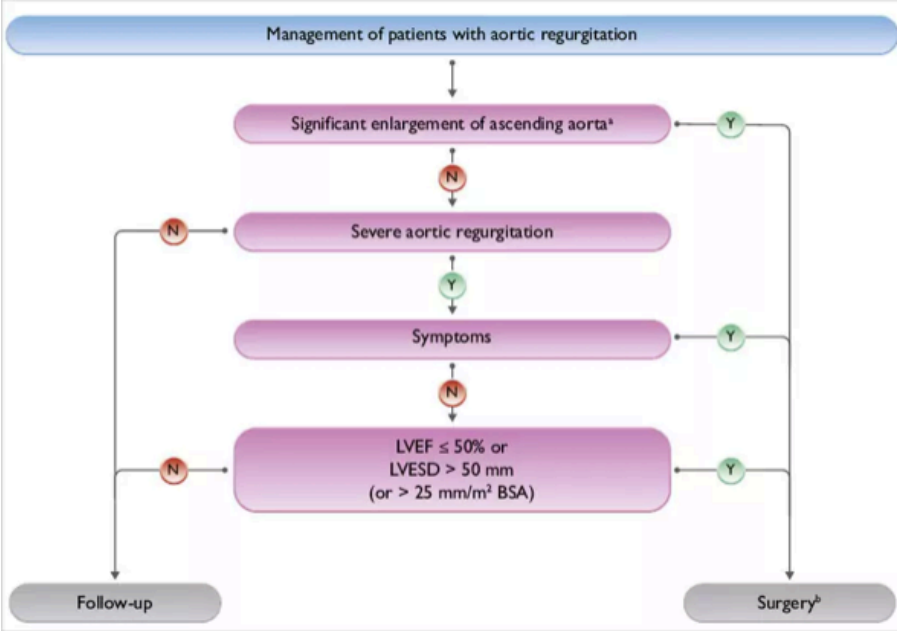

FIGURE 17. CLASSIFICATION OF AORTIC INSUFFICIENCY (74)

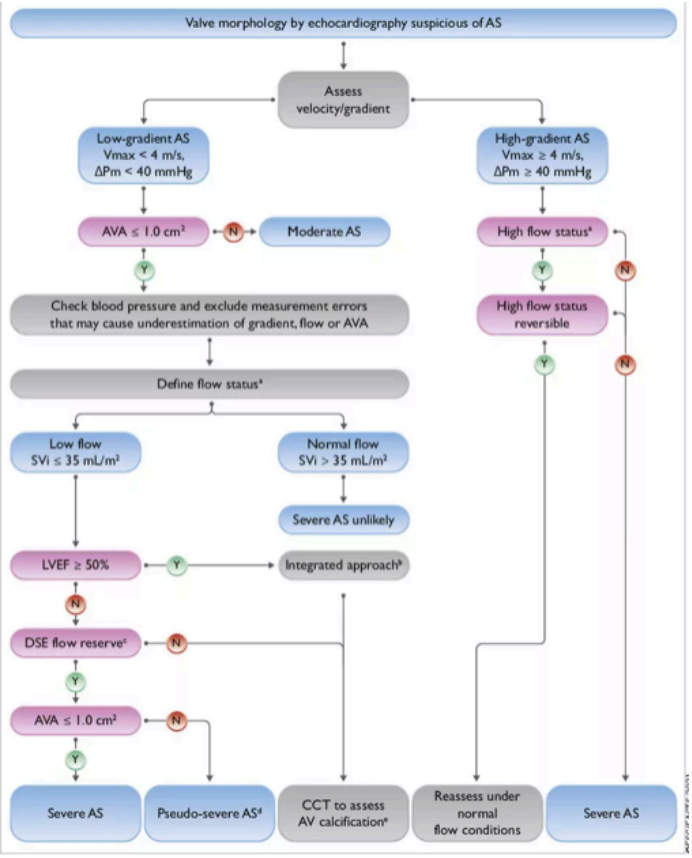

FIGURE 18. CLASSIFICATION OF AORTIC STENOSIS (74)

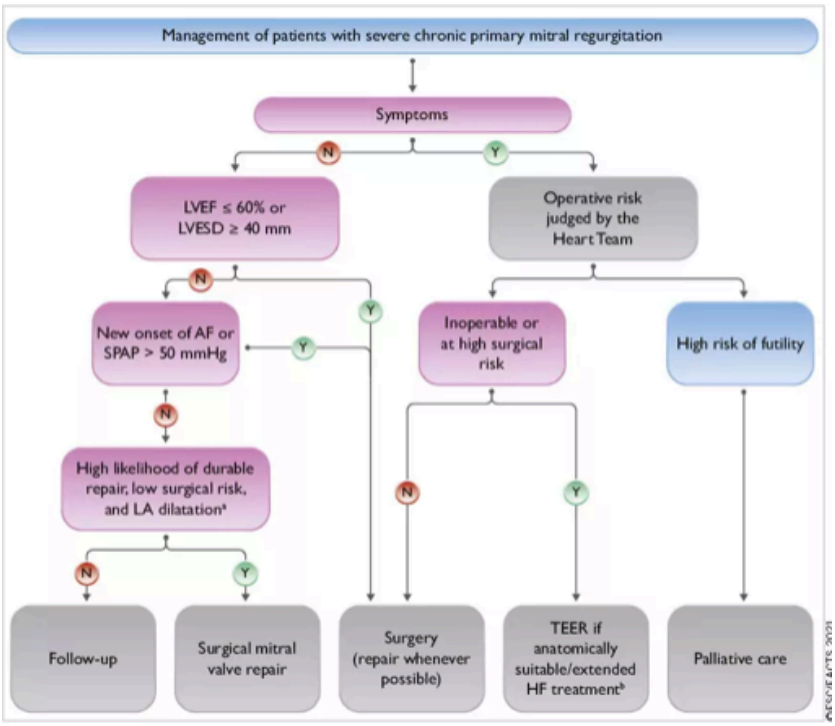

FIGURE 19. CLASSIFICATION OF MITRAL INSUFFICIENCY (74)

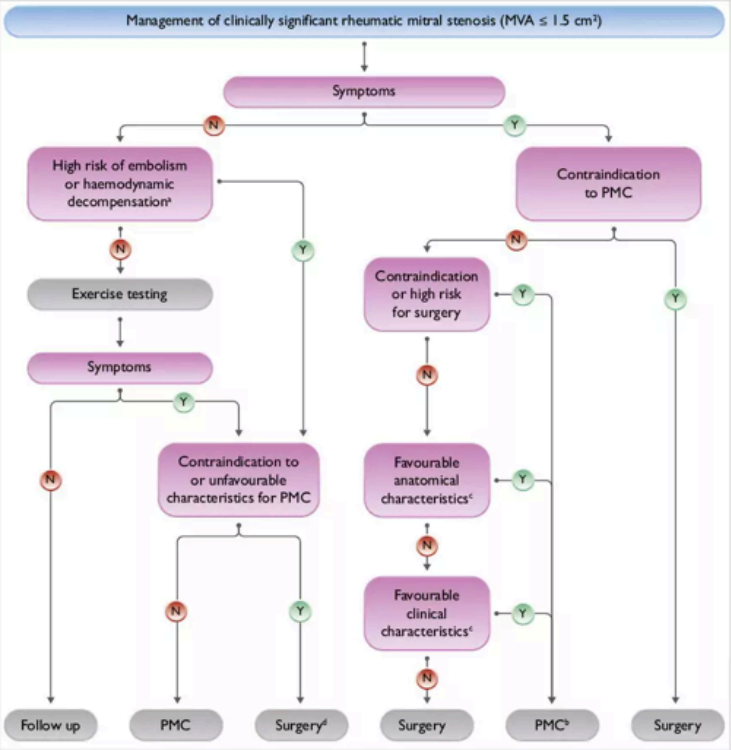

FIGURE 20. CLASSIFICATION OF MITRAL STENOSIS (74)

Rhythm of the AF

It is a **dichotomous qualitative nominal** variable with "rhythmic" or "arrhythmic" depending if the patient has a sinus rhythm or, otherwise, an atrial fibrillation in the initial test.

On the first visit, the investigator will proceed to realize some test to have initial baseline data of the patient and, thus, be able to compare them with those of the following scheduled visit controls. One of the tests to be carried out will be an **ECG-Holter 24 hours** to evaluate the rhythm.

LVEF

The ejection fraction is defined as a measurement of the quantification of blood leaving the heart to aorta each time it contracts. It is seen in the **echocardiography** and the value is in percentage (%) with absolute numbers. So, it's a **continuous quantitative**.

