Universitat de Girona

COMPARISON OF PROGNOSIS BETWEEN PATIENTS WITH ACUTE CORONARY SYNDROME AND NON OBSTRUCTIVE CORORNARY ARTERY DISEASE WITH THOSE WITH SIGNIFICANT CORONARY ARTERY DISEASE: A COHORT STUDY

Final Degree Project

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Acknowledgements:

To my mother

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1. Abbreviations

MI: Myocardial infarction

NOCAD: No obstructive coronary artery disease

OCAD: Obstructive coronary artery disease

ACS: Acute coronary syndrome

ECG: Electrocardiogram

TCM: Tako-Tsubo cardiomyopathy

SCAD: Spontaneous coronary artery dissection

KS: Kounis Syndrome

CMR: Cardiac magnetic resonance

OCT: Intracoronary optical coherence tomography

IVUS: Intravascular ultrasounds

NO: Nitric Oxide

CVRF: Cardiovascular risk factors

MACE: Mayor Adverse Cardiac Events

2. Abstract

Introduction: The universal definition of myocardial infarction (MI) indicates that MI is diagnosed when there is a rise and fall of cardiac biomarkers such as troponin in combination with ischemic symptoms, ischemic ECG changes, imaging evidence of loss of viable myocardium, or identification of an intracoronary thrombus. Coronary obstruction is not required according to this definition. Angiography in patients with myocardial infarction most commonly reveals one or more significantly narrowed coronary arteries, but a substantial minority of patients with spontaneous MI have no obstructive coronary artery disease (NOCAD) at angiography. In the last years several studies have been done to determine if, as it is said in clinical practice, these patients have a favourable prognosis in comparison with significant occluded coronary arteries.

Objective: The goal of this study is to determine the long-term prognosis of patients who suffer from a myocardial infarction and do not have significant obstructive coronary artery disease in comparison with patients who undergo myocardial infarction and have obstructive coronary artery disease, in Catalonia, using ultrasensitive troponins for the diagnostic.

Design: A Multi-centric study in the cardiology department of *Hospital Universitari Doctor Josep Trueta (Girona), Hospital Sant Joan de Deu (Barcelona), Hospital Germans Trias i Pujol de Badalona (Badalona), Hospital del Mar (Barcelona).*

Methods: 1328 patients undergoing ACS will be submitted to a coronary angiography. In those with no culprit lesion in coronary arteries, intracoronary optical coherence tomography (OCT) will be performed in order to determine the aetiological mechanism of myocardial infarction, apply a suitable treatment and to evaluate the prognosis at one year. This prospective cohorts study will be realised in 3 years at the area of Catalonia (Spain).

Key words: Myocardial infarction, Acute coronary syndrome, No obstructive coronary artery disease, Prognosis, Intracoronary optical coherence tomography, Ultrasensitive troponins.

3. Introduction

<u>DEFINITION</u>

Ischemic heart disease has always been related to atherosclerosis, which is a systemic condition that affects the arteries of the body. When coronary arteries are affected, it can produce an obstruction causing a myocardial infarction. Nevertheless, not all myocardial infarctions are caused by atherosclerosis. A significant proportion of patients who suffer heart attack, around 7-12% (1–4), do not have significant damage in the subsequent coronary angiography. Even though it has been said that these patients have a favourable prognosis compared to patients affected by coronary artery disease, there is an unclear conclusion about this matter (5–7). That is why we propose this study. Determining the prognosis of patients who suffer a MI and with NOCAD can improve the knowledge of the disease as well as optimizing the management of the disease in our population.

<u>EPIDEMIOLOGY</u>

Despite improvements in diagnosis and therapy over the last years, mortality among patients with acute coronary syndrome is still high. Cardiovascular diseases are the main global cause of death. An estimated 17.5 million people died from cardiovascular disease in 2012, representing 31% of all global deaths. Of these deaths, 7.4 million were due to coronary heart disease. The mortality rate of ischemic heart disease has been decreasing in the last 4 decades. However, it remains being the cause of one-third of deaths in people aged over 35 years. Moreover, one half males and one-third of females will suffer some symptoms of ischemic heart diseases in the USA. In Europe, calculations have shown that, 4 million people death because of heart attack, which implies 47% of deaths in Europe. Additionally, this means a total cost of 196.000 million euros, around 54% of the total health inversion (8).

A significant proportion of patients with ACS, between 7-12% depending on the series, have no culprit lesion in the subsequent coronary angiography (1–4). We can define two types of ACS with no obstructive coronary artery disease (NOCAD). Patients with normal coronary arteries, which are defined as healthy epicardial arteries, without irregularities or stenosis in coronary angiogram. And patients with no significant coronary artery disease, which is defined as an obstruction of less than 50% the lumen. The incidence of both groups are about 1-5% and 10-14% of patients undergoing ACS, respectively. However, in this survey, both groups will be considered as one, as it is known that the two types of patients have the same prognosis at short and long term (4). Patients with ACS and normal or near normal coronary arteries are

most frequently younger people than obstructive coronary artery disease (OCAD) patients, specially women and black race (1,9–11).

ETIOLOGY

Atherosclerosis has always been the main cause of myocardial infarction (12,13). It produces alterations in the vessel wall resulting in atherothrombotic plaque. These atheroma plaques develop due to some conditions such as smoking, Diabetes Mellitus, dyslipidaemia, high blood pressure or obesity. These risk factors injure the wall vessel causing an endothelial dysfunction. LDL molecules accumulates in subendothelial area, where they are converted convert into Foam cells, and causes inflammation mediated by macrophages. Thus, atheroma plaque grows and it can produce ischemic events. Ischemic myocardial affection can be produced by two mechanisms: firstly, a chronic occlusion may produce myocardial affection. But the slow reduction of coronary flow, due to a chronic event, might be compensated with other coronary vessels contribution. Secondly, an acute event, which will be caused by erosion or disruption of atheroma plaques producing an ACS with an infarcted area. In both situations, subsequent coronary angiography will be pathognomonic, and can show one or several occluded arteries, that indicates atherosclerosis aetiology. Therefore, doing an exhaustive clinical interview about cardiovascular risk factors is very important, in order to guide us to atherosclerosis aetiology or other mechanisms.

Nevertheless, ACS is not always associated with the detection of angiographic significant lesions in epicardial coronary vessels (Annex 1.1). The aetiology in patients undergoing MI with NOCAD can be different (14,15). Several mechanisms can produce flow restriction and ischemia without significant obstruction of coronary vessels:

Plaque erosion and plaque disruption:

This is the most frequent mechanism (14,15). A transient occlusive thrombosis, as atherosclerotic MI mechanism, may occur, in non-significant atheroma plaque, with spontaneous thrombolysis or that vasospasm and/or embolization of atherothrombotic material may cause infarction. In support of this hypothesis is the well-known limitation of conventional angiography. This technique only demonstrates plaque that encroaches on the lumen. Thus, other techniques, such as OCT or Intravascular ultrasounds (IVUS) can demonstrate this mechanism as a frequent cause of MI with NOCAD (Annex 1. Figure 2).

Calcified nodule:

A minority of plaques with thrombosis exhibit nodular calcification that protrudes into the lumen. These could be chronic plaques that have developed a calcium cape (14)(Annex 1. Figure 2).

Vasospasm:

Coronary artery vasospasm is an important cause of chest pain syndromes that can lead to MI, ventricular arrhythmias, and sudden death. It also plays a key role in the development of atherosclerotic lesions. Unlike patients with typical angina, these patients, had normal exercise tolerance, and their pain patterns tended to be cyclical, with most episodes occurring during the early hours of the day without considering cardiac workload. This syndrome is known as Prinzmetal or variant angina, and is known to be due to vasospasm in coronary arteries without significant obstructive lesions.

The age at which symptoms first appear is highly variable. Variant angina is believed to be more common in female patients. Japanese patients are much more likely to develop coronary artery vasospasm than Caucasian patients (16,17).

The pathophysiologic mechanisms leading to coronary artery vasospasm are not yet completely understood. Coronary arterial tone varies normally via physiologic mechanisms, but the degree of vasoconstriction can range along a spectrum extending from undetectable constriction to complete arterial occlusion.

In some patients with partial vasoconstriction, symptoms can arise with activities that exceed a threshold of myocardial demand, while other patients, constriction may be so severe that myocardial ischemia develops at rest. Many observers use the presence of constriction-induced ischemia as the threshold for defining clinical coronary artery vasospasm, which has also been called vasospastic angina or variant angina.

In many cases, coronary artery vasospasm can occur spontaneously without an identifiable cause. Known triggers of spasm in susceptible patients include hyperventilation, cocaine or tobacco use, and administration of provocative agents such as acetylcholine, ergonovine, histamine, or serotonin. That coronary artery vasospasm can be induced through stimulation of alpha-receptors or intracoronary injection of the parasympathetic neurotransmitter acetylcholine which indicates that there are different mechanisms of action.

Acetylcholine causes coronary vasodilation in healthy coronary arteries through the release of endothelial nitric oxide (NO); however, in atherosclerotic arteries, vasoconstriction ensues instead. Patients with coronary artery vasospasm appear to have a heightened vasoconstrictor response to acetylcholine as well as an enhanced response to the vasodilator effects of nitrates, an observation that is consistent with a deficiency of endogenous NO activity (18).

Thus, NO deficiency is believed to play an important role in the development of coronary artery vasospasm. This may also explain the correlation between coronary artery vasospasm and increased intimal thickening (14,19) (Annex 1. Figure 3): NO deficiency results in enhanced activity of potent vasoconstrictors and stimulators of vascular smooth muscle proliferation, such as angiotensin II and endothelin 1.

Tako-Tsubo cardiomyopathy:

Tako-Tsubo cardiomyopathy (TCM) is a transient cardiac syndrome that involves left ventricular apical akinesis and mimics acute coronary syndrome. Patients often presented with chest pain, have ST-segment elevation on electrocardiogram, and elevated cardiac enzyme levels consistent with a myocardial infarction. However, when the patient undergoes cardiac angiography, no significant coronary artery stenosis is presented and there is a left ventricular apical ballooning.