In this draw we can see the old classification range and the actual, determined by BSE.

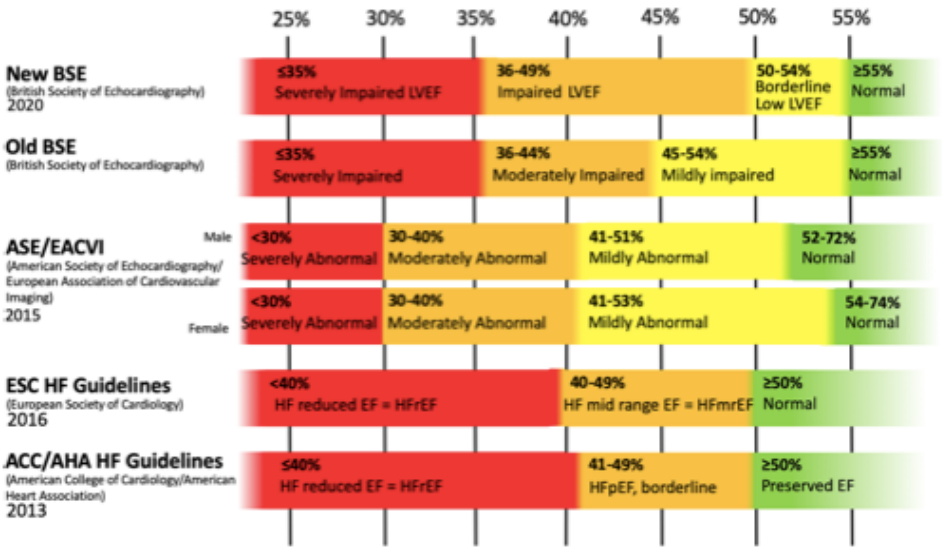

FIGURE 21. CLASSIFICATION PUBLISHED ON A HUDSON'S ARTICLE (82)

CO-VARIABLES	Type of variable	Measure	Possible results
Age	Discrete quantitative	Anamnesis + Clinical History	Any year (absolute number)
Sex	Dichotomous qualitative nominal	Anamnesis + Clinical History	Male Female
Type of valve disease	Polytomous qualitative nominal	Anamnesis + Clinical History + echocardiography	Mitral regurgitation Mitral stenosis Aortic regurgitation Aortic stenosis Nothing (in case of ischemia)
Severity of the valve disease	Ordinal qualitative	Anamnesis + Clinical History + echocardiography + Doppler	Mild Moderate Severe
Rhythm of the AF	Dichotomous qualitative nominal	Anamnesis + Clinical History + ECG-Holter 24 hours	Rhythmic or Arrhythmic
LVEF	Continuous quantitative	Echocardiography + Clinical History	Absolute numbers in percentage (%)

TABLE 4. CO-VARIABLES (OWN CREATION)

7.5. STUDY INTERVENTION AND FOLLOW-UP

Our goal is to study if Cox-Maze IV surgical technique is better in maintain sinus rhythm in the patients with atrial fibrillation than the other procedure less complex which have been over the years.

The study intervention and the follow-up have three phases:

1) The intervention: the **surgical operation.**

Nonetheless the patient has atrial fibrillation, they will enter to operation room also for another disease which have an indication to treat in a surgical way. In the inclusion criteria, we decided to study the patients who has:

- Valve disease, concretely mitral or aortic dysfunction, either due to insufficiency or stenosis.
- Ischemia which can be treated with a myocardial revascularization, also called coronary artery bypass grafting.

So, during the operation, the surgeons will repair this defect.

The other part of the interventions is to treat the atrial fibrillation. And this is when, depending the group, will have one procedure or another in this **concomitant cardiac surgery**.

In addition, all patients will have a **LAA excision or exclusion** (with a clamp) because it has been demonstrated that this technique reduce a high percentage of thromboembolism episodes.

- The experimental group is which will proceed to do a **Cox-Maze IV intervention**. The procedure starts with a median sternotomy, establishing cardiopulmonary bypass via bicaval cannulation, clamping the aorta and arresting the heart. Then, the lesion set included bilateral pulmonary vein isolation, roof and floor lesions, a lesion to the left atrial appendage, the mitral isthmus lesion, right intercaval lesion, right appendage lesion, right medial wall lesion to the tricuspid annulus, and right free-wall lesion to the tricuspid annulus.

This technique utilizes **radiofrequency** in all of these lesions (the system that we will use is AtriCure Synergy bipolar) except for the completion of three lesions which terminate onto the mitral valve and the tricuspid annuli, which we will use a **cryoablation**.

- The group control will have a procedure less complex which is an **isolated pulmonary vein ablation**. It is defined as an electric ablation of pulmonary vein since this location is where the most arrhythmia are originated.

  The procedure starts with the same as the group experimental since all patients has to have an open-cardiac surgery. However, the difference is that only the lesions are in the pulmonary vein with **RF** (AtriCure Synergy bipolar). Basically, the jaws of the clamp are placed around the left atrial adjacent of pulmonary veins to do the ablation.

2) The **post-operative week**. The patients must be in the hospital to control the success of the intervention. If everything continues as expected and there are no complications, surgical discharge will be given in one week. Before leaving, the patient will be checked-up with a basic test and an echocardiography.

3) The follow-up is done with sequential **medical visits** to control by the investigator and the nurse. At each visit, the patient will receive:

First of all, the medical control will start with an **anamnesis**. This interview between the investigator and the patient has to have all the next features and all information given will be also verified with the clinical history.

- Any symptom experimented since the intervention, using the **EHRA symptom scale** *(figure 2)* (26).

- The quality of life of the patient. The investigator will use the QoL questionnaire (**SF-36**) *(annex 7)* (79).

- Any **complications** post-surgery that could appear.

- Documentation of any signs of **failure**: cardioversion, drug therapy or implantation of pacemaker.

In addition, emphasis will be placed on any doubt that patient could have about any part of the study which will be explained.

This visit is followed by the **physical exploration.** A general one to see appearance and condition, with any signs of atrial fibrillation, and later a cardiac examination with the palpation and auscultation.

Suspicious signs of atrial fibrillation:

- In the auscultation:
    - Fluctuation in the intensity of the **first sound**.
- Rapid and irregular **pulse**.
- Absence of **"a" wave** in the jugular venous pulse.

And finally, the visit will be finished with an **ECG-Holter 24** hours to evaluate the rhythm.

Consecutive visits for follow-up will be made at the hospital where the intervention was performed. The first medical visit will be done **one-month** after surgery, and the others will be scheduled after **3**, **6**, **9** and **12** months. From the year, there will be an **annual** check-up to **5** years.

Subsequently, you are able to see a figure *(figure 22)* that represents the **patient's diagram**, which it is useful to see all tests and procedures that will be performed on each individual throughout the entire study.

	W	E	E	K	S			Y	E	A	R	S
	-2	-1	0	1	2	5	13	25	37	1	2	3	4	5
GIVING INFORMATION TO THE PATIENT	X													
RECRUITMENT OF SUSCEPTIBLES PATIENTS		X												
INFORMED CONSENT DOCUMENT		X												
VISIT TO SELECTION		X												
SUBJECT REGISTRATION		X												
VERIFYING INCLUSION AND EXCLUSION CRITERIA		X												
SIMPLE RANDOMIZATION			X											
CODE NUMBER ASSIGNATION			X											
REGISTER ON THE DATABASE		X												
REGISTER ON THE MEDICAL CLINICAL HISTORY		X												
FIRST VISIT		X												
ANAMNESIS		X				X	X	X	X	X	X	X	X	X
PHYSICAL EXPLORATION		X				X	X	X	X	X	X	X	X	X
BLOOD ANALYSIS		X		X	X									
ECG-HOLTER 24 H		X				X	X	X	X	X	X	X	X	X
ECHOCARDIOGRAPHY		X			X	X								
SURGICAL INTERVENTION				X										
HOSPITAL SURGICAL DISCHARGE (IF THERE ARE NO COMPLICATIONS)					X									
MEDICAL VISIT					X	X	X	X	X	X	X	X	X	X

FIGURE 22. DIAGRAM OF THE PATIENT'S INTERVENTION DURING THE STUDY (OWN CREATION)

7.6. DATA COLLECTION

First of all, before the intervention, it will be an elaboration of a **database**. It includes the most relevant demographic, social and clinical variables of all the patients, identified each one with a **code number** to maintain the anonymity. Additionally, we hire a **data quality control** service to supervise the process and guarantee a correct data collection.

The following table contains all the information necessary to fill out once the patient has signed the informed consent document. The mainly characteristics correspond to the covariates. This activity will be done in the first visit with the investigator, who will verify the data provided with the medical clinical history of the patient.

Sex and age of the patient	Medication and allergies
Medical history	Cardiac disease
History of the arrhythmia	Type of atrial fibrillation
Inclusion criteria	Exclusion criteria

TABLE 5. INITIAL DATA OF THE PATIENT (OWN CREATION)

Later, in the follow-up, each patient will have **consecutive scheduled interviews** and **medical visits** with the investigator and the nurse to report a form filling out with measurements, vital constants and results from **ECG-Holter 24 hours**. Every investigator of each center will do the same as they were trained in the second stage of the work project.

Symptoms	Alternative treatment in case of failure
Other aspects relevant from anamnesis	Physical exploration
Quality of life evaluation	ECG-Holter 24 hours

TABLE 6. OBJECTIVES TO EVALUATE IN THE MEDICAL VISIT (OWN CREATION)

Although the responsible will have a detailed paper *(annex 8)* with all the suitable aspects to look for, they are able to decide whether to use it or not. Because, what they will have to do compulsorily is fill out the report in the online database.

A system will be set up to automatically upload the data collected by the investigators of each hospital on an excel after each visit for a later analysis.

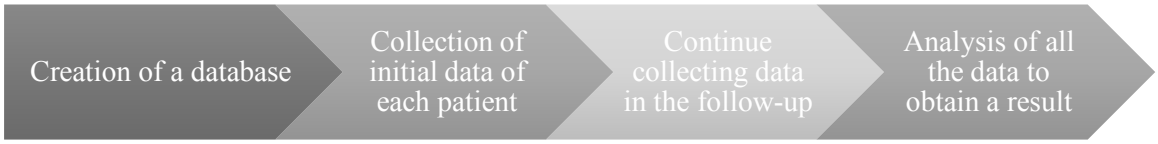

FIGURE 23. SUMMARY OF THE DATA COLLECTION (OWN CREATION)

7.7. FLOW CHART

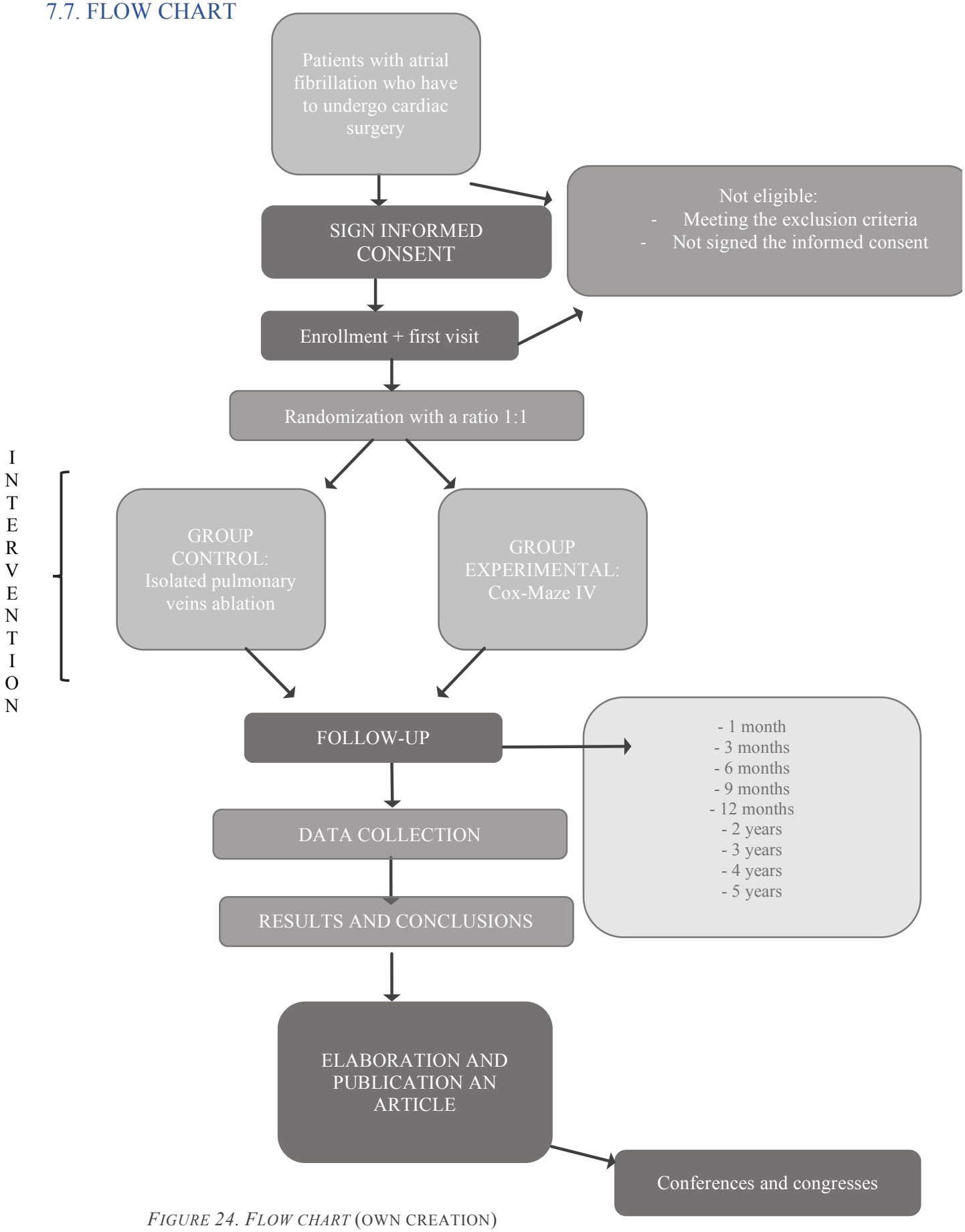

FIGURE 24. FLOW CHART (OWN CREATION)

8. STATISTICAL ANALYSIS

This part of the study will be carry out by the statistical analyzer, who will be hired to do this work in a blinded-way in order to reduce the possible bias.
The software will be SPSS and we will consider a "p" value of <**0.05** to consider significant.

Univariate descriptive analysis

We will summarize the dependent variables depending on her type of variable.

The **qualitative or categorical** variables, specifically, in our study only have nominal and dichotomous variables (*AF recurrence at 1 year, in each type, at short-term and long-term, the incidence of stroke and thromboembolism events, incidence of electrical cardioversion, management of antiarrhythmic treatment post-surgery, requirement of an implantation a pacemaker and mortality*) and one **polytomous** variable (*complications post-surgery*). So, these variables will be summarized by percentage (%), which means **proportions**.

On the other hand, the only **quantitative** variable (*Quality of life*), which it is discrete, will be summarized using **median** and **interquartile range**.

We will repeat these analyses stratifying by the independent variable (intervention), and the last analysis we will be stratified by the co-variables. Quantitative variables will be properly categorized by quartiles.

Bivariate interference

In order to analyze result we will need to realize a statistical hypothesis testing. First of all, our main variable will be tested using the **relative risk with a 95% confidence interval**.

Moreover, since we are dealing with independent data because there are two groups that we are going to compare, the statistical procedure will be different depending on the type of the result's variable that we will study.

The variable which are nominal, the difference of proportions will be tested by a **Chi-Square test** (X^2). In addition, we will have to apply the **Yates correction** because the sample size is less than 200 individuals.

Also, when in the Chi-Square contingency table there are less than 5 individuals in more than 25 percent of the cells, the **Fisher's exact test** will have to be performed.

On the other hand, the discrete quantitative variable will be tested by **T-Student test** since in our study there will be two groups with independent data, and as long as it follows a parametric distribution. Otherwise, in the event that the variable does not follow a normal or Gaussian distribution, the best option to test would be the **Mann-Whitney test**.

These analyses will be stratified by the covariates.

Multivariate analysis

One part of the statistical study will be a multivariate analysis which it allows to quantify the influence of the intervention. Otherwise, since our study is designed with randomization, we **not expect any differences between the two groups**.

But if there were, the regression is useful to predict values that the dependent variables will take from the independent one and to avoid bias due to confounding factor.
In the study are two variables independents, so the equation is a multivariate or multiple regression. And to specify more, since the dependent variables are qualitative, the **regression** is **logistic**. There is only the exception of the only quantitative variable (*QoL*) which will have a **linear regression**.

In the case of the polytomous variable (*complications post-surgery*) we will use a **multinominal regression**.

All data will be adjusted by co-variables.