The modified Mayo Clinic criteria for diagnosis can be applied to a patient at the time of presentation and must contain all 4 aspects:

- Transient hypokinesis, dyskinesis, or akinesis of the left ventricular mid segments, with or without apical involvement (Annex 1. Figure 6); the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present.

- Absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture (Annex 1. Figure 1).

- New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin level.

- Absence of pheochromocytoma or myocarditis.

The exact aetiology of Tako-Tsubo cardiomyopathy is still unknown, but several theories have been proposed and are being investigated. These include mainly endogenous catecholamine-induced myocardial stunning and micro infarction. But also other theories, such as multivessel coronary artery spasm, impaired cardiac microvascular function, impaired myocardial fatty acid metabolism and acute coronary syndrome with reperfusion injury, have been reported. A significant emotional or physical stressor normally typically precedes the development of the TCM.

According to Spanish National Register of Tako-Tsubo syndrome (RETAKO), around 1.2 % of the patients who had suspected acute coronary syndrome, in the Spanish population, were subsequently diagnosed with TCM. Patients are 98% Caucasian, report an average patient age of 70 years, although cases of TCM have occurred in children and young adults. Nearly 91% of reported cases involve postmenopausal women (11).

The prognosis in Tako-Tsubo cardiomyopathy is excellent, mostly patients experience a complete recovery within 4-8 weeks. The annual recurrence rate is approximately 0-15% but that the frequency of ongoing symptoms is greater. Estimates of hospital mortality rates have ranged around 0.8%.(11,20).

Complications occur in 20% of TCM cases and include the following (21):

- Left heart failure with and without pulmonary edema
- Cardiogenic shock
- Left ventricular outflow obstruction
- Mitral regurgitation
- Ventricular arrhythmias
- Left ventricular mural thrombus formation
- Left ventricular free-wall rupture

Spontaneous coronary artery dissection:

Spontaneous coronary artery dissection (SCAD) is a rare but increasingly recognized cause of acute coronary syndrome or sudden cardiac death. It can be primary or secondary. Primary dissections occur spontaneously whereas secondary dissections occur as an extension from aortic root dissection or following an insult as a consequence of coronary angiography, coronary intervention, cardiac surgery or chest trauma. Dissection of the coronary artery results in separation of the different layers of the arterial wall with the creation of a false lumen.

The incidence of SCAD in angiographic series varies widely from 0.07% up to 1.1% for patients who are referred for coronary angiography. The average age at presentation is 30-45 years. More than 80% of SCAD cases are women, and in approximately 18% it occurs during the peripartum period (14,22).

SCAD remains an unclear pathophysiologic entity. The most common pathologies associated with SCAD are, on one hand, vascular changes occurring during the peripartum period, and on

the other hand, coronary atherosclerosis. Other causes of SCAD are connective tissue disorders, especially fibromuscular dysplasia (22), and also systemic lupus erythematosus vasculitis, cocaine abuse, vigorous exercise, and prolonged sneezing. However, a large number of cases must be classified as idiopathic because no underlying condition can be detected. The possibility of a SCAD should be suspected and an urgent coronary angiography considered. In patients with ACS and NOCAD with suggestive clinic as young pregnant woman, diagnose procedure should be done with IVUS or OCT technique (Annex 1. Figure 4).

There is no specific guideline on how to manage patients with SCAD. Treatment options for SCAD include medical therapy, percutaneous coronary intervention, or coronary artery bypass graft surgery. The decision to manage SCAD conservatively with medication or to perform PCI or CABG must be individualised based on both clinical and angiographic factors.

Myocarditis:

Myocarditis is an inflammatory disease of the myocardium, which is often underdiagnosed, caused by different infectious and non-infectious triggers. Although the main cause are infectious agents of viral type (enterovirus, parvovirus), myocarditis may also be caused by other infectious agents, such as Lyme disease or Chagas disease. Also drugs and other toxins may cause it.

Myocarditis is regarded as a precursor of dilated cardiomyopathy, which is currently the most frequent reason for heart transplantation. Post-mortem data identify myocarditis in 8.6% to 12% of cases of sudden death in young adults (23). Long-term follow-up studies in patients with acute myocarditis have documented the development of DCM in 21% of patients over a mean follow-up period of 3 years (23).

The clinical manifestation of myocarditis varies with a broad spectrum of symptoms ranging from asymptomatic courses to presentations with signs of myocardial infarction to devastating illness with cardiogenic shock. Chest pain, cardiac arrhythmias, and acute or chronic heart failure, can occur during the course of the disease.

The ECG findings in patients with myocarditis vary from nonspecific T-wave and ST-segment changes to ST-segment elevation mimicking an acute myocardial infarction (23–26). Echocardiography allows the evaluation of cardiac chamber sizes and wall thickness as well as systolic and diastolic function in patients with myocarditis. CMR imaging has evolved as a non-invasive and valuable clinical tool for the diagnosis of myocarditis. In particular, the initial changes in myocardial tissue during the first phase of myocardial inflammation represent attractive targets for a successful CMR-based imaging approach. Thus, CMR has a key role in the management of patients who undergo MI an have NOCAD in the subsequent angiography,

in order to differentiate them from patients who suffer a myocarditis with a non aggressive technique (24–26) (Annex 1. Figure 5). However, the gold standard in diagnosis of myocarditis is still the endomyocardial biopsy (EMB).

Myocarditis treatment is the same as in the heart failure, including treatment with angiotensin modulators (ACE inhibitors or ARBs), Beta-blockers and diuretics. Specific treatment based on immunosuppression and immunomodulation has produced conflicting results. Currently, immunosuppression is basically recommended in specific conditions, such as giant cell myocarditis, cardiac sarcoidosis, and myocarditis associated with autoimmune diseases.

Kounis Syndrome:

Kounis Syndrome (KS) is defined as a ACS caused by an allergic reaction or anaphylaxis. The diagnosis is based on clinical symptoms and the relation with an anaphylactic event. There are two types of KS. KS type 1 is caused by an allergic reaction with normal coronary arteries, through inducing vasospasm. While in KS type 2 the mechanism consists in an acute release of inflammatory mediators causing a rupture or ulceration of an atherosclerotic plaque (27).

Regarding the treatment of these patients, adrenaline is needed in acute anaphylaxis treatment although it can exacerbate the ischemic event, induce vasospasm and arrhythmias. Also liquid administration and antihistaminic drugs should complete the acute treatment. There is controversy regarding the administration of glucocorticoids, due to the fact that can produce a thinning of myocardial wall and originate cardiac rupture or an aneurysm (27).

Prognosis of these patients is said to be excellent. In addition, there is a resolution of the cardiac wall damage in the following weeks after the event. Obviously, the exposure to the allergen that caused the allergic reaction must be controlled.

The approach of the etiologic diagnosis of ACS without significant coronary lesions is of great importance and future clinical research and interim recommendations for treatment require an understanding of the mechanisms. The treatment of MI with NOCAD is likely to differ substantially based on mechanism. For example, the best treatment of MI with open arteries due to disrupted plaque is likely to be the same as typical spontaneous MI due to disrupted plaque. The best treatment of plaque erosion remains unknown but would likely include antiplatelet agents and possibly statins, depending on the composition of the underlying plaque. The best treatment of vasospasm may be different, perhaps including calcium channel blockers and nitrates. Spontaneous coronary artery dissection is frequently not due to atherosclerosis and therefore treatment might not include statins. Myocarditis is not true MI and therefore the treatment with secondary prevention measures is not appropriate, though

some medications might be considered for primary prevention. Thus, a rational approach to the treatment cannot be undertaken without knowledge of the mechanism or mechanisms of MI without obstructive coronary artery damage.

<u>DIAGNOSTIC</u>

The ACS diagnostic include clinical presentation, physical exploration, ECG features, analytic parameters and myocardial imaging techniques such as coronary angiography, CMR and OCT.

Clinical presentation

Clinical history

Clinical history has a key role to diagnose, not only ACS whit OCAD, but also NOCAD patients. Cardiovascular risk such as hypertension, Diabetes Mellitus, smokers or overweight can guide to an atherothrombotic event (12). Nevertheless, patients with normal or near normal coronary arteries may also have cardiovascular risk factors (CVRF), but this is a controversial matter. Some series reached the conclusion that both groups of patients have similar prevalence of CVRF (1,2,5,10,28), while other studies argued that NOCAD patients are less likely to have CVRF (7,29). On the other hand, as said, personal clinical history of a pregnant woman with previous diagnostic of fibromuscular dysplasia can guide us to SCAD diagnostic. Cocaine consumption, cold intolerance or acute stress situation can indicate vasospasm mechanism of ACS. Postmenopausal and hypertensive women with a history of stressful event may lead to a Tako-Tsubo syndrome.

Signs and symptoms

ACS symptoms are the same for both groups with and without OCAD. The most common symptom is chest or epigastric pain, irradiated or not to arm or jaw, at rest with a duration of more than 20 minutes. It may be the first episode (20%) or a progressive number of anginas concluding on an ACS (80%). Other typical symptoms are diaphoresis, nausea, dyspnea, abdominal pain, or syncope. This is the paradigm of heart attack clinical presentation (13,30).

ECG features

The ECG is the main technique to demonstrate acute myocardial ischemia. It should be done at the first 10 minutes after patient arrival. The typical abnormalities are found in the ST segment with a persistent elevation (STEMI) that indicates transmural ischemia or a depression of ST (Non-STEMI), which indicates subendocardial ischemia (13,30).

Biomarkers

Biomarkers reflects different pathophysiological aspects of ACS such as myocardial cell damage, inflammation and platelet activation. Troponin and Creatine Phosphokinase (CK) are the main parameters studied. Unlike other studies that used Troponin I, in this study Ultrasensitive troponins will be used as main biomarker. The studies have concluded that these innovative troponins can make better diagnosis, in reference to frequency and speed of MI diagnosis (31). In *Jaffe,Allan S* review (31), it was determined that using UT in MI diagnosis they detected 27% more patients undergoing MI. This should have big impact in the prognosis of the disease, because more patients may be diagnosed and the diagnostic may be done faster, when the myocardial damage is minimum.