The correlation measures the degree of association by a coefficient of correlation. We will use **Pearson's "r" coefficient**.

9. ETHICAL AND LEGAL CONSIDERATIONS

First of all, this protocol will be presented to **"Comitè Ètic d'Investigació Clínica"** (CEIC) from all centers participating in the study, that includes Hospital Universitari Dr. Josep Trueta, Hospital Clínic i Provincial de Barcelona and Hospital General Universitario Gregorio Marañón, in order to achieve the approval, and only after that, we will carry out the project. The committee will ensure that the proposal fits the ethical requirements and any modifications will be considered and introduced.

This clinical trial will be conducted under the ethical principles and guidelines established by **The World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects** (1964), and **The Principles of Biomedical Ethics** redacted by **Tom L. Beauchamp** and **James F. Childress** (1979).
There are 4 ethical principles due to respect and guarantee human right throughout the duration of a study:

The first in mention is the **autonomy**. It is the obligation to respect the values and personal opinions of each individual in the basic decisions that could affect them. In order to embrace that, before entering the study, we will inform to our subjects how it is going to be all process, including the intervention and the follow-up, through an **information sheet** *(annex 1-2)* due to guarantee the compliment of "*Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomia del paciente y derechos y obligaciones en materia de información y documentación clínica".*

Once read this information, together with the personal's explanation with completely understanding, and with the patient's will of accepting to be part of the project, he or she will be able to sign the **informed consent document** *(annex 3-4)*, which it is necessary and above all, the first thing to do. Besides, they will be told that they are free to refuse our invitation, either the right to **withdrawal** from the study whenever they decide *(annex 5-6).* Another important point to emphasize is the **non-influence** and **non-coercive** action of the professionals since the patients are free to decide what they want to do in any time of the duration of the trial.

All personal data will be treated, processed and collected with the purpose of assist the study, and only for that objective. It will be always guaranteed study subject's **anonymity** and **confidentiality**, according to *"Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales",* specifically the *Additional Disposition 17.2,* and the and also according *"Regulación (UE) 2016/679 del Parlamento y del Consejo Europeo, Abril 27, 2016", concerning the protection of natural people with regard to the processing of personal data"*. In order to accomplish this, the study will provide anonymity by identifying each patient with a code number.

The second principle is **benefit**, that is based in the moral obligation to act for the benefit of the persons, with a major benefit obtained than risk. As a consequence, all actions must be made thinking about what is best for our patients. In the study is reflected with the fact that every person will be treated for atrial fibrillation, and both treatment options are currently indicated as good practice. Further, if the clinical trial wields significant results, it may have optimal benefits for these patients with arrhythmia, from better quality of life to better prognosis.

Third principle to comply is the **non-maleficence**. No malicious intent is being done to the patients that participate. As we mention before, neither of the two treatment has negative consequences. In addition, the research team will be competent, trained and with the capacity to execute a reliable, valid and high-level study.

And the last one is **justice**. The significance of that aspect is the equitable distribution of the benefits avoiding any discrimination. In this study, no participant will be discriminated for their ethnicity, socioeconomic status or other aspects that may imply discrimination.

Besides, this clinical trial will under the regulation of the *"Law 14/2007, July 3rd, of Biomedical research"* which is the Spanish applicable legislation in terms of biomedical research, since this study is about **invasive procedures**. Also, it is a **low level of intervention** since both treatments which will be compared in the trail are indicated for atrial fibrillation, with no risk of affecting negatively the health of our patients (13). Because of that, it's not necessary insurance.

10. WORK PLAN AND CHRONOGRAM

10.1. Team of the project

The research team will be formed by:

- **The general coordinator**. This person will be the most responsible for all of the project. He/she will be a cardiac surgeon in the Hospital Universitari Dr. Josep Trueta since this center is the principal place of study. This person is in charge to control the procedures in all of the three centers, and do meetings with the surgeons of each hospital.

- **Principal investigator**. He or she will be a cardiac surgeon in HUJT, who will do the surgery with their team.

The general coordinator with the principal investigator of HUJT will be the most responsible, in charge of assigning the secondary researchers and the work team, the order of the procedures, the communication among all and with the analyst. Also, the elaboration and discussion of results, conclusions and the article.

- **Other surgeons**. They will be the surgeons in the Hospital Clínic i Provincial de Barcelona and Hospital General Universitario Gregorio Marañón.

- **Surgical team**: They will be anesthesists, nurses, assistants and perfusionists among others who are essential to perform cardiac surgery, together with the second assistant surgeon. One team for each center. The three teams will be trained by the same surgeon.

- **Secondary investigators**: the investigators of the three centers: HUJT, Hospital Clínic i Provincial de Barcelona and Hospital General Universitario Gregorio Marañón. They will be able to do the medical control visits, together with the providing all data to the analyst.

The investigator and the nurse will do the patient's control with the anamnesis, physical exploration and ECG-Holter 24h. The data obtained will be added to the registry.

- **Surgeon experienced**: One surgeon specialized in the ablation of PV and the Cox-Maze IV to train the different teams so that they could performed the same procedures following the same steps. In addition, he or she will train the investigators with the goal of evaluating the ECG in the same way.

- **The statistical analyzer**. We will hire a person who will carry out the statistics based on the data found in the registry, in a completely blind way since he or she will not know which patients are from one or another group.

10.2 STUDY STAGES

All procedures and activities that will happen in our study are divided in the following stages:

Stage 0: STUDY DESIGN → *August 2022 to November 2022*

It's the beginning of our project that includes the **first meeting**, the **bibliographic research** and finally, the **protocol elaboration**. The principal investigator, together with the general coordinator are the responsible for turning a simple idea into a protocol with the capacity to be able to reproduce it correctly and completely, starting from a problem that we want to resolve.

The first meeting and the bibliographic research have the use to know the viability, do the main hypothesis and establish the objective.

The protocol will be elaborated with a detailed explanation, including from the variables, their measurement and the work plan, to analytical and statistical data, as well as ethical considerations, limitations and budget.

Other step that will be developed is the **research of our team** and **assignment of tasks** to all team members, decided by the principal investigator and the coordinator, and reflected in the protocol with the chronogram *(available in the next section).* We will must contact to an operative surgeon and their team in each hospital: HUJT, Hospital Clínic i Provincial de Barcelona and Hospital General Universitario Gregorio Marañón.

These two will hold several **meetings** within 2-3 months to control the entire study and its progression.

Stage 1: ETHICAL AVALUATION AND STUDY APPROVAL → *December 2022 to January 2023*

Basically, in this period of the study we will wait until we have the **revision** and **approval** by the ethics committee of our study. As it's a multicenter project, we need the approve of the **CEIC** in each center. So, it would be the "Comitè d'Ètica d'Avaluació Clínica" of the HUJT, Hospital Clínic i Provincial de Barcelona and Hospital General Universitario Gregorio Marañón.

Any changes that this organization will recommended will be considered.

Stage 2: INITIAL COORDINATION → *February 2023 to March 2023*

In this phase, once the study is approved, the principal investigator and the general coordinator will **create a database** in order to be able to start entering data when they begin to contemplate patients and enter them into the study. Nowadays, technology is present in our life, and obviously, this study will be carried out with software and methods such as the cloud to save data, as well as the online register of the measurements in the visits.

Another step that will happen is the **first meeting** of all the team selected by the principal investigator and the coordinator. The aim is to explain with detail all the content, phases and work plan. The staff will be experienced in the area of investigation, meaning that they will be assistants, nurses, surgeons, perfusionists, anesthesists experienced, along with a statistical analyzer. Also, if that was the case to require a meeting with a specific member, it would be held to avoid any unforeseen.

As it is very important that the procedures of the two groups are performed identically to avoid biases and limitations, in addition to being done respectively in three centers, all personal participating on the surgeries will be do a **training formation** with an experienced professional who knows all techniques. Each team will perform a 10 hours course in order to do the same procedures with the same steps. Because, although all three teams will be professionals, it's important to standardize the process due to avoid limitations or confusion factors.

Also, the person in each center who will do the medical control with the ECG-Holter 24h will receive a formation course to standardize the way to evaluate this test and to obtain the results.

Stage 3: PARTICIPANTS RECRUITMENT AND DATA COLLECTION →*March 2023 to March 2028*

This phase will last **five years** with the aim to give a valid conclusion, either in a short-term as a long-term result.

For a year it will do a **patient's recruitment** by the cardiologist and surgeons involved in this study. Also, we have to take into consideration that this is an estimated time, and in the first months of work, we will be able to adjust if it necessary.

Moreover, any health professional who know the existence of this study and think that their patient could be a participant could give the **information sheet** *(annex 1-2)* and our contact number. Always without coercing or influencing, respecting the ethics aspects. Any doubt will be clarified by the investigators with total transparency and with all necessary details so the patient could make his decision with total will. This selection of patients will be made in the three hospitals.

Further, anytime that the patient wants to leave the study, they will be able, with the **withdrawn document** *(annex 5-6).*

Once the patients have firmed the **informed consent document** *(annex 3-4)*, they will have a medical control visit with the investigator in the hospital to verify if he or she meet the inclusion and exclusion criteria. If all it is correct, he or she will **become a participant**.

Once the **sample collection** is progressing, the next step will be the **randomization** obtaining two groups similar in which one intervention or another will be executed. The ratio is 1:1.

Additionally, the investigators also will do the **baseline data collection** of all the participants due to have data to compared. The investigator will provide a code number to each patient in

order to maintain the confidentiality and the anonymity. The investigators will **register** in a database all the information of the course, since the first visit to select which patients could be a participant, to every medical visit to do a follow-up. Also, in the first visit they will register the participation of the patient in her/his medical clinical history.

There are two types of intervention to treat the atrial fibrillation, apart from the surgical procedure to fix the valve disease or do a bypass to revascularize the myocardial. One is the isolated pulmonary vein ablation, and the other is the Cox-Maze IV. The patient will be given one or the other surgery depending on the group in which he/she is, who never will know what operation has been done to him/his, just like the analyzer. Instead, the surgeon and their team does since double-blinding is not possible.

All team will have **continuous meetings** to inform how it is going the process or if anything could improve or have any limitations. In any case, if it is needed of any changes it will be realized.

The **follow-up** will last five years with some controls at one month, 3, 6, 9 and a year, followed by annual medical control visit until five years post-procedure. The investigators will be the responsible to explore the patient and record the data in the software, with the help of a nurse. The report will include: history of any symptom and quality of life, any alternative method used to restore the rhythm in case of failure, a physical exploration and an ECG-Holter 24 hours to determine the rhythm.

Every six months, a **data monitoring and data quality control** will be carried out. This process is especially important to obtain data that can be used later.

Stage 4: STATISTICAL ANALYSIS AND DATA INTERPRETATION → *April 2028 to June 2028*

This will be the phase of the masked statistic who will realize an **analysis** of the data collection. Each patient will be given a code number that will include all his/her information and data collected in their visits.
Finally, this person will do a revision of all the process to give a **final result**.

Then, the principal investigator and the study coordinator will do the task of **interpretation** the analyst report with the medical knowledge and expertise with the purpose of do a conclusion and a discussion of this topic.

Stage 5: ELABORATION AND PUBLICATION → *September 2028*

The final phase, thanks to the principal investigator and the coordinator, will be to prepare the **article** and **publish** it. The clinical trial will be published on different scientific journal articles, and it will be presented to Sociedad Española de Cardiología (SEC) and the European Society of Cardiology (ESC).

In addition, we are going to hold **conferences** to export our information and be able to help improve the decision of selection technique.

10.3. CHRONOGRAM

Figure 25. Chronogram (own creation)

STAGES AND ACTIVITIES		Responsible	2022				2023								2024								2025		2026	2027	2028				
			Aug	Sep-Oct	Nov	Dec	Jan	Feb	Mar	Apr	Mar	Apr	May	Mar	Apr	May	Mar	Mar	Mar	Mar	Apr	May	Jun	Sep							
STAGE 0: STUDY DESIGN	1° meeting	PI and General Coordinator (GC)																													
	Bibliographic Research	Principal investigator (PI)																													
	Protocol Elaboration	PI and GC																													
STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL		CEIC																													
STAGE 2: INITIAL COORDINATION	Database Creation	PI and GC																													
	Research team meeting	All team																													
	Training	All team																													
STAGE 3: PARTICIPANT'S RECRUITMENT AND DATA COLLECTION	Patient's recruitment	Cardiologist and surgeons in their consults																													
	Sample Randomization	Investigators																													
	Baseline data collection	Investigators																													
	Intervention	Surgeons and their team																													
	Coordination meeting	All team																													
	Follow-up	Investigators																													
	Data monitoring and quality control	Investigators																													
	Record of data	Investigators																													
STAGE 4: STATISTICAL ANALYSIS AND DATA INTERPRETATION	Statistical analysis	Statistic																													
	Final statistical analysis	Statistic																													
	Data interpretation	PI and GC																													
	Data discussion	PI and GC																													
STAGE 5: FINAL ARTICLE ELABORATION AND PUBLICATION OF THE RESULTS	Article redaction	PI and GC																													
	Article publication	PI and GC																													
	Congress	PI and GC																													

11. BUDGET

The expenses necessaries to carry out the study are the consecutives ones. They are detailed below but can also be seen in the table *(table 7)* which are in the end of the section.

Personnel expenses

The health care professionals who will attend the patients and do the interventions in the operation room are part of the National Health System. Therefore, this will not add extra cost. The investigator and the nurse who do the medical visits to follow-up are also part of the public health. Their reward will be the scientific progress and satisfaction for improving the quality of the patients and the health of the population.

Otherwise, it will be necessary to contract and pay a **surgeon specialized** to do the training to all of the surgical team and investigators. So, this salary will be 50€/hour and approximately 30 hours of formation, which is 10 hours in each hospital. The responsible of the **formation** will be who will move into Barcelona or into Madrid to teach the surgical team in those hospitals. We approximately calculate 105 km between HUJT and Hospital Clínic i Provincial de Barcelona, at 0,19€/km with a diet supplementation (20€) for each day. And on the other hand, to arrive to Hospital General Universitario Gregorio Marañón, he/she will take an AVE that have a price of approximately 130€. This cost for each day of formation (10 hours) with their respective diets will be added to the budget. So accordingly, the final price that has the surgeon trainer is 3.799€.

It will be necessary hire a qualified **statistical** to analyze the data collection and do the statistical part. The salary will be 35€/ hour and approximately 100 hours of work.

In the third part of the research, it will do a **data validation and quality control** of all the data collected in the study, in case that there is any incident that can be corrected and modified. This task will be carried out by an external company and we estimate a service of 3.960 € (paid at 30€ per patient).

Material

The equipment necessary to do the interventions and to do the medical visit have no expense since it's a routine practice in a clinical patient with atrial fibrillation condition. So, since operation room with surgical material to electrocardiograph and consults have no cost.

But the material which have a cost is the **printing**. The total cost is about 90 €.

It is necessary to print copies of the informed consent document *(annex 3-4)*, the information sheet *(annex 1-2)* and the withdrawn consent *(annex 5-6)*. Also, we will print additional information sheet to give to all the professionals in consults or in the hospitals with the objective to inform them. As a consequence, they will be able to inform their patients.

Also, we need copies for the case report form *(annex 8)* to fill out by the investigators during the control visits. Although, the valid data will be in the cloud, in the software designed for the study, we recommended to the investigators to write the information during the interview and the exploration in the sheet and, then, introduce it in the database.

We will have to pay the **license** of software program with an approximately price of 500 €.

Insurance Policy

In the insurance topic, we don't have to pay for anything since our clinical trial is a low risk type, so it's no needed for covered insurance.

Fees

In this section, the cost is for **publication**, that means open access publication, revision, edition, formatting, layout, graphic design and preparations of the digital metadata. We calculate a number close to 2.000€.

Other aspect to consider is the English **translator** specialized in medical language to traduce this study in other languages as Spanish, and the cost would be about 1.000€.

We will do **conferences and congresses**, so we have to take into consideration the payment of inscription, travels, accommodation and diets. The responsible for this kind of activity are the study coordinator and the principal investigator. If it's a national congress the price would be approximately 1.000€, but if it is international the price is higher. So, we consider that we will do one of each, so the price total would be about 3.000€.

	Expenses	Cost per units	Number of units	Subtotal
Personnel expenses	Training surgeon	Formation: 50 €/hour Diet: 20€ Displacement: - Barcelona: 0,19€/km x (105km x 2) - Madrid: 130€	30 hours (10 hours in Girona, 10 hours in Barcelona and 10 hours in Madrid) 10 trips to Barcelona 10 trips to Madrid	1.500€ 600€ 399€ 1.300€
	Statistical	35€/hour	100 hours	3.500 €
	Data validation and quality control	30€/patient	132 patients	3.960 €
Material	Printing costs: Information sheet, Informed consent document, withdrawn consent and case report **It will be possible to make more copies if it is necessary*	0.05 €/page	200 copies of information sheet and informed consent document and case report **150 additional copies of information sheet for other professionals* **50 copies of withdrawn consent*	90 €
	License of software program			500€
Insurance				0 €
Fees	Publication costs			2.000 €
	Translator			1.000 €
	Conferences and congresses		National congress International congress	3.000 €
			TOTAL:	17.849 €

TABLE 7. BUDGET (OWN CREATION)

12. STUDY LIMITATIONS

The clinical trial has limitations for which we will implement a variety of methods and techniques to minimize them.