Coronary angiography

All patients undergoing ACS will be submitted to a coronary angiography in order to diagnose and, if necessary, to treat the occluded artery. Depending on the context severity, angiogram will be done faster in patients with persistent elevation of ST segment, with high increasing of UT. In patients with NOCAD it will be a normal coronary angiography or with no significant artery damage (annex 1.1).

Intracoronary optical coherence tomography

Intracoronary optical coherence tomography (OCT) is a recently developed high-resolution intravascular diagnostic technique. Initially, it was mainly used for characterizing atherosclerotic plaque because it served a number of functions, from identifying plaque with high lipid content to detect macrophage accumulation, both of which are associated with plaque instability. Currently, there is growing interest in the value of optical coherence tomography in the area of coronary intervention, where the technique offers significant advantages over more widespread intravascular diagnostic techniques such as intravascular ultrasound: the higher resolution means that the vessel lumen diameter can be measured more precisely, periprocedural complications such microdissection of the coronary artery can be detected, stent apposition relative to the vessel wall can be optimized, neointimal hyperplasia can be detected after stent implantation, and neointimal thickness can be measured (32)(Annex 1. Figures 2,3,4).

In our study, OCT will be used for diagnosis of etiologic mechanism of MI with non-critical angiographic coronary stenosis, especially those with plaque disruption/erosion (Annex 1), calcified nodule (Annex 1), and SCAD (Annex 1). In addition, recent reports which used OCT,

have suggested that there may be characteristic findings (intimal thickening and/or intima–media separation) in patients with vasospasm (Annex 1)(14). In order to do a suitable approach of treatment of the different aetiologies and improve the prognosis of these patients. In reference, *"Navarro Valverde,C et.al"* (4), suggested the utilization of OCT technique to be more accurate in the management of these patients.

Echocardiography

Echocardiography will be conducted for two basic tasks: to measure the left ventricular ejection fraction, which is the main prognostic factor of these patients. Furthermore, this technique is basic to diagnose a TCM, defined as a left ventricular apical dyskinesia (20).

Cardiac magnetic resonance

Several studies explained the use of CMR in the management of patients undergoing MI and with a difficult diagnosis, as for example patients with symptoms of MI, elevated troponins and normal coronary angiography. CMR is the best imaging technique to diagnose irreversible myocardial damage not only because it has a high sensitivity to diagnose very little damage, but also because different patterns can give information about aetiological mechanism. CMR is especially useful to distinguish between myocarditis and MI (25,26,33)(Annex 1.5).

TREATMENT

Treatment of ST elevation ACS and without ST elevation, is clearly established in the clinical practice guidelines of the Spanish Society of Cardiology, European Society of Cardiology and American Heart Association (13,30,34).Simplifying the mechanism behind the SCA, we could outline the treatment for each case:

- Plaque disruption/ erosion: Antiplatelet/ anticoagulant therapy.
- Vasospasm: calcium channel blockers and nitrates.
- TCM: Heart failure treatment until left ventricular recovery.
- SCAD: collocation of a stent

In addition, though there is not significant coronary artery damage, heart failure should be considered and treated likewise OCAD patients with heart failure. Heart failure is defined as the disability of the heart to plump the necessary blood to supply the metabolic requirements of the body (34). Drugs, such as Beta-blockers, ACE- inhibitors or diuretics will be necessary. Moreover, management of CVRF with statins, anti-diabetic drugs or stop smoking therapies is a major aspect as secondary prevention.

4. Justification

Heart attack remains being the disease with the biggest morbidity and mortality rates, despite being one of the most studied illnesses in the Western world. However, often doctors realise that some patients with clinical, electrocardiographic or analytic signs of MI have non obstructive coronary artery disease in the subsequent coronary angiography. As said, the incidence of these clinical presentation is not insignificant. Most series reached the conclusion that around 12% of patients with suspected MI have no coronary lesions (1–4).

In medical practice, patients who suffered a MI and do not have significant obstructive findings in the coronary angiography are said to have a lower risk in comparison with those with significant atherosclerotic affection (3,10,16). However, with regard to prognosis determination of other series, long term prognosis of OCAD patients depends on the number of coronary arteries affected. Mostly series conclude that prognosis varies significantly depending on the number of coronary vessels affected. In this manner, only patients with atherosclerotic affection of 3 coronary vessels or even the left main, will have an unfavourable prognosis compared with those with no coronary artery damage (7,28). The high incidence of Major Adverse Cardiac Events (MACE) showed in other series in NOCAD patients is surprising. MACE is used to define the end-point in cardiovascular research. It includes, among others, re-ischemia, arrhythmias, sudden death, and cardiac death. There are two points that could explain these highs rates of MACE in patients with no significant coronary artery disease: insufficient diagnostic methods and unsuitable chronic treatment.

On the first hand, it is well known that coronary angiography can underestimate coronary atherosclerotic burden. The main controversial about this matter is whether it is necessary to improve the diagnostic measures. Therefore, it will be necessary to establish a suitable diagnose protocol including innovative techniques such as OCT and CRM, which can reach an etiological diagnosis and improve the treatment of NOCAD patients. OCT technique will be used for the aetiological estimation. This intracoronary technique can make a more accurate diagnosis. This mean a better treatment, because, as we know there are different aetiologies that involve several differences in treatment and, consequently, in the prognosis (14). Moreover, over the last years, a new type of troponin determination has begun to use, these are the ultrasensitive troponins. This new techniques of troponin determination can improve upon the diagnosis of MI up to 26% (31). Furthermore, unlike there are other studies with the same approach performed in Spain (4,6,7), in which ultrasensitive troponins were not used, in our study this innovative analytic parameter will be used.

On the other hand, the matter of chronic treatment in NOCAD patients. *"Minha,S et.al "*(1) and *"Chilappa,K et.al"* (28) states that NOCAD patients were less treated in the chronic

follow-up than OCAD patients. The fact that these patients do not receive a suitable treatment of secondary prevention can change the prognosis. Acute Therapies of NOCAD patients depends on the mechanism diagnostic, but some drugs such as Beta-blockers or ACE-inhibitors are necessary in patients who develop significant damage and suffer heart failure, in order to decrease cardiac work and optimize the heart function. This matter is included in *"Redondo-Diéguez,A et.al"*.(7) and it is unclear whether the less drug administration in the group of NOCAD could have interfered in the final prognosis of patients included in that study.

Currently, as commented in clinical history subsection, there is not a global agreement about whether these patients are related to have a high prevalence of cardiovascular risk factors as patients with coronary artery occlusion. Some studies have shown that patients without culprit lesion have the same incidence of CVRF that OCAD patients. In addition, *"Minha,S et.al"* (5) explains that the most important finding in their study was that patients with NOCAD in the setting of ACS share similar risk factors as OCAD patients. Moreover, this study reports that despite having the same incidence of cardiovascular risk factors (CVRF), NOCAD patients tend to receive less standard medical therapy during the hospitalization and even more, at discharge. As said in the last paragraph, this could change the prognosis of NOCAD patients, if a better treatment is performed.

With reference to the latter, in our specific population prognosis should be better. For the reason that several reports have shown that "Mediterranean" population have less incidence of cardiovascular events despite having the same rate of cardiovascular risk factors (CVRF), by the fact of Mediterranean alimentation or genetic heritage (35). This is an important point in our project, for the fact that the aim of this study is to compare the prognosis of this two types of myocardial infarction in four hospitals in Catalonia (Spain), where, as has been demonstrated, the cardiovascular risk is different from other populations in Europe or USA (35), where similar studies have been performed (1,3,10).

The conclusion regarding treatment at discharge, the studies explained that NOCAD Patients were less treated at discharge than OCAD patients in their sample. Not only in regard to heart failure drugs, but also in reference to CVRF prevention measures. According to some studies, NOCAD and CAD patients share the same percentage of CVRF (5). So this point could have interfered in the outcomes as a confounding bias. In our study an exhaustive examination will be done and treated at hospital discharge.

Due to all this, new studies are necessary to determine the prognosis of these patients. As commented, several improvements in diagnostic techniques and also in treatment approach will enhance the survival of patients who suffer a MI and do not have significant coronary artery damage.

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6. Hypothesis

Patients who suffer from a myocardial infarction without a significant coronary lesion have a favourable prognosis in comparison with patients who suffer a myocardial infarction and have a significant coronary lesion, in Catalonia.

7. Objective

This study aims to determine the long-term prognosis of patients who suffer from a myocardial infarction and do not have culprit lesion in comparison with patients who undergo myocardial infarction and have obstructive coronary disease, in Catalonia.

Secondary objectives:

- This study aims to determine the short-term prognosis of patients who suffer myocardial infarction and do not have culprit lesion in comparison with patients who undergo myocardial infarction and have obstructive coronary disease. In Catalonia.

- To describe the epidemiologic characteristics of patients who attend to our hospitals in Catalonia and are diagnosed of myocardial infarction and do not have coronary significant damage.

- To describe the differences between both groups of patients, regarding the incidence of each complication included in MACE, occurring at 30 days and one year after the myocardial infarction.

- To describe the differences regarding the incidence of each etiological mechanism that causes a myocardial infarction, in patients who suffer from a MI and have no significant obstructive coronary artery disease.

8. Materials and methods

7.1. Study design

This study is designed as a prospective, cohorts, multi-centric study, with the purpose of comparing the prognosis between patients who suffer from a myocardial infarction and do not have significant coronary artery lesion and patients with heart attack and significant atherosclerotic lesion. It will be performed in the Cardiology Department at different Hospitals in Catalonia: *Hospital Universitari Doctor Josep Trueta (Girona), Hospital Sant Joan de Deu (Barcelona), Hospital Germans Trias I Pujol de Badalona (Badalona), Hospital del Mar (Barcelona)* in a period of time of three years.

7.2. Population

The study population will include patients between 18 and 80 years who suffer a myocardial infarction and receive immediate treatment at the four hospitals in Catalonia, previously mentioned, which have similar population.

Inclusion criteria:

- Patients between 18 and 80 years.
- Patients with diagnostic criteria of a myocardial infarction, according to clinical guidelines of Spanish Society of Cardiology.
- Patients with first episode of myocardial infarction.
- Patients who undergo a coronary angiography.
- Patients who agree to participate in the study.