Selection bias

The first limitation is based on the **selection**. As our study is using a non-probabilistic sampling method, it is known that there is a possibility to obtain a non-representative sample as the subjects do not have the same chance to be selected. However, we are using a **consecutive technique** because is the most effective to reduce bias in all non-probabilistic methods.
The medical professionals in the hospital and consults are the responsible to invite the patients to study in their criteria, so this could generate a selection bias. For prevent that, our **inclusion and exclusion criteria** are detailed and designed to assume that all participants have the same characteristics.

The second bias in the selection phase is the **participation rate**, as we assume that with one year of recruitment will be enough to achieve an ideal number to start the intervention. Otherwise, if it will not happen, we could lengthen the selection period. Another strategy to improve this error would be to incorporate another study center, since we would have no problems doing this because our study is **multicenter**.

Also, another limitation would be a higher rate of lost patients, which cause an **attrition bias**. However, the data of the lost patients will be used as data equivalent to the living patients, since the last value will be the corresponding one for the controls that cannot be done, and this is what is known as **"analysis by intention to treat".** Despite of, we prevent this by setting a fairly high rate compared to what we think is going to happen. We assume a high value of **10%** to avoid this bias.

Methodological bias

In the intervention period, it could appear the **detection bias** and the **realization bias** as we use a simple-blinded method. Only the surgeon will know which patients are in the control group and which are in the experimental group. On the other hand, neither the patient, nor the

researchers who perform the control and nor the analyzer will know in which group each one belongs. The optimum would be triple-blind, but this is impossible since the surgeon needs to know what operation he is performing, so we used a **simple-blind**, and **observer-blind** technique respectively.

The limitation based on the **differences** of the surgeons and their performances have already been taken into account, so the **training** to standardize all the steps should be good enough to minimize this risk. In addition, the training is also for the investigators who do the medical control, so there is agreement among them when it comes to seeing the electrocardiogram.

Personal bias

To add information that supports in reducing the previous limitation, the investigators and all the professional who participate in the study will have **experience** in this area and receive an extending training to ensure the process. In all centers only qualified personnel will be recruited.

Confounding bias

First of all, I have to mentioned the fact that we don't expect any differences between both groups since our clinical trial will use **randomization**. We accepted these variables, called co-variables, in our study and they will be distributed equally in both groups. Moreover, the design of this randomization includes a **stratification** process by the underlying pathology that leads the patient to cardiac surgery.

Another prevention action used in this study in the **exclusion criteria**.

Otherwise, if there is a case scenario of existing confounding factors that could influence the outcome, we will have technique to minimize the effect. The **multivariate** part of the statistical analysis we include these confusion data such as age, sex, previous function and severity among others, which will adjust the result, indicating exclusively the risk attributable to each of them.

13. FEASIBILITY

This study is feasibly since we have all needing to carry out this specifically research:

- A **location** to realize the intervention and the visit controls, defined as a hospital, and our study have three centers: **HUJT**, **Hospital Clínic i Provincial** de Barcelona and **Hospital General Universitario Gregorio Marañón**. Also, in order to be a suitable place, it must have an operating room adapted for cardiac surgeries with all the necessary material, and these three hospitals have it.

- A suitable **sample** to realize the study with a large percentage of a result which will be significant. We calculate the size with an application based on statistical.

- Adequate and sufficient **staff** to do all the process. We have an investigator, surgeons with their surgical team and an analyst to do the statistical part, and all of that will be a group of experts with research experience.

- We will have an **economic resource** to face all possible costs which includes a training surgeon and a statistical, as well as pay all necessary material and publication cost.

- Finally, one relevant aspect is the fact that this study could improve our society and do an **impact** of the national health system, and this project justifies this because it's a prevalent disease with great association with strokes, with mortality and adverse effects that disappear when the rhythm is controlled.

14. IMPACT ON NATIONAL HEALTH

Currently, it has been demonstrated that the atrial fibrillation and its management is not optimal, nor controlled by the professionals. Even more, it is expected that the prevalence will increase much more, and therefore, the **severity** of the situation.

Before has been mentioned the reason why atrial fibrillation is **importance** and why is so relevant to improve the control of the rhythm. There is a public need to be able to control this arrhythmia since it implies a worse quality of life, apart from the risk of stroke that it entails.

And for all this, this study has to be carried out, for all that it will involve. It will have an **impact on the national system,** with an improvement in the management, treatment and prognosis of patients, including their complications and thromboembolic events.

Additional, this may arise other benefits, apart from the **better patient's quality of life**:

- **Less economic cost** in health system since stroke is one of major causes of economic burden.
- **Less mortality and less complications** since the rhythm will be controlled. So, the disease burden will be inferior.
- No more additional operation risk in the concomitantly cardiac surgery.
- **Better efficacy** in avoid recurrence and failure of the treatment.

To the end, this study could improve the life of the patient with atrial fibrillation and, consequently, everyone around them.

15. PERSONAL REFLECTION

In my opinion, this work project could arise several **benefits** such better management, better future health and less comorbidities and complications to these patients who are elderly and a diagnose of arrhythmia may worse their life style.

Currently, both techniques are indicated for atrial fibrillation and the principal reason to not add this procedure in order to fix the arrhythmia in concomitantly cardiac surgery is because surgeons think that it is not necessary. So, if this study reveals a significant outcome with controlling rhythm, I hope that this may change the conventional procedures with adding this technique.

However, surgeons did realize the occlusion and exclusion of LAA due to its simplicity and rapidity, and sometimes, the ablation of pulmonary veins. But it is not enough to avoid recurrence since there are other ectopic focus outside the pulmonary veins.
Therefore, if the study supports my hypothesis, it will be a **good decision** as a surgeon to perform a slightly longer procedure but with such proven and true efficacy that they cannot avoid doing it.

The final issue that I will address is the association with stroke and thromboembolism events which are almost the highest one. Consequently, if there exist an improvement of maintaining sinus rhythm, also there will be a less stroke episodes. And it is well known than stroke is one of the major causes of **incapacity** and disease **burden** worldwide.

16. CONFLICT OF INTERESTS

We declare that the results that we will obtain will be published transparently. Also, we announce that any investigator or author of this study have conflict of interest.

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18. ANNEXES

ANNEX 1 – Protocol information sheet in catalan

FULL D'INFORMACIÓ PER AL PACIENT

TITOL DE L'ESTUDI:
CENTRE:

Estimat pacient,
Ens dirigim a vostè per informar sobre un estudi d'investigació anomenat *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial",* en el qual se li convida a participar.
Aquest estudi ha estat aprovat pel Comitè d'Ètica d'Investigació Clínica pel centres organitzadors, els quals són l'Hospital Universitari Dr. Josep Trueta de Girona, l'Hospital Clínic i Provincial de Barcelona i el Hospital General Universitario Gregorio Marañón a Madrid.

L'objectiu d'aquesta fulla d'informació és permetre donar-li tota la informació necessària, suficient i comprensible pel fet de que vostè sigui capaç d'avaluar i jutjar si decideix participar-hi.
Per tant, si vostè es vol llegir aquesta fulla informativa, a posterior li aclarirem qualsevol dubte que pugui tenir. A més, també pot consultar-ho amb qualsevol persona si vostè volgués i ho considerés oportú.

Ha de saber que la participació en aquest estudi és totalment voluntària i que, per tant, pot decidir si participar-hi o no, sense rebre cap perjudici en cas d'una negativa. També ha de tenir clar que en qualsevol moment pot canviar d'opinió i decidir retirar-se sense cap explicació.

Quin és el motiu d'aquest estudi?

La fibril·lació auricular és l'arritmia més prevalent a nivell mundial, i s'espera que en els següents anys augmenti el nombre de casos pel fet de la existència d'un actual i millorat

"screening" i de la millor precisió per diagnosticar persones asimptomàtiques. A més, és una malaltia que augmenta clarament amb l'edat, conjuntament amb influència d'altres factors com el sexe, factors de risc cardiovasculars o patologies subjacents.

Té un maneig multidisciplinar on inclou, en primer lloc, evitar fenòmens tromboembòlics com l'ictus, ja que s'ha establert una gran associació, fet que ocasiona que sigui tant important tractar i controlar aquesta arrítmia. Es pot tractar amb diversos procediments, ja sigui teràpia farmacològica, ablació o cirurgia. Aquesta última està agafant èmfasis degut a una tècnica anomenada Cox-Maze IV on s'està demostrant una gran eficàcia.

Així doncs, el nostre projecte es basa en valorar si, aquelles persones que tenen indicació quirúrgica d'entrar a quiròfan per una cirurgia cardíaca (patologia valvular d'origen mitral o aòrtic o isquèmia) i, a més, presenten fibril·lació auricular, els hi resulta un benefici significatiu el fet d'utilitzar aquest nou procediment quirúrgic envers a una ablació simple.

Per què la convidem a vostè?

La convidem a participar-hi ja que sembla que pot complir els criteris d'inclusió i excloure els d'exclusió, els quals són els següents:

<u>Criteris d'inclusió:</u>

- Pacient entre 18 i 75 anys
- Diagnòstic de fibril·lació auricular
- Indicació d'operar-se de cirurgia cardíaca: ja sigui patologia valvular aòrtica o mitral, o una revascularització miocàrdica (bypass coronari)
- Disposició i capacitat de seguiment de 5 anys

<u>Criteris d'exclusió:</u>

- Contraindicació d'entrar a quiròfan
- Previ tractament per a la fibril·lació auricular, ja sigui farmacològic, ablació o cardioversió
- Situació d'emergència (en aquest cas es procedeix a una cardioversió immediata)

- No disposició d'una historia clínica completa

- No capacitat de seguiment durant l'estudi

Què haig de fer si decideixo participar?

Davant de la decisió de participar en l'estudi, recordant-li que sempre és voluntària i si decideix que no, no li afectarà en la seva assistència per part de l'investigador ni rebrà perjudicis.

Primerament haurà de signar el consentiment informat, i a posterior, els investigadors recolliran les dades personals i li programaran una visita amb l'objectiu d'explicar tot el procediment de l'estudi amb la verificació dels criteris d'inclusió i exclusió per decidir finalment si pot ser un participant. Aquestes dades seran anònimes.

Què passa amb la meva informació i les meves dades?

Com hem dit anteriorment, totes les dades i informació recollida en l'estudi serà confidencial segons el "Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, del 27 de abril del 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos", i la "Ley Orgánica 3/2018 de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".

Cada pacient obtindrà un número d'identificació amb un codi per garantir l'anonimat.

En la publicació de resultats de l'article i, conjuntament, amb les conferències i congressos, les dades continuaran sent tractades de forma anònima.

Obtindré algun benefici per participar?

Al tractar-se d'un assaig clínic amb l'objectiu de generar coneixement no s'obtindrà cap benefici, ni econòmic ni cap altra mena de compensació. D'altra banda, sí que contribuirà a l'avanç científic i al benefici social.

Quins riscs o inconvenients hi ha al participar?

Les dues tècniques que es poden realitzar a la intervenció són quirúrgiques, per tant, sempre hi ha el simple fet del risc quirúrgic. Tot i així, l'estudi no comporta cap risc afegit, ja que són dues tècniques indicades i que s'utilitzen actualment a la pràctica clínica. A part, el nostre personal té experiència en aquest àmbit amb alta formació.

Moltes gràcies per llegir la fulla informativa. Si té alguna pregunta no dubteu en realitzar-la a l'investigador. Si decideix participar a l'estudi, se li entregarà una còpia d'aquest full i del consentiment informat.

(firma)

Coordialment

Paula Martí Fructuoso

Principal Investigadora de l'estudi *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial",*

ANNEX 2 – Protocol information sheet in spanish

HOJA INFORMATIVA PARA EL PACIENTE

TÍTULO DEL ESTUDIO:
CENTRO:

Querido paciente,
Nos dirigimos a usted para informarle sobre un estudio de investigación llamado "*"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial",* en el cual se le invita a participar.
Este estudio ha estado aprobado para el "Comitè d'Ètica d'Investigació Clínica" por los centros organizadores, los cuales son el Hospital Universitari Dr. Josep Trueta en Girona, el Hospital Clínic i Provincial de Barcelona y el Hospital General Universitario Gregorio Marañón en Madrid.

El objetivo de esta hoja informativa es permitir darle a usted toda la información necesaria, suficiente y comprensible con el fin de que usted sea capaz de avaluar y juzgar si decide participar.

Por tanto, si usted se quiere leer toda la hoja informativa, a posterior le aclararemos cualquier duda que pueda tener. Además, también puede consultarlo con cualquier persona si usted desea y lo considera oportuno.

Tiene que saber que la participación en este estudio es totalmente voluntaria, y que, por tanto, puede decidir si participar o no, sin recibir ningún perjuicio en caso de decir que no. También tiene que tener claro que en cualquier momento puede cambiar de opinión y decidir retirarse sin dar explicaciones.

Cuál es el motivo de este estudio?

La fibrilación auricular es la arritmia más prevalente a nivel mundial, y se espera que en los siguientes años aumente el número de casos por el simple hecho de la existencia de un actual y mejorado "screening" y de la mejor precisión para diagnosticar las personas asintomáticas. Además, es una enfermedad que aumenta claramente con la edad, conjuntamente con la influencia de otros factores como el sexo, factores de riesgo cardiovascular o patologías subyacentes.

Tiene un manejo multidisciplinar donde incluye, en primer lugar, evitar fenómenos tromboembólicos como el ictus, ya que se ha establecido una gran asociación, hecho que causa que sea tan importante tratar y controlar esta arrítmia. Se puede tratar con varios procedimientos, ya sea terapia farmacológica, ablación o cirugía. Esta última está en énfasis debido a una técnica llamada Cox-Maze IV, donde se está demostrando una gran eficacia.

Así, nuestro proyecto se basa en valorar si, aquellas personas que tienen indicación quirúrgica de entrar a quirófano por una cirugía cardíaca (patología valvular de origen mitral o aórtica o isquemia), y además, presentan fibrilación auricular, les resulta un beneficio significativo el hecho de utilizar este procedimiento quirúrgico nuevo en lugar de una ablación simple.

Porqué la invitamos a usted?

La invitamos a participar ya que parece que pueda cumplir los criterios de inclusión, y excluir los de exclusión, los cuales son los siguientes:

<u>Criterios de inclusión:</u>

- Paciente entre 18 i 75 años
- Diagnóstico de fibrilación auricular
- Indicación de operarse de cirugía cardíaca: ya sea patología valvular aórtica o mitral, o una revascularización miocárdica (bypass coronario)
- Disposición y capacidad de seguimento de 5 años

Criterios de exclusión:

- Contraindicación de entrar a quirófano
- Tratamiento previo para la fibrilación auricular, ya sea farmacológico, ablación o cardioversión
- Situación de emergencia (en este caso se procede a una cardioversión inmediata)
- No disposición de una historia clínica completa
- No capacidad de seguimento durante el estudio

Qué tengo que hacer si decido participar?

Delante de la decisión de participar en el estudio, recordando de antemano que la participación es voluntaria y que si decide no participar, no le afectará en su asistencia por parte del investigador ni recibirá perjuicios.

Previamente tendrá que firmar el consentimiento informado, y a posterior, los investigadores recogerán sus datos personales y se le programará una visita con el objetivo de explicarle todo el procedimiento del estudio con la verificación de los criterios de inclusión y exclusión para decidir, si finalmente, puede ser un participante. Estos datos serán anónimos.

Qué va a pasar con mi información y mis datos personales?

Como hemos dicho anteriormente, todos los datos y información recolectada en el estudio será confidencial siguiendo el "Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, del 27 de abril del 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos", y la "Ley Orgánica 3/2018 de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".

Cada paciente obtendrá un número de identificación con un código para garantir el anonimato.

En la publicación de los resultados del artículo, y conjuntamente, con las conferencias y congresos, los datos continuaran siento tratados de forma anónima.

Voy a obtener algún beneficio por participar?

Al tratarse de un ensayo clínico con el objetivo de generar conocimiento, no se obtendrá ningún beneficio, ni económico ni de ninguna otra forma de compensación. De otra banda, sí que contribuirá al progreso científico y al beneficio social.

Qué riesgos o inconvenientes existen al participar?

Les dos técnicas que se realizan en la intervención son quirúrgicas, por tanto, siempre hay el simple hecho del riesgo quirúrgico. Aparte de eso, el estudio no conlleva ningún riesgo añadido, ya que son dos técnicas indicadas y que se utilizan actualmente en la práctica clínica. Además, nuestro personal tiene experiencia en este ámbito con alta formación.