Exclusion criteria:

- Patients with diagnose of myocarditis or severe valvular disease.
- Patients with terminal disease or another disease that could interfere in prognosis of patients with heart disease.
- Patients undergoing MI living in other places who cannot be followed.

7.3. Sample

Sampling method

A consecutive non-probabilistic sampling will be performed as population undergoing myocardial infarction and simple recruitment will take place during 1 year.

Patients undergoing ACS will be invited to participate in our study after the coronary angiography procedure. The information document and the informed consent of the coronary angiography (Annex 3), as well as the information document and the informed consent about OCT (Annex 4) will be given to all patients before the catheterization procedure. Patients will be informed about the study after the acute treatment. The information document and the informed consent of the study will be given to all participants. All patients will be summoned for an appointment in cardiology outpatient hospital visit to do the follow-up on different times including 30 days and one year after the hospital discharge.

Sample size

In the Cardiology Unit of our four hospitals, approximately 400 patients with our inclusion criteria will be attended during one year in each one. According to data from these Cardiology Departments, in 2014, 360 patients with criteria of myocardial infarction with OCAD and 40 patients with heart attack and NOCAD were diagnosed. Our simple size was defined taking into account these data and the number of patients analysed in other previous similar studies about long term prognosis of heart attack without culprit lesion (3).

According to epidemiology of patients undergoing MI with NOCAD and the incidence of MACE in the study (3), we sought a minimum relative risk of 0,25 (6), and a dropout rate of 0,1. Thus, the final sample size will be 160 NOCAD patients and 1168 CAD patients recruited of our 4 hospitals. We have calculated the sample size using an online tool –GRANMO ®-.

7.4. Variables. Methods of measurement

<u>Independent variable: Patients who suffer from a myocardial infarction and do not have coronary artery disease</u>

Recruited patients will be organized in two groups: Patients with MI and with obstructive coronary artery disease in the subsequent coronary angiography, and patients undergoing MI with non obstructive coronary artery disease.

Diagnostic procedure: Patients with clinic diagnosis of myocardial infarction with analytic or electrocardiographic typical changes will be submitted to a coronary angiography in the hemodynamic service of our four hospitals.

In the hemodynamic service, a coronary catheterization will be performed after asking the patients to sign the informed consent of the catheterization and OCT (Annexes 3,4). The study participation information sheet and the informed consent to participate in the study will be given to participants after the acute event (Annexes 2,5). In the case that patients were unable to decide, for instance if they were unconscious, the responsible person would make the decision. Following, cardiologists will perform a cardiac catheterization entering in the body circulation by the radial artery or, if not possible, femoral artery. They will reach the coronary vessels and put some iodinated contrast to view the condition of the coronary vessel. In the whole proof right coronary artery and left coronary artery (anterior descending artery and circumflex artery) will be examined.

Obstructive coronary disease will be defined as a vessel obstruction of more than 50% of the lumen. Thus, patients will be classified as:

- Patients with significant coronary artery disease, when the vessel obstruction is more than 50% of the lumen.

- Patients without significant coronary artery disease, when the coronary obstruction is less than 50% of the lumen. Patients with a diagnose of non obstructive coronary arteries will be submitted to an OCT and classified as:

    A. <u>Arteries with no plaque</u>: This group includes vasospasm, SCAD and TCM.

    B. <u>Arteries with no complicated plaque</u>: Calcified nodule.

    C. <u>Arteries with a complicated plaque</u>: Plaque disruption and plaque erosion.

Patients will be treated according to the aetiology of MI:

- Patients with obstructive coronary artery disease will be treated with a stent collocation, 1 year of double antiplatelet agents, and depending on the heart function cardiologist will add other drugs such as Beta-blockers, ACE-Inhibitors or diuretics. Moreover, CVRF will be controlled with statins, anti-diabetic drugs or stop smoking therapies.

- Patients with no significant obstructive coronary artery disease imaging in the coronary angiography will be treated depending on the mechanism, the heart function and the CVRF of the patient with:

  - Plaque disruption/ erosion and calcified nodule: Antiplatelet/ anticoagulant therapy.
  - Vasospasm: calcium channel blockers and nitrates.
  - TCM: Heart failure treatment until left ventricular recovery.
  - SCAD: collocation of a stent

The heart function and the CVRF of the patient will be treated similar than patients with OCAD, as said in the introduction section.

Dependent variable: Incidence of MACE in the first year after the myocardial infarction

Our outcome variable is the prognosis at the first year after de myocardial infarction. To measure this variable Mayor Adverse Cardiac Events (MACE) will be used. MACE were defined as the occurrence of the following episodes during the follow-up: heart failure, ischemic heart disease (angina or acute myocardial infarction), stroke (established or transient), peripheral vascular disease (clinical signs of intermittent claudication or demonstrated by echo-Doppler), cardiac arrhythmias (atrial fibrillation, ventricular tachycardia, and atrial flutter), cardiovascular death, and sudden death. All complications listed in MACE will be analysed separately in both groups, in order to examine the differences between the two groups of patients regarding the type of MACE occurred.

The follow-up data will be obtained from the hospitals and health centre data, once patients have signed the informed consent of the study. In the informed consent there is an explanation of the confidentiality and anonymity of patient information. Patients will be cited to be controlled in the health centre several times. The first date will be 30 days after de MI, and then another will be made at the first year after the event. At these dates, clinical, analytic and electrocardiographic features will be analysed. Also MACE events will be registered in hospitals data.

Covariates

These covariates can also serve to make an epidemiological characterization of patients who suffer from a heart attack and do not have coronary artery disease. All these covariates will be collected at the hospitalization by clinical interview, physical exploration, analytic, electrocardiographic and echocardiographic measurements.

Baseline characteristics [n (%)]:

- Age: years
- Female sex
- Hypertension: Yes/No, according to Spanish clinical guidelines of hypertension.
- Diabetes mellitus: Yes/No according to Spanish clinical guidelines of DM.
- Dyslipidemia: Yes/No according to Spanish clinical guidelines of Dyslipidemia.
- Family history for obstructive coronary artery disease.
- Current smoker: Yes/No.

Baseline hemodynamic and laboratory findings (mean and SD):
- Heart rate (bpm)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Peak creatine kinase (mg/dl)
- HDL (mg/dl)
- LDL (mg/dl)
- Peak Ultrasensitive troponins (ng/ml)
- Creatinine (mg/dl)

Medical therapy at discharge [n (%)]:
- Aspirin
- Clopidogrel
- Anticoagulants
- Beta-Blockers
- Calcium-Blockers

Electrocardiographic and echocardiographic features [n (%)]:
- Persistent ST- Elevation: yes, or no.
- Non ST-Elevation: yes, or no.
- Left ventricular ejection fraction: Preserved (>50%), Slight (40-50%), Moderate (30-40%) and severe (<30%).

9. Work Plan

The research team will be constituted by different specialists, who have long experience, not only in the research, but also in the use and interpretation of the innovative diagnostic techniques in our study. Each of them will have a task assigned during the different phases of this study. There will be 16 cardiologists, four of which will be principal researchers, and 32 nurses. A statistician will be employed for statistical analysis. The whole project will last over 3 years.

Initial coordination (2 months): This will be an all-member meeting to start the project, to define the roles of each participant, and to create a chronogram clarifying the different phases of the study. This type of coordination meetings will be repeated during the study to debate if there are any problems and also if any modification needs to be done. The whole research team will keep in contact via e-mail, just in case there is a need for improvisation and an extraordinary meeting is needed to be organized. In addition, a master class about OCT use will be provide to cardiologist and nurses, with a view to achieving a thorough diagnostic.

Protocol development (3 months): Once the bibliography research is done, the whole protocol for the study will be written with the collaboration of all the research team, as before carrying it out approval from ethical committee (CEIC) will be needed.

Data collection (2 years): If the study is approved to be done, the data collection process will start. In these two years there will be different tasks: one year to recollect patients and another to do the follow-up. In hemodynamic unit, each coronary angiography is performed by one cardiologist and two nurses. We have contact with 16 cardiologists and 32 nurses. Four doctors and eight nurses will work in the project in each hospital, in order to attend all patients, those who attend at day and at night. A schedule will be made to distribute tasks (Annex 8).

1. Hemodinamists Cardiologist: They will give informed consent about coronary angiography and OCT before starting the catheterization procedure (Annexes 3,4). According to the coronary angiography and OCT results, patients will be classified in two groups:

   - Patients with imaging of OCAD in coronary angiogram, who meet inclusion and exclusion criteria, will be informed about the study and the information document and informed consent (Annexes 2,5) will be given by the interventional cardiologists.

- Patients with no coronary significant disease or no coronary artery disease, who meet inclusion and exclusion criteria, will be also informed about the study and information document and informed consent of the study will be given by hemodinamists cardiologist (Annexes 2,5).

2. Cardiologist: They will treat patients until the hospital discharge. Doctors will do an exhaustive clinical interview and physical exploration, saving all details into the hospitals data bases. A suitable treatment will be given to NOCAD and CAD patients according to Spanish clinical guidelines of ACS and the etiologic mechanism of NOCAD patients. Before leaving, patients will be called for an appointment after the first 30 days after leaving. Moreover, diagnose information sheet will be written by main researchers of each hospital (Annex 6.1).

30 days after hospital discharge, at the hospitals consulting room, doctors will do a clinical interview asking about signs and symptoms of heart disease complications defined as MACE. Moreover, patients will be submitted to an ECG, a blood analysis, and an echocardiography to evaluate the heart function. All this information will be written in the information sheets (Annex 6.2). Patients who do not assist to the medical appointment will be called for another appointment. If a patient cannot be localized nurses will contact their family practitioner. Nurses will search for any patient who have suffered from some major heart disease event between the discharge and the first medical appointment. This medical intervention will be repeated a year later and the same mechanism of action will be done. All data will be collected in the study data base, and analysed by a statistician.

3. The four principal researchers will assist weekly to their assigned hospitals to recollect patients and procedures information and save it all in a common data base. A schedule will be made to distribute the main tasks of the principal researchers. There will be three different data sheets: One for the diagnose, and two more with information about MACE incidence at 30 days and one year after MI. (Annexes 6.1,6.2,6.3)

Data analysis and final elaboration (3 months): Once the data collection is finished according to our sampling, the whole data will be organized in a database by the research team. Also the necessary descriptive, bivariate and multivariate analyses will be performed by the statistician in this period. Final elaboration will be done by the research team once the data has been analysed and concluded.

Publication and dissemination of results (5 months): This will be done by the research team once the data has been analysed and concluded. The final article will be published in different medical journals in order to make a correct diffusion of the results.

10. Chronogram

TASKS	2015				2016												2017												2018							PERSONAL
	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	
TASK 1: PREPARATION AND COORDINATION PHASE																																				
- Protocol elaboration and evaluation	▓	▓	▓	▓																																Main Researcher team (CEIC)
- Coordination of research team			▓	▓																																All research team
TASK 2: FIELD WORK AND DATA COLLECTION																																				
-Patients recruitment					▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓																				Cardiology team
-Sample collection					▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓	▓								Scholarship holders
TASK 3: DATA ANALYSIS AND FINAL EVALUATION																																				
- Statistical analysis																													▓	▓						Statistician
- Analysis and interpretation of results																													▓	▓						All research team
- Final report elaboration																														▓						
TASK 4: PUBLICATION AND DISSEMINATION																																				
-Scientific publications																													▓	▓	▓	▓	▓			Cardiology team
- SEC and ESC congresses*																													▓	▓	▓	▓	▓			

Figure 1.* SEC: " Sociedad Española de Cardiología" / ESC: " European Society of Cardiology"; CEIC " Comité ético de investigación clínica".

11. Statistical analysis

- *Descriptive analysis*: The main variables of our study are both qualitative and categorical. Regarding covariates, some are qualitative and others are quantitative. For qualitative categorical variables, results will be expressed as percentages. For quantitative variables, assuming that they are not normally distributed, median will be estimated. In case that they follow a normal distribution, arithmetic mean and typical deviation will be calculated.

- *Bivariate analysis*:

    - Percentages for categorical variables will be shown in a contingency table and chi square test (x^2) will be used to compare prognosis of patients at 30 days and 1 year before the myocardial infarction. The study outcomes of the comparison between both groups in the study will be expressed with relative risk and Kaplan-Meier estimator will be used to derive the event rates at follow-up and to plot the time-to-event curves.

    - Percentages for categorical variables will be shown in a contingency table and chi square test (x^2) will be used to compare the incidence of different type of MACE in both groups. And to compare the incidence of different aetiologies in the groups without significant coronary artery disease.

    - To analyse the patient characteristic of the two groups qualitative and quantitative covariates *t-student test* will be used. To compare variables with ≥ 3 categories, Kruskal-Wallis test will be performed to test differences. In case that we finally found that it follows a normal distribution, we will use parametrical tests as the analysis of variance to check significance distances between groups.

- *Multivariate analysis*: COX model will be used to analyse the association between the exposition variable and the outcome variable. These variables are patients undergoing MI with NOCAD and incidence of MACE at 1 year after the heart attack, respectively. The logistic model analysis will be adjusted for covariates statistically significant (p<0,05) in order to adjust for potential confounders.

12. Ethical considerations

This study will be conducted according to the ethical principles established by World Medical Association in the Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects (36). The research protocol must be presented and submitted for consideration, guidance and approval by the Clinical Research Ethical Committee (CEIC, "Comité Ético de Investigación Clínica") of all four Hospitals in our study before the study begins, and at the end of the study, the final report must also be submitted to the CEIC.

According to "Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal", personal and clinical information of participants will be confidential and only used for the purpose of the research. All participants will be personally informed by researchers and an information document about the study will be given to them (Annex 2). Participants will have to sign voluntarily the informed consent (Annex 5) before being included in the study after receiving the appropriate information about procedures, according to "Ley 41/2002 Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica". Written information about the coronary angiography and OCT procedure and informed consent before the technique performance (Annexes 3,4) is also necessary.

The investigators of this project declare that there are no conflicts of interests.

13. Study limitations

Analysing our study, we detected and took into account some limitations which interfere in the research. The most relevant limitations are explained below:

1. The main bias that must be considered in this study is the "selection bias". We will measure all covariates that could interfere in the association between prognosis of a heart disease. These covariates are cardiovascular risk factors, such as hypertension or Diabetes Mellitus. The measure of these parameters will provide the study of a good external validity. Moreover, other possible confounders could be, among others, personal background of ischemic heart

disease. Thus, some conditions that could interfere in the outcome are reflected in our inclusion and exclusion criteria.

2. Other typical biases of cohorts studies are: "information bias" due to lack of assistance to medical appointments. We will solve this bias controlling via telephone all patients who do not assist to the medical appointments.

3. Withdrawal bias was taken into account when sample size was calculated. Nevertheless, if the expected loss of patients occurs, especially, in the group of patients without significant coronary lesion, it would produce a significant bias.

4. Finally, external validity could be affected in reference to OCT technique. As said in the introduction part, OCT is an innovative technique that might not be in all hospitals in Spain. Nevertheless, is a technique that will be registered in subsequent years in all hospitals of occidental world.

14. Budget

Most of the stages in the study, such as bibliography research, redaction, information collection and publication, will be performed by the research team. The only extra personnel needed will be a statistician, a computer scientific and an English translator.

On the first hand, regarding the material availability, all electrocardiogram and echocardiogram machines as well as OCT machine, are available in our four hospitals. And the costs attributable to their use are included in routine clinical practice expenses. Nevertheless, the fact that OCT technique is an innovative skill, a master class about OCT employment will be given to all cardiologist in the research team. The cost of this master class including the hiring of a specialist in OCT management, the rent of a suitable place in "Hospital del Mar" (Barcelona), and the transport for those researchers who live in other places of Catalonia, will be of 400€.

On the other hand, the statistician will be employed for the data analysis, which is estimated to take about 90 hours of work. For rate of 35€ per hour, it will be of a total cost of 3150€. Furthermore, one computer will be necessary to store all information and a computer scientific will be hired to create the data base where all information will be saved. The cost of this service will be of 700€ and 70€, respectively.

Various coordination meetings will be needed. We calculate that a total of 6 meetings will take place, but, perhaps, some more extraordinary meetings will be necessary. These meetings will be made, especially, in the coordination of the research team phase and also in the interpretation of results and final report elaboration stage. We estimate an approximate cost of 200€ per meeting (including transport of research team). Thus, a total cost of 1200€ for the 6 meetings. The redaction and the diffusion of the final article is task of the research team, but the cost of the English translation and publication in the scientific journals increase the cost until 2.000€. Later this project will be presented at the *"Sociedad Española de Cardiología"* and "European community of cardiology" congresses. This national and international conferences will need a budget of about 3.000€, to fulfil the needs of the participation cost, plane tickets, hotel reservation for three of the team members. (Annex 7)

15. Clinical and healthcare impact

The main impact of this study will be an optimization in the management of patients who suffer from a MI and have no obstructive coronary artery disease in the subsequent coronary angiography. These involves improving the prognosis of these patients and also reduce healthcare cost of hospital readmissions.

The outcomes of this study may have important implications regarding clinical practice. Several studies showed that the prognosis was less favourable than thought (28)(7)(4). This approach indicates that an etiological diagnose should be made. The implementation of innovative techniques, such as OCT should be part of clinical action to discriminate, among others, between complicated plaques, SCAD or vasospasm. In order to do a suitable treatment. Including this mechanism diagnosis into clinical practice may be very expensive. However, if we compare the costs of standardising these innovative techniques with the short and long term hospital readmissions of NOCAD patients due to MACE we will, surely, realise that making a suitable diagnosis is not as expensive as earlier assumed.

In conclusion, we have tried to improve the points that other studies defined as limitations. In order to do a good approach to a perfect management of these patient.

16. Annexes

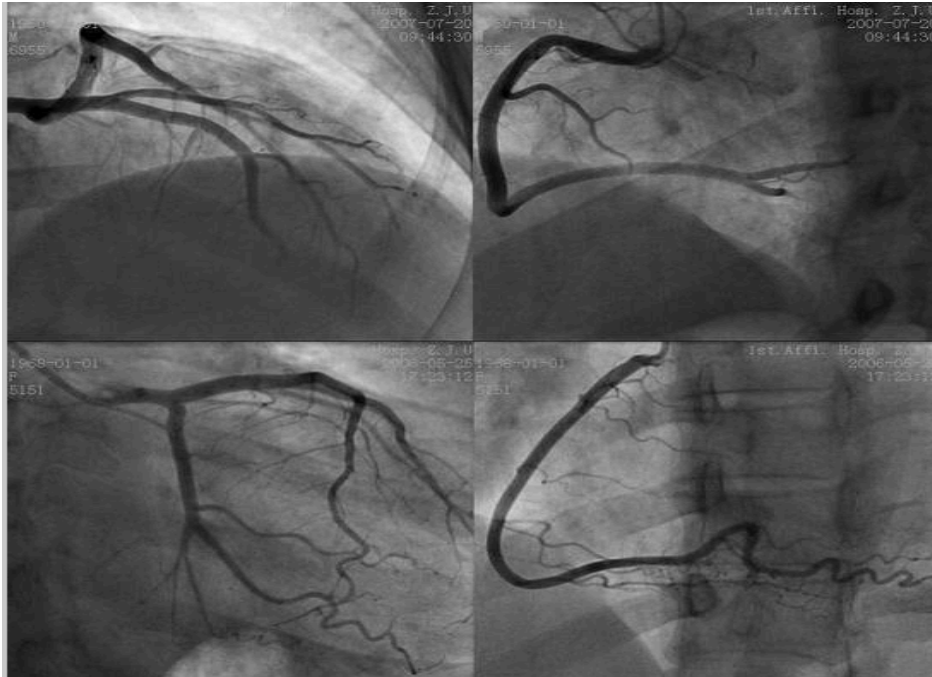## Annex 1. Diagnostic imaging

Figure 1. Normal coronary angiography imaging showing left coronary artery (anterior descending artery and circumflex artery) and right coronary artery without significant disease in a patient diagnosed of TCM. Images from data base of Cardiology department of *"Hospital Josep Trueta" (Girona)*.
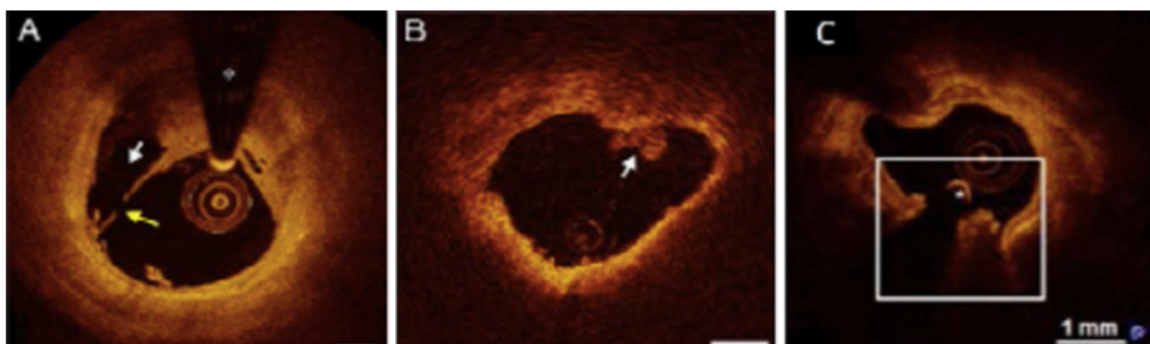

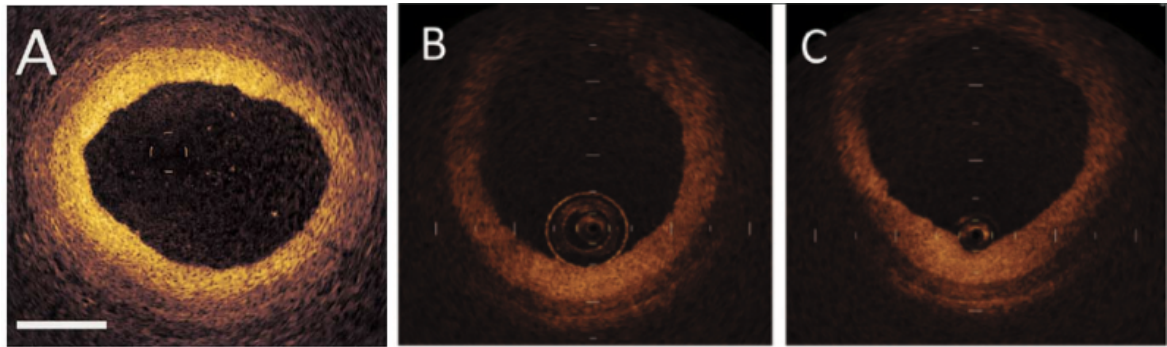**Figure 2.** Representative images of (A) plaque rupture, (B) Plaque erosion and (C) Calcified nodule (14).

Figure 3. Intracoronary optical coherence tomography imaging in a patient diagnosed of myocardial infarction with non obstructive coronary artery disease caused by vasospasm. Suspected vessel changes of intimal layer thickening (19).
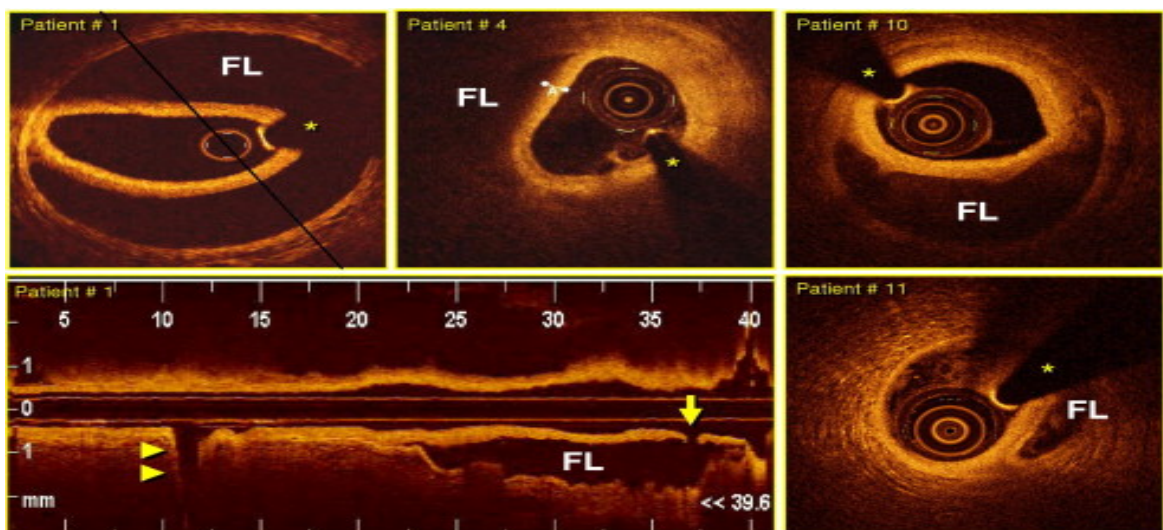

Figure 4. Representative images of intramural hematoma from SCAD. Images from data base of Cardiology Department of *"Hospital Josep Trueta"*(Girona).
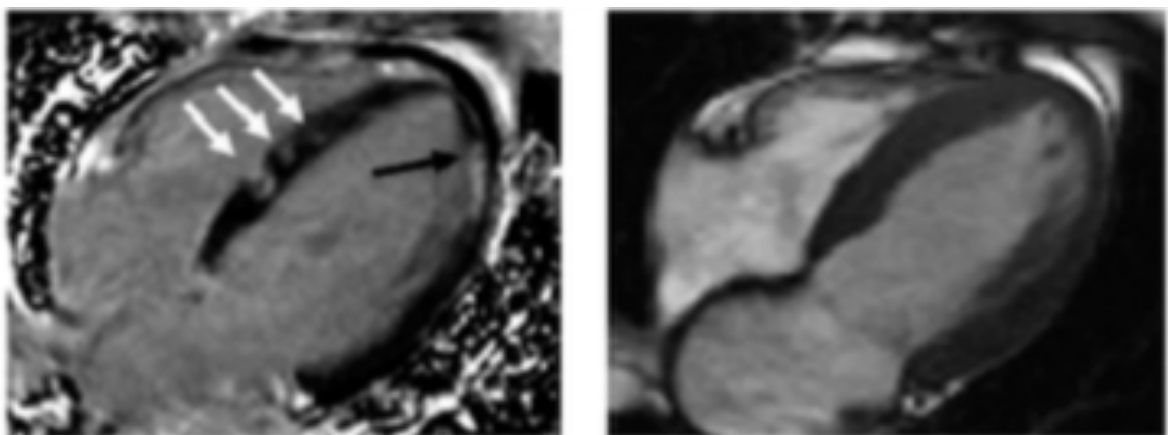

Figure 5. CMR imaging of myocarditis: patchy areas of LGE, primarily midwall, with some septal areas extending to the right ventricular sub endocardium (white arrows) and a nearly transmural area in the apical lateral wall (black arrows) (14).
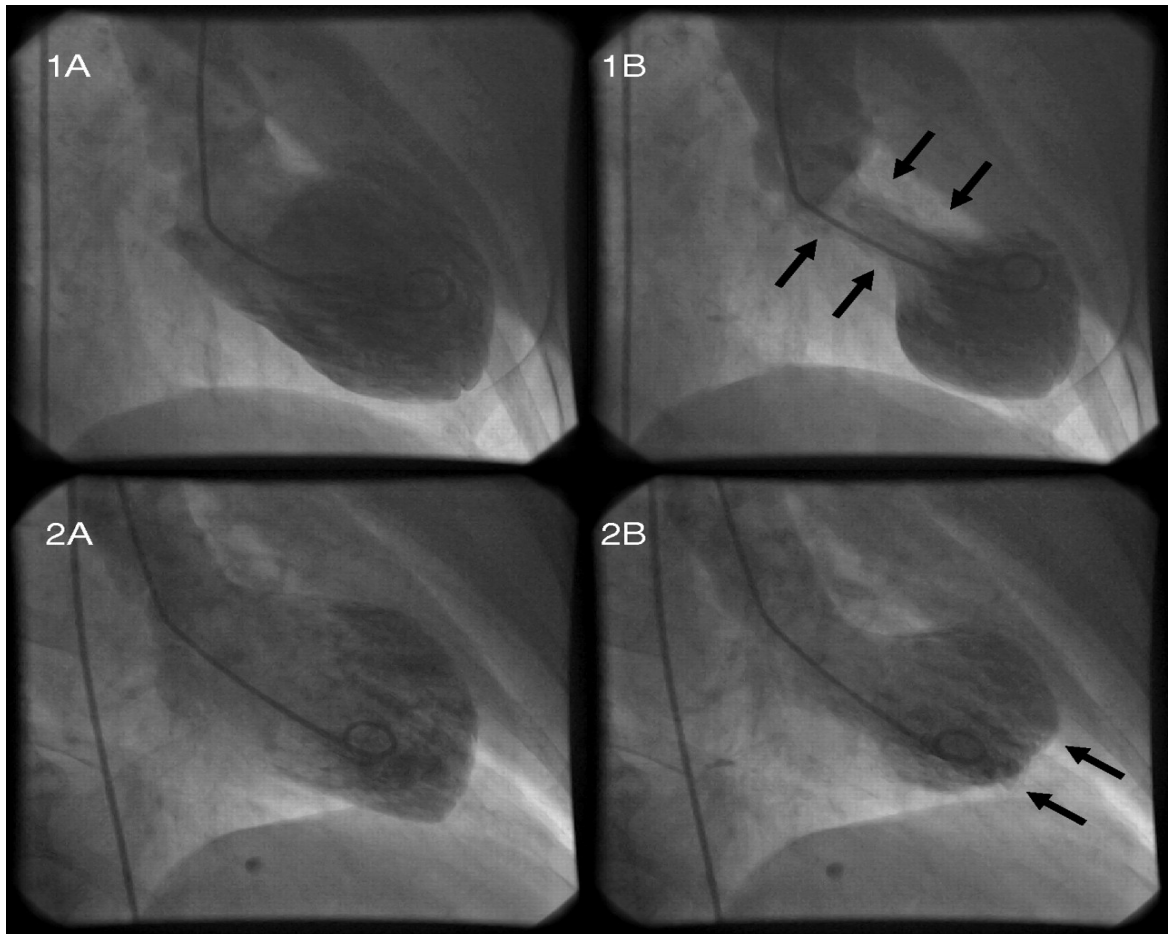
Figure 6. Coronary angiography imaging of a left ventricule contraction with iodinate contrast. It can be seen the apical akinesia of the left ventricule, as the typycal image of TCM. Images from data base of Cardiology Department of "*Hospital Josep Trueta*" (Girona)

Annex 2. Information from the study

**Hospital Universitari de Girona
Doctor Josep Trueta**

Hoja de información para el participante

INVESTIGADORES PRINCIPALES: Xavier Albert, Claudio Torán, Javier Conejos, Josep Iglesias.

CÓDIGO DEL PROYECTO:

1) **Generalidades del proyecto:** El presente estudio se llevará a cabo en los departamentos de cardiología en: "Hospital Universitari Doctor Josep Trueta" (Girona), Hospital Sant Joan de Deu" (Barcelona), "Hospital del Mar" (Barcelona) y "Hospital de Badalona" (Badalona) en un periodo de 3 años. El proyecto de investigación ha sido aprobado por el comité de ética de investigación clínica de cada uno de los centros mencionados. Los pacientes colaborarán en el estudio dando permiso para utilizar sus datos tras un año de seguimiento después del infarto

2) **Objetivos y finalidad del estudio:** Con este estudio se pretende determinar si existe un mejor pronóstico en los pacientes que han sufrido un infarto de miocardio y que tienen unas arterias coronarias sanas, después de establecer un protocolo de actuación con técnicas de diagnóstico novedosas. Por lo tanto, ayudará a mejorar el pronóstico de este tipo de pacientes.

3) **Participación:** Su participación en este estudio es totalmente voluntaria. El participante es libre de dejar el estudio si así lo desea en cualquier momento, sin necesidad de justificación, y sin que esa decisión afecte en su asistencia sanitaria. La participación en el estudio es totalmente gratuita y no se obtendrá ninguna compensación económica por su participación.

4) **Confidencialidad y protección de datos:** Se adoptaran las medidas para garantizar la confidencialidad de sus datos en cumplimiento de la Ley Orgánica 15/1999 y la información recogida será gestionada de forma anónima y solo se utilizarán en fines de investigación. También se garantizarán los principios establecidos por la Ley de Investigación biomédica 14/2007.

5) **Colaboración del paciente en la recogida de información:** El paciente deberá firmar la hoja de participación en el estudio. 30 días y un año después del alta hospitalaria se le dará cita en la que información de su persona será recogida y añadida al estudio. Si por alguna razón ha tenido que acudir antes al hospital o no acude a la cita previamente concertada, nos pondremos en contacto con usted para ofrecerle otra fecha.

6) **Resultados y beneficio de la participación:** El paciente esta en su derecho de ser informado de los resultados de la investigación, así como de no ser informado acerca de estos. Los beneficios derivados de la investigación, pueden beneficiar al participante como a otras personas, y estos serán adecuadamente utilizados para conseguir los objetivos del estudio y servirán de base para futuras investigaciones en este ámbito.

Gracias por participar

Figure 7. Study information sheet. It will be given to all patients after acute treatment.

Annex 3. Informed consent of the coronary angiography

Hospital Universitari de Girona
Doctor Josep Trueta

ESTUDI HEMODINÀMIC/INTERVENCIONISME CORONARI (ANGIOPLÀSTIA)

Per què us hem de fer aquesta exploració?
Per conèixer l'estat del vostre cor, com us haurà explicat el vostre metge.

En què consisteix?
En la introducció d'uns catèters (tubs molt fins de plàstic) dintre de les artèries i les venes, mitjançant de la punció d'una agulla d'injecció.

Com us prepareu?
Heu d'estar en dejuni de 6 hores.
Us heu de dutxar el mateix dia.
Us rasuraran l'engonal o el braç.

Com es desenvolupa la tècnica?
Es fa en una mena de quiròfan, en condicions d'esterilitat.
Us donaran un tranquil.litzant i us posaran anestèsia local a la zona de la punció (preferentment l'engonal).
A continuació us introduiran uns catèters a través de les artèries i excepcionalment de les venes de la zona, dirigint-los fins al cor mitjançant control per radioscòpia.
Us injectaran un contrast per poder veure el funcionament del vostre cor i de les seves artèries, valorant així les possibles lesions que les poguessin obstruir.
Si veiem que té lesions que obstrueixen les artèries del cor i que es compleixen les condicions necessàries (el diagnòstic està prou clar, vostè i el seu/seva metge/ssa hi estan d'acord) podem fer-li la possible intervenció o angioplàstia en el mateix acte.

En què consisteix l'angioplàstia?
En desobstruir les lesions que té mitjançant un catèter molt fi provist d'un globus a la punta que s'infla a pressió, dilatant la zona obstruïda, millorant el pas de la sang en aquest nivell. Aquest procediment pot repetir-se. De vegades cal col.locar dintre de l'artèria una malla metàl.lica (pròtesi intravascular o stent). L'elecció de cada tècnica dependrà del tipus de lesió coronària existent.

Quan s'acaba?
Quan es retiren els catèters i es fa la compressió del lloc de la punció per tal d'evitar que sagni. Si s'ha fet l'angioplàstia, s'hi deixa un petit introductor durant unes hores per seguretat, que es retirarà de la mateixa manera. La durada del procediment és variable, i un cop finalitzat el pacient romandrà al llit durant vàries hores. L'èxit inicial s'obté en més del 90% dels casos.

Us farà mal?
El tranquil.litzant i l'anastèsic local eviten pràcticament el dolor.

Figure 8. Informed consent sheet of the catheterization procedure. It will be given to all patients before starting the coronary angiography.

Hospital Universitari de Girona
Doctor Josep Trueta

Quines molèsties i complicacions podeu tenir?

Podeu notar palpitacions provocades pels catèters o al injectar-vos el contrast, notant una sensació passatgera i tolerable de calor, induïda pel mateix contrast o algunes medicacions administrades. Rarament, reaccions al.lèrgiques imprevistes.

Podeu tenir molèsties lleus en la zona de punció i/o en certs casos aparèixer un hematoma que s'absorbirà quasi espontàniament. Tanmateix, podeu notar dolor al pit (angina) en el moment de fer la dilatació.

En certs casos poden presentar-se altres complicacions greus (hemorràgia que requereixi transfusió, arítmies severes), i molt ocasionalment infart de miocardi (3-5%), o dissecció coronària que precisarà cirurgia cardíaca (2%). Si fos el cas, aquesta cirurgia es practicaria en el nostre Hospital de referència (Hospital Clínic de Barcelona), traslladant-se en les millors condicions possibles. El risc de mort és excepcional (al voltant de l'1%). En tot cas els beneficis derivats d'aquesta tècnica superen els esmentats riscs, i en el cas d'aparèixer complicacions, el personal mèdic i d'infermeria està altament qualificat, disposant dels medis adequats per solventar-los.

En cas que sorgeixin situacions imprevistes durant l'actuació, autoritzo per realitzar el que en aquell moment es condireri el més convenient i necessari, sempre i quan no sigui possible un nou full de consentiment.

Altres riscs o complicacions que podrien aparèixer, donada la vostra situació clínica i les vostres circumstàncies personals són:

_____
_____
_____

Autorització

He rebut la suficient informació sobre l'exploració, tractament i/o intervenció quirúrgica que em realitzaran. He pogut fer preguntes sobre aquesta al/la Dr/Dra _____ . Puc canviar d'opinió en qualsevol moment, abans de la realització del procediment, si així ho crec convenient. He comprès la informació que m'ha estat donada, i per això conscientment autoritzo que es porti a terme el dit procediment.

Autorització del representant legal (en cas de malalts incapacitats o menors d'edat)

Atès que el malalt no pot donar el seu consentiment de voluntat pròpia, declaro com a representant legal d'aquest, haver rebut informació suficient i haver comprès la informació rebuda referent al procediment al qual se sometrà el malalt, per això, conscientment:

Aquest consentiment es formula d'acord amb allò que Estableix a l'Ordre de la Generalitat de Catalunya, Publicada en el DOGC nú. 1477, de 7 d'agost de 1991.

A Girona, _____ de _____ de _____

Figure 9. Informed consent sheet of the catheterization procedure. It will be given to all patients before starting the coronary angiography.

Annex 4. Information and informed consent of the OCT

**Hospital Universitari de Girona
Doctor Josep Trueta**

CONSENTIMIENTO INFORMADO DE ESTUDIO CON TOMOGRAFÍA DE COHERENCIA ÓPTICA INTRACORONARIA (OCT)

1. ¿Por qué hacemos esta prueba?

   Esta prueba la haremos porque hemos visto que sus arterias coronarias están sanas. Con esta prueba podremos saber qué es lo que ha causado el infarto de miocardio y así poder tratar mejor la enfermedad.

2. ¿En qué consiste?

   Después de la coronariografía, introduciremos un catéter (tubos muy finos de plástico) dentro de las arterias y venas. Usted no notará nada distinto a la coronariografía previa. De hecho, se hace continuadamente tras esta última, una vez dentro de la circulación.

3. ¿ En que me beneficiará esta prueba?

   Con esta técnica podremos observar mucho mejor sus arterias, y así intentar determinar cual es la causa del infarto. De esta manera podremos tratar su enfermedad lo más adecuadamente posible.

4. ¿Qué molestias y complicaciones puede tener?

   Usted podrá notar palpitaciones provocadas por le catéter. En ciertos casos pueden presentarse complicaciones graves (hemorragia que requeriría transfusiones, arritmias graves), y muy ocasionalmente infarto de miocardio (3-5%), o disección coronaria que requeriría que requeriría cirugía cardiaca (2%).

   Yo …………………………. he recibido suficiente información acerca de la prueba de OCT y autorizo para ser intervenido con esta técnica. En caso de que el paciente no pueda dar el consentimiento se dará este consentimiento al representante legal del mismo.

   Firma paciente: Firma médico:
   (__/__/____)   (__/__/____)

Figure 10. OCT Information and informed consent will be given yo patients with no corornary artery disease.

Annex 5. Informed consent from the study

**Hospital Universitari de Girona
Doctor Josep Trueta**

Consentimiento informado del Estudio

Yo,_____.

- He leído la hoja de información sobre el estudio que se me ha entregado.

- He podido hacer todas las preguntas necesarias respecto al estudio.

- He recibido suficiente información acerca del estudio.

- He estado informado sobre el investigador……………………..de las implicaciones y la finalidad del estudio.

- Entiendo que mi participación es voluntaria.

- Entiendo que los datos facilitados por mi persona serán totalmente confidenciales.

- Entiendo que puedo revocar mi consentimiento informado de participación en el estudio, sin tener que dar explicaciones y sin que ello afecte a mi asistencia sanitaria.

➢ ¿Acepta que los investigadores del estudio puedan contactar con usted si en un futuro se considera oportuno?

Sí   No

➢ ¿Da su consentimiento para que información de su persona sea utilizada en el estudio?

Sí   No

Firma del participante   Firma del investigador

Fecha: ____/____/____   Fecha: ____/____/____

Figure 11. Informed consent of the study. Patients must will receive it after the acute treatment.

Annex 6.1. Information about the patient in diagnose

Hospital Universitari de Girona Doctor Josep Trueta

HOJA DE DIAGNÓSTICO DE PACIENTE Nº_____

- Edad:
- Sexo (hombre/mujer):
- Hipertensión arterial (si/no):
- Diabetes mellitus (si/no):
- Dislipidemia (si/no):
- Antecedentes familiares de cardiopatía isquémica (si/no):
- Fumador (si/no):

- Frecuencia cardiaca (lpm):
- Presión sistólica (mmHg):
- Presión diastólica (mmHg):
- HDL (mg/dl):
- LDL (mg/dl):
- Pico Troponinas ultrasensibles (ng/dl):
- Creatinina:

- Elevación del ST:
- No elevación ST:
- Fracción eyección (preservada(>50%), Moderada (30-40%), Severa<30%):
- Tratamiento previo:
    - Aspirina:
    - Beta bloqueantes:
    - Clopidogrel:
    - Anticoagulantes:
    - Bloqueadores del canales del calcio:

DIAGNÓSTICO

- Infarto de miocardio con coronarias sin obstrucción significativa:

- Infarto de miocardio con coronarias con obstrucción significativa:

    - Placa complicada:
    - Nódulo calcificado:
    - Vasoespasmo:
    - Síndrome de tako-tsubo:
    - Disección coronaria espontánea:

Firma becario (__/__/____):   Firma médico responsable (__/__/____):

Figure 12. Diagnose sheet, in which epidemiological information wil be written.

Annex 6.2. Information sheet at 30 days

**Hospital Universitari de Girona
Doctor Josep Trueta**

HOJA DE SEGUIMIENTO A LOS 30 DIAS DE PACIENTE Nº_____

IMPRESIÓN MÉDICA:

DIAGNÓSTICO:

- Infarto de miocardio con coronarias sin obstrucción significativa:

- Infarto de miocardio con coronarias con obstrucción significativa:

  - Placa complicada:
  - Nódulo calcificado:
  - Vasoespasmo:
  - Síndrome de tako-tsubo:
  - Disección coronaria espontánea:

INCIDENCIA DE MACE A LOS 30 DIAS:

- Insuficiencia cardiaca:
- Reinfarto o angina:
- Accidente cerebrovascular
- Patología vascular periférica:
- Arritmias:
- Muerte por causa cardiovascular:
- Muerte súbita:
- Muerte por otra causa:
- No incidencia de MACE:

Firma becario (__/__/____):   Firma médico responsable (__/__/____):

Figure 13. Sheet where incidence of MACE at 30 days after myocardial infarction will be collected.

Annex 6.3. Information sheet at 1 year

Hospital Universitari de Girona
Doctor Josep Trueta

HOJA DE SEGUIMIENTO A LOS 365 DIAS DE PACIENTE Nº_____

IMPRESIÓN MÉDICA:

DIAGNÓSTICO:

- Infarto de miocardio con coronarias sin obstrucción significativa:

- Infarto de miocardio con coronarias con obstrucción significativa:

  - Placa complicada:
  - Nódulo calcificado:
  - Vasoespasmo:
  - Síndrome de tako-tsubo:
  - Disección coronaria espontánea:

INCIDENCIA DE MACE A LOS 365 DIAS:

- Insuficiencia cardiaca:

- Reinfarto o angina:

- Accidente cerebrovascular

- Patología vascular periférica:

- Arritmias:

- Muerte por causa cardiovascular:

- Muerte súbita:

- Muerte por otra causa:

- No incidencia de MACE:

Firma becario (__/__/____):   Firma médico responsable (__/__/____):

Figure 14. Sheet where incidence of MACE at 1 year after myocardial infarction will be collected.

Annex 7. Budget

EXPENSES	COSTS
1.Personal expenses	
2.Executive expenses	
Diagnostic Equipment	
Services procurement	
OCT utilization master class	400€
Statistical Analysis (x90h, per 35€/h)	3150€
Computer scientific and computer	770€
Coordination meetings	1.200€
3.Publications and dissemination expenses	
Scientific publications and English translation	2.000€
Attendance to medical congresses (SEC and ECC)	1.500x2= 3.000€
TOTAL	10.520€

Table 1. SEC: "Sociedad Española de Cardiología" / ESC: "European Society of Cardiology"; OCT: intracoronary optical coherence tomography.

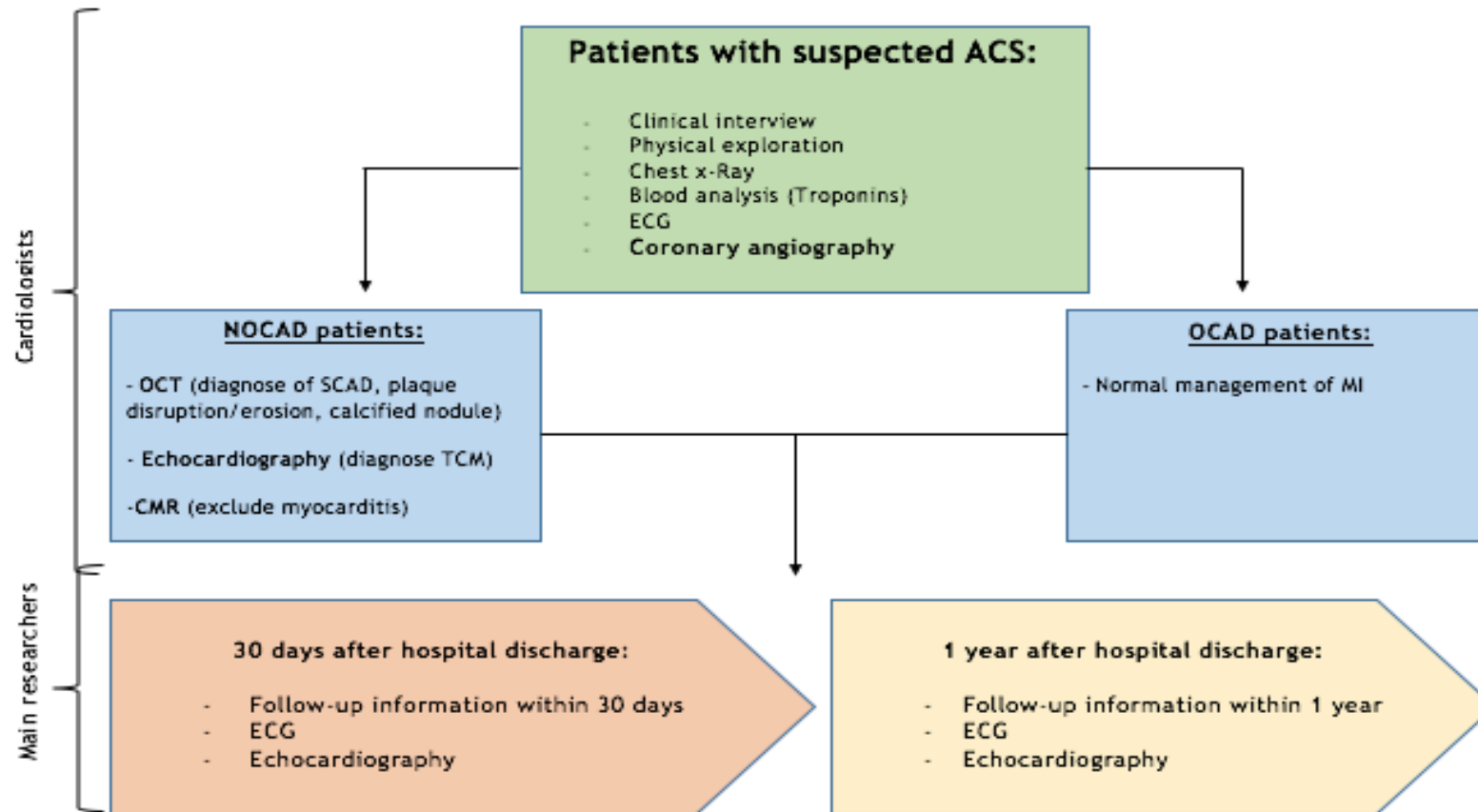# Annex 8. Patient chronogram

Figure 15. This is the patient chronogram. The diagnose task will be done by all the cardiologist. While the main researchers will be in charge of the follow-up of the study, as we can see in the figure. ACS: "Acute coronary syndrome; NOCAD: "No obstructive coronary artery disease"; OCAD: "obstructive coronary artery disease"; OCT: "intracoronary optical coherence tomography"; SCAD: "Spontaneous coronary artery dissection"; TCM: "Tako-Tsubo cardiomyopathy"; CMR: "Cardiac magnetic resonance"; ECG: "Electrocardiogram"; MI: "Myocardial infarction".