Muchas gracias por leer esta hoja informativa. Si tiene alguna pregunta no dude en realizarla al investigador. Si decide participar en el estudio, se le entregará una copia de esta hoja conjuntamente con una copia del consentimiento informado.

(firma)
Cordialmente
Paula Martí Fructuoso
Principal Investigadora del estudio *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial"*

ANNEX 3 – Informed consent document in catalan

FORMULARI DE CONSENTIMENT INFORMAT

Consentiment de l'estudi *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial"* explicat i donat per l'investigador responsable _____ amb DNI/Passaport nº _____, en el centre _____

Sr/Sra._____ amb DNI/Passaport nº_____, amb domicili a _____, actuant en el meu propi nom i sent major d'edat,

MANIFESTO QUE:

1. Accepto participar de forma voluntària en l'estudi *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial"*.
2. He llegit la Fulla d'Informació, comprenent tots els beneficis i riscos que pot comportar, juntament amb la importància que contribuiria a la ciència i a la medicina. He rebut una informació adequada i he pogut aclarir qualsevol dubte de forma satisfactòria.
3. Afirmo que la meva participació és voluntària i que em puc retirar o sol·licitar que retirin les meves dades i/o mostres sempre que vulgui, sense donar cap explicació.
4. He estat informat/da per l'investigador en que consisteix la meva implicació en l'estudi: assistir a les visites programades i seguir amb les pautes indicades pels doctors de l'estudi.
5. Dono permís per la utilització de les meves dades i de la meva història clínica pels investigadors per fins relacionats amb l'estudi.

6. Dono el meu permís pel fet de que els investigadors contactin amb mi novament si sóc apte per entrar a l'estudi a través del telèfon mòbil. Seguidament indico el meu número de contacte: _____
7. Dono permís per ser informat, a través dels doctors, sobre els resultats de les proves i intervencions realitzades durant l'estudi i que siguin rellevants per la meva salut.
8. Dono permís per que els investigadors guardin els resultats i les dades de seguiment en el registre corresponent amb el fi d'analitzar-les per l'estudi.
9. Comprenc que no rebré beneficis directes per la meva participació en aquest estudi i que no rebré cap benefici econòmic en el futur.
10. Comprenc que la informació de l'estudi serà confidencial i que cap persona no autoritzada tindrà accés a les dades.
11. Sé como posar-me en contacte amb els investigadors de l'estudi
12. Declaro que se m'ha entregat una còpia del Full d'Informació i una còpia d'aquest document firmat.

Firmes

Participant	*Persona de l'estudi responsable de donar el consentiment*

Data (dia/mes/any):

Contacte: En el cas de necessitar contacte amb els investigadors de l'estudi pot trucar al telèfon XXXXXXXXX per parlar amb l'investigador principal: PAULA MARTÍ FRUCTUOSO

Aquest document es signarà per duplicat quedant-se una còpia l'investigador i una altra el pacient.

ANNEX 4 – Informed consent document in Spanish

FORMULARIO DEL CONSENTIMENTO INFORMADO

Consentimento del estudio *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial"* explicado y dado por el investigador responsable _____ con DNI/Pasaporte nº _____, en el centro _____

Sr/Sra._____ con DNI/Pasaporte nº_____, con domicilio a _____, actuando con nombre propio y siendo mayor de edad,

MANIFESTO QUE:

1. Acepto participar de forma voluntaria en el estudio *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial"*.
2. He leído la Hoja Informativa, comprendiendo todos los beneficios y riesgos que puede comportar, junto con la importancia que contribuiría a la ciencia y a la medicina. He recibido una información adecuada i he podido aclarar cualquier duda de forma satisfactoria.
3. Afirmo que la mi participación es voluntaria i que puedo retirarme o solicitar que retiren mis datos y/o muestras siempre que quiera, sin dar explicaciones.
4. He sido informado/a por el Investigador en que consiste mi implicación en el estudio: asistir a las visitas programadas y a seguir con las pautas indicadas por los doctores del estudio.
5. Doy permiso para utilizar mis datos y de mi historia clínica por los investigadores con fines relacionados con el estudio.
6. Doy mi permiso para el hecho de que los investigadores contacten conmigo nuevamente si soy apto para entrar en el estudio a través de mi teléfono móvil. Seguidamente, indico mi número de contacto: _____

7. Doy permiso para ser informado, a través de mis doctores, sobre los resultados de las pruebas e intervenciones realizadas durante el estudio, y que sean relevantes para mi salud.
8. Doy permiso para que los investigadores guarden mis resultados y los datos de mi seguimiento en el registro correspondiente con el fin de analizarlas para el estudio.
9. Comprendo que no voy a recibir beneficios directos por participar en este estudio y que no recibiré ningún beneficio económico en el futuro.
10. Comprendo que la información del estudio será confidencial y que ninguna persona no autorizada tendrá acceso a mis datos.
11. Sé cómo ponerme en contacto con los investigadores del estudio.
12. Declaro que se me ha entregado una copia de la Hoja Informativa y una copia de este documento firmado.

Firmas

Participante	*Persona del estudio responsable de dar el consentimento*

Fecha (día/mes/año):

Contacto: En el caso de necesitar contacto con los investigadores del estudio puedes llamar al teléfono XXXXXXXXX para hablar con el investigador principal: PAULA MARTÍ FRUCTUOSO

Este documento se signará por duplicado quedando una copia para el investigador y otra para el paciente.

ANNEX 5 – Withdrawn consent in catalan

REVOCACIÓ DEL CONSENTIMENT

Sr/Sra. _____ amb DNI/Passaport nº_____, revoco el consentiment informat en la participació de l'estudi *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial"*.
Firmes

Participant	*Persona de l'estudi responsable de donar el consentiment*

Data (dia/mes/any):
Contacte: En el cas de necessitar contacte amb els investigadors de l'estudi pot trucar al telèfon XXXXXXXXX per parlar amb l'investigador principal: PAULA MARTÍ FRUCTUOSO

Aquest document es signarà per duplicat quedant-se una còpia l'investigador i una altra el pacient.

ANNEX 6 – Withdrawn consent in spanish

REVOCACIÓN DEL CONSENTIMENTO

Sr/Sra. _____ con DNI/Pasaporte nº_____, revoco mi consentimento informado en la participación del estudio *"A comparative study on the efficacy of the Cox-Maze IV procedure versus pulmonary veins ablation for atrial fibrillation in concomitantly cardiac surgery: a multicenter, randomized and controlled clinical trial"*.

Firmas

Participante	*Persona del estudio responsable de dar el consentimento*

Fecha (día/mes/año):

Contacto: En el caso de necesitar contacto con los investigadores del estudio puede llamar al teléfono XXXXXXXXX per hablar con el investigador principal: PAULA MARTÍ FRUCTUOSO

Este documento se signará por duplicado quedando una copia para el investigador y otra para el paciente.

ANNEX 7 –SF-36 Questionnaire (quality of life)

Medical Outcomes Study Questionnaire Short Form 36 Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please circle the number that best describes your answer.

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5
2. Compared to one year ago,	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
(Circle One Number on Each Line)

	Yes, Limited a Lot (1)	**Yes, Limited a Little (2)**	**No, Not limited at All (3)**
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3

g. Walking **more than a mile**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?
(Circle One Number on Each Line)

	Yes (1)	**No (2)**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(Circle One Number on Each Line)

	Yes	**No**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks?	
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. **(Circle One Number on Each Line)**

9. How much of the time during the **past 4 weeks** . . .

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (Circle One Number)	
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you. (Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

ANNEX 8 –CASE REPORT FORM FOR THE FOLLOW-UP

FOLLOW-UP MEDICAL VISITS
CASE REPORT FORM

Code number of the patient: _____

Nº of session: _____

Time since the intervention (months-years): _____

Hospital center: _____

Investigator's name: _____

1st PART: ANAMNESIS

Vital constants:

Any symptom: _____

Quality of life with SF-36: _____

Complications: _____

Documentation of:

Cardioversion ☐ Drug therapy ☐ Implantation of pacemaker ☐

Others:

2nd PART: PHYSICAL EXPLORATION

General exploration:

_____

Cardiac examination:

_____

_____

_____

3rd PART: ECG-HOLTER 24 HOURS

Results:

_____

_____

_____

** *You have to attach the electrocardiographic report*

ADDITIONAL PART:

ECHOCARDIOGRAPHY: _____

BLOOD ANALYSIS: _____

OTHERS: