# BENEFITS IN LEFT VENTRICULAR EJECTION FRACTION AND GLOBAL LONGITUDINAL STRAIN OF PERCUTANEOUS CORONARY INTERVENTION VS OPTIMAL MEDICAL THERAPY IN PATIENTS WITH CORONARY TOTAL OCCLUSIONS

**A MULTI-CENTRIC, RANDOMIZED, OPEN AND CONTROLLED CLINICAL TRIAL**

FINAL DEGREE PROJECT

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*M'agradaria donar les gràcies al meu tutor Daniel Rivero per la seva dedicació i disposició en tot moment.*

*Així com al servei de Cardiologia de l'Hospital Universitari Dr Josep Trueta per fer-me sentir com una més.*

*Per últim a la meva família, pel recolzament infinit que em donen dia a dia, sense vosaltres no seria la persona que sóc avui.*

# INDEX

# ABREVIATION LIST

| | |
|---|---|
| **ACS** | Acute coronary syndrome |
| **CABG** | Coronary artery bypass grafting |
| **CAD** | Coronary artery disease |
| **CART** | Controlled antegrade and retrograde tracking |
| **CMR** | Cardiac magnetic resonance |
| **CTO** | Chronic total occlusion |
| **CVRF** | Cardiovascular risk factor |
| **DAPT** | Dual antiplatelet therapy |
| **GLS** | Global longitudinal strain |
| **HUDJT** | Hospital Universitari Doctor Josep Trueta |
| **IHD** | Ischemic heart diseases |
| **LV** | Left ventricle |
| **LVEDV** | Left ventricular end-diastolic volume |
| **LVEF** | Left ventricular ejection fraction |
| **MACCE** | Major adverse cardiovascular and cerebrovascular events |
| **OMT** | Optimal medical therapy |
| **PCI** | Percutaneous coronary intervention |
| **STEMI** | ST-elevation myocardial infarction |
| **TIMI** | Thrombolysis in myocardial infarction |

# ABSTRACT

**BACKGROUND**

Chronic total occlusions (CTO) are observed in approximatively 20% of patients with coronary artery disease undergoing coronary angiography. This fact reflects that CTO involves a significant amount of population. However, treatment of CTO lesions has been a matter of controversy and revascularization rates have historically been low. Percutaneous coronary intervention (PCI) is performed only in 15% of the patients with CTO, most of the them are treated with optimal medical therapy (OMT) alone. Despite the low rate of revascularization, there are many observational studies that have reported clinical benefits of successful CTO-PCI, but only four clinical trial are published until now. Within this four, only one has evaluated the ventricular function and did not show differences between the two groups, in addition it only evaluate patients with STEMI. Nevertheless, observational studies and the clinical practice has shown that a successful revascularization improve the left ventricular function. For that reason is still a need to carry out more randomized clinical trials.

**OBJECTIVES**

The aim of the study and primary objective is to compare the left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) values between the two arms of treatment after 4 and 12 months. One arm of treatment will be PCI plus OMT, and the other will be only OMT. Secondary objective will be to evaluate major adverse cardiovascular and cerebrovascular events (MACCE) occurrence during follow-up.

**METHODS**

It will be a phase IV, prospective, multi-centric, open-label, randomized, controlled clinical trial with parallel groups. Patients diagnosed with a CTO will be randomly assigned with a ratio 1:1 to receive strategy with OMT, or PCI in the CTO plus OMT. The population of the study will be patients with an age over 18 years old diagnosed with at least one CTO in the three principle arteries in reference hospitals of Catalonia.



**KEYWORDS**

Chronic Total Occlusions; Percutaneous Coronary Intervention; Optimal Medical Therapy; Left Ventricular Ejection Fraction; Global Longitudinal Strain.

# 1. INTRODUCTION

## 1.1. CORONARY CIRCULATION

### Right coronary artery

It originates from the right aortic sinus of the ascending aorta. It runs along the coronary groove surrounding the heart to the posterior wall, over the diaphragmatic face and base of the heart (figure 1). During this path numerous branches appear:

- Branch of the sinoatrial node.
- Right marginal branch.
- Posterior interventricular branch or posterior descending artery: it is its major terminal branch. The dominance of the coronary arterial system is defined by the artery which gives rise to this branch. Approximately 70% of the population has right dominance. It also sends septal branches to the interventricular septum.
- Atrioventricular node branch.
- Right posterolateral branch.

It irrigates the following parts: right atrium and ventricle, sinoatrial and atrioventricular nodes, interatrial septum, part of the left atrium, 1/3 posteroinferior of the interventricular septum, part of the back of the left ventricle (LV) (1–3).

### Left coronary artery

It originates from the left aortic sinus of the ascending aorta. It is divided into its two terminal branches:

- Circumflex branch: it goes through the coronary groove to the left, to go to the posterior heart wall. From it, the left marginal branch is born. In 40% of population, the sinoatrial node branch originates from the circumflex.
- Anterior interventricular branch or anterior descending artery: is the main artery of the heart, it descends through anterior interventricular groove to the apex. During this path it can originate one or two diagonal branches that descend diagonally across the anterior surface of the LV. It also gives rise to several septal branches that supply the interventricular septum.

It irrigates the following parts: most of the atrium and LV, part of the right ventricle, 2/3 of the interventricular septum, including the atrioventricular fascicle (1–3) (figure 1).

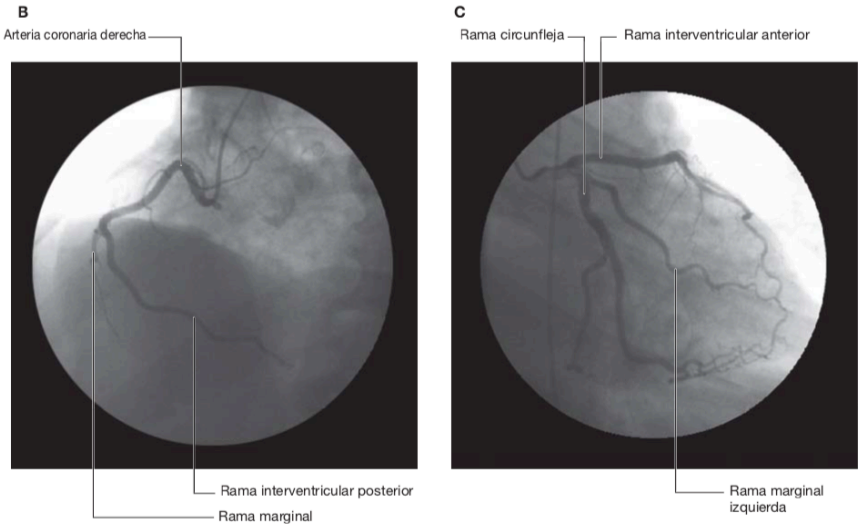


*Figure 1. B. Oblique left anterior vision of the right coronary artery. C. Oblique right anterior vision of the left coronary artery from (3).*

**Venous system**

Cardiac veins run mostly along with the coronary arteries as major, middle and minor cardiac veins and meet in the coronary sinus that flows into the right atrium (1–3).

## 1.2. DEFINITION OF CHRONIC TOTAL OCCLUSION

Coronary CTO is defined as "100% stenosis with Thrombolysis In Myocardial Infarction (TIMI) (ANNEXE 1) grade 0 flow for more than three months" (4) (Figure 2 and 3).

Non-intra-luminal collaterals may provide antegrade flow to the distal vessel and give a false functional incomplete occlusion, for that reason it has to be distinguished from flow within the occluded segment by careful frame-by-frame assessment using different angiographic planes (4–6).

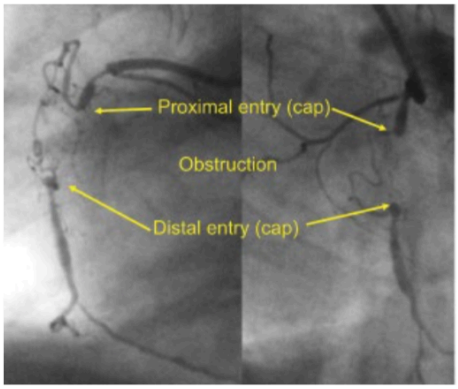


*Figure 2. The basic features of chronic total coronary occlusion (a and b) from (13).*

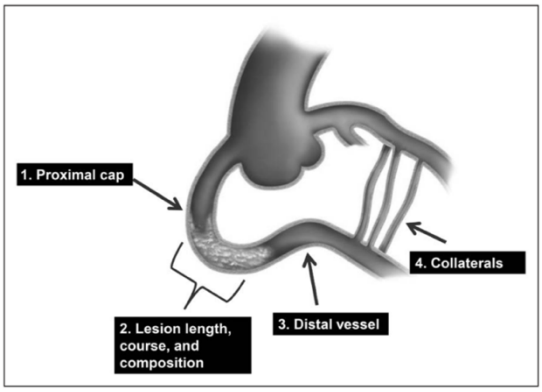


*Figure 3. The 4 key angiographic parameters that need to be assessed to plan chronic total occlusion percutaneous coronary intervention from (14).*

### 1.2.1. Occlusion duration

Sometimes the duration of the occlusion is difficult to determine and the EuroCTO Club has suggested 3 levels of certainty (6):

a) Certain (angiographically confirmed): the minority of cases where a previous angiogram (for instance before a previous coronary artery bypass grafting (CABG) operation, or after an acute myocardial infarction) has confirmed the presence of TIMI 0 flow for $\geq 3$ months prior to the planned procedure.
b) Likely (clinically confirmed): objective evidence of an acute myocardial infarction in the territory of the occluded artery without other possible culprit arteries $\geq 3$ months before the current angiogram.
c) Possible (undetermined): a CTO with TIMI 0 flow and angiographic anatomy suggestive of long-standing occlusion (collateral development, no contrast staining) with stable anginal symptoms unchanged in the last 3 months or evidence of silent ischemia; in case of recent acute ischemic episodes (acute myocardial infarction or unstable angina or worsening effort angina), a culprit artery other than the occluded vessel should be present.

### 1.2.2. Collateral circulation in CTOs

As we have already said, CTO typically have collateralization of distal vessel on coronary angiography, and is found in ~90% of cases. Developing this network is related to the distribution extent of the donor artery, microvascular function, chronicity of occlusion and left ventricular function, and its circulation may be bidirectional.

In general, collaterals are able to maintain baseline myocardial blood supply, but they are limited in their functional reserve and will not prevent exercise induced ischemia, resulting in anginal symptoms.

Moreover, the presences of collaterals does not predict viability, as they also found in patients with prior myocardial infarction and large akinetic territories, so viability stills needs to be tested in well collateralized CTOs (4,6–8).

## 1.3. EPIDEMIOLOGY

CTO are observed in approximatively 15-20% of patients with coronary artery disease (CAD) (defined as $\geq$ 50% stenosis in at list one coronary artery) undergoing coronary angiography.

The CTO prevalence is higher in patients with prior CABG (~90%), an lower in patients referred for ST-Elevation Myocardial Infarction (STEMI) where is only a 10%.

The right coronary artery is the most common CTO vessel, representing about half of the CTO cases.

Despite this, the true prevalence of CTO in general population is unknown as a certain proportion of patients with CTO are asymptomatic or minimally symptomatic (4,9).

## 1.4. CLINICAL PRESENTATION

The clinical characteristics can be variable; some of them are patients with stable angina, exercise limitation, dyspnea, silent ischemia or heart failure of ischemic origin, and others are patients with new-onset angina or undergoing primary PCI due to acute coronary syndrome (ACS) in a different culprit vessel, and in whom a CTO is revealed as an incidental finding (6,9).

## 1.5. TREATMENT

The mode of treatment selected for a patient with CTO is individualized an it is based on the severity of symptoms and ischemia and on the severity of concomitant CAD.

As with any patient with stable CAD, treatment should include OMT, and patients who remain symptomatic or have a large burden or ischemia despite maximal medical therapy can be considered for revascularization (8).

### 1.5.1. Optimal medical therapy

As with any patient with stable CAD, treatment should include anti-anginal therapy and therapies to prevent new events (10).

*Table 1. Optimal medical therapy in patients with chronic coronary syndrome (10, 34-36).*

| | | | |
|---|---|---|---|
| **EVENT PREVENTION** | **ANTIPLATELET DRUGS** | - Aspirin<br>- Clopidogrel (alternative in patients with aspirin intolerance)<br>- Other options: Ticagrelor or Prasugrel | All patients should take it. |
| | **STATINS** | Goal of treatment: A therapeutic regimen that achieves ≥ 50% LDL reduction from baseline and an LDL goal of < 55 mg/dL. | |
| **ANTI-ANGINAL THERAPY** | **CHRONIC TREATMENT** | - First choice: beta-adrenergic blockers<br>- Second choice: calcium channel blockers<br>- Others: long-acting nitrate formulations, ivabradine… | Response to initial anti-anginal therapy should be reassessed after 2-4 weeks of treatment initiation. |
| | **RESCUE THERAPHY (for acute effort angina)** | - Sublingual or spray nitroglycerin | The patient should rest in a sitting position.<br>Take 0,3 – 0,6 mg tablet sublingually or 0,4 mg spray every 5 minutes until the pain disappears or a maximum of 1,2mg has been taken within 15 min.<br>During this time frame, if angina persist, immediate medical attention is needed.<br>*Prophylaxis: before physical activities known to provoke angina. |
| If the patient has HF or reduced LVF, we have to ADD the following therapies: | | | |
| **HEART FAILURE or REDUCED LEFT VENTRICULAR FUNCTION** | **GENERAL TREATMENT** | - ACE inhibitors<br>- ARB as an alternative in patients who do not tolerate ACEI<br>- MRA: we added in patients with persistent symptoms and LVEF ≤35%<br>- ARNI: patients LVEF ≤35% who remain symptomatic despite OMT with ACEI + BB + MRA. It is recommended as a replacement for an ACEI | The start of treatment should be when LVEF <45-50% despite the patients persist asymptomatic. |
| | **SYMPTOMATIC TREATMENT** | - Diuretic therapy: in symptomatic patients to relieve symptoms or signs of congestion | |

*ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BB = beta blocker; HF = heart failure; LVEF = left ventricular ejection fraction; LVF = left ventricular function; MRA = mineralocorticoid receptor antagonist; OMT = optimal medical therapy.*

### 1.5.2. Myocardial revascularization

#### 1.5.2.1. Coronary artery bypass grafting surgery

For patients with CTO and significant concomitant left main and/or multivessel CAD, CABG is often chosen, given the complexities involved with PCI in this setting and the greater likelihood of achieving complete revascularization compared with PCI (8).

The choice of one technique or the other is based, among other things, in the SYNTAX score, that reflects a comprehensive anatomical assessment, with higher scores indicating more complex coronary disease; low score is defined as ≤22, intermediate score as 23 to 32, and high score as ≥33 (11). CTO is a major contributor to a high SYNTAX score (ANNEXE 2).

#### 1.5.2.2. Percutaneous coronary intervention

Current guidelines recommend (class IIa B) that percutaneous revascularization of CTOs should be considered in patients with angina resistant to medical therapy or with a large area of documented ischemia in the territory of the occluded vessel (12).

Despite this, there is no robust evidence on the benefits of this treatment (4) so, in order to identify patients and select specific lesions that are likely to benefit from myocardial revascularization, in addition to OMT, we should evaluate some important points:

1. Presence of collaterals:

   It is an indispensable prerequisite to opening a CTO because in the absence of collaterals, no viable myocardium would have survived. On the other hand, an optimum assessment of collateral function demonstrated that even angiographically well-developed collaterals this are not sufficient to prevent ischemia and cannot be an excuse for not trying to revascularize a CTO (13).
2. Demonstration of ischemia and viability:

   We can use different non-invasive imaging tools: non-invasive stress imaging (Cardiac magnetic resonance (CMR), stress echocardiography, SPECT or PET) may be considered before the decision on revascularization (12).
3. Patients who would be able to achieve some of the basic goals of CTO-PCI:
   - Relive exercise limiting symptoms of angina or dyspnea, especially in patients with preserved left ventricular function, or to resolve ischemia caused by the CTO, similar to the indication in stable angina caused by non-occlusive lesions.
   - Improve regional left ventricular dysfunction in the territory of the occluded artery, provided there is residual viability (13).
4. Evaluation of anatomic and clinical complexity:

   The J-CTO score is the most used, and is used to estimate the probability of success of the procedure within 30 minutes. It include some predictors of failure which are; prior failed attempt, angiographic evidence of heavy calcification, bending $\geq$ 45º within the occluded segment, blunt proximal stump, and occlusion length >20mm. CTO lesions are graded as easy, intermediate, difficult and very difficult (4) (ANNEXE 3).
5. Assessment within the medical equipment:

   Finally, with all the information, the responsible team should make the decision to revascularize, taking into account the objective probability of achieving angiographic/clinical success with PCI (4).

Is important to know that success rates are strongly dependent on operator skills, the experience with specific procedural techniques, and the availability of dedicated equipment, these rates vary from 60–70% to >90% (12).

The figure 4 represents a treatment algorithm.

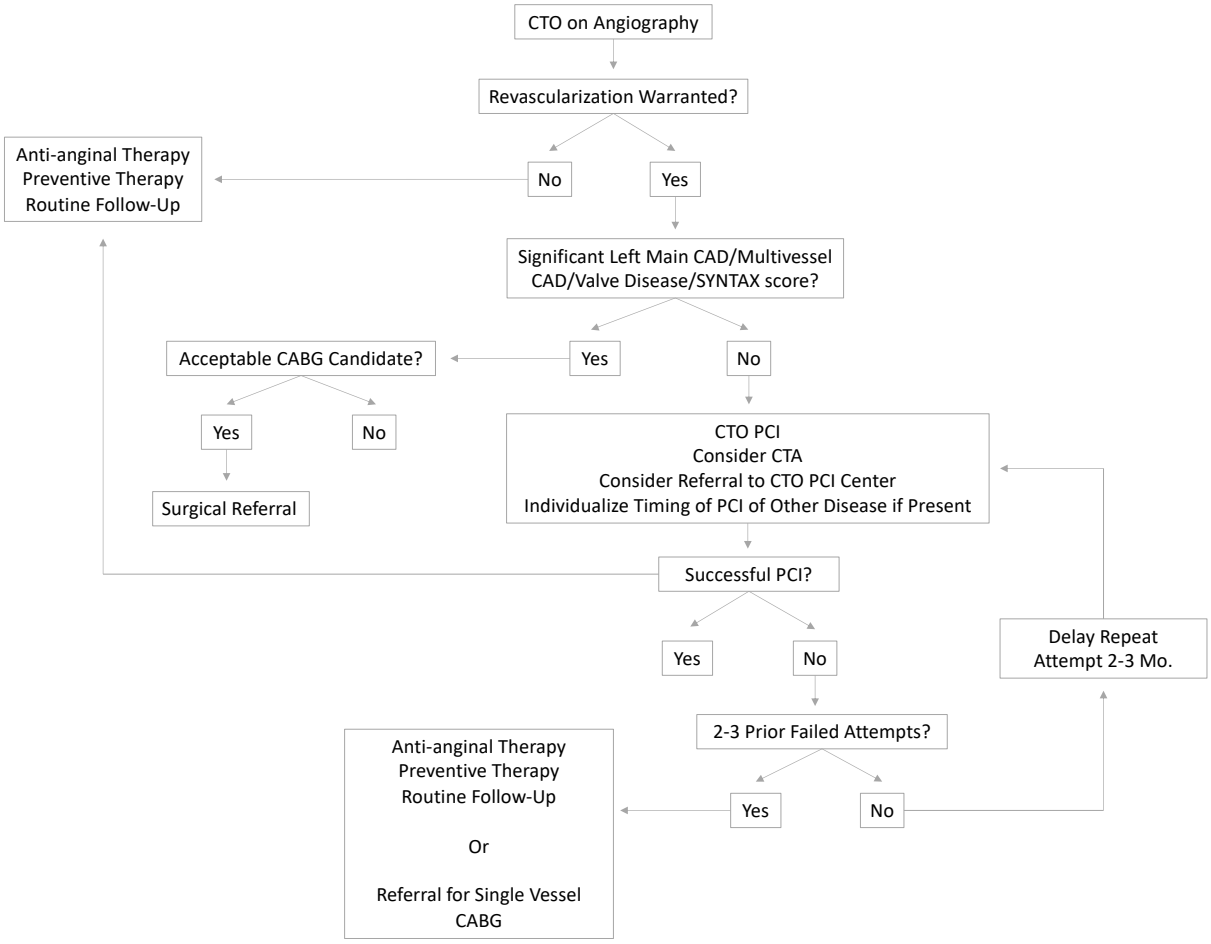


*Figure 4. Suggested management algorithm for a patient with coronary chronic total occlusion (CTO). CAD indicates coronary artery disease; PCI, percutaneous coronary intervention; CTA, computed tomographic angiography; and CABG, coronary artery bypass graft surgery, adapted from (8).*

### 1.6. PCI TECHNIQUE IN CTO

CTO recanalization is a complex technique that must be performed by a professional with experience and involves more time and effort than a non-CTO artery revascularization. The most different aspects are; more radiology exposure, more contrast needed and more technical difficulty.

It is mandatory to ensure an optimal guide catheter support with a large enough lumen to host devices in parallel, as well as two arterial sheaths for contralateral injections. The double injection can improve procedural safety by clarifying guidewire location during crossing attempts.

The different choices for access are: bifemoral artery, biradial artery, radial and femoral, and two ipsilateral femoral sheaths. While the radial approach appears more complicated, especially in very complex CTO procedures, none of the approaches was shown to be superior to any other (4).

### 1.6.1. Periprocedural anticoagulation

Regarding periprocedural anticoagulation, an initial bolus of intravenous unfractionated heparin (100 IU/kg) is generally administered. The activated clotting time is monitored every 30 minutes to determine to control if an additional bolus of unfractionated heparin is necessary to maintain an activated clotting time >250-300 seconds (4).

EuroCTO club members suggested not to use the other anticoagulants because in case of blood extravasation anticoagulation can not be reverted (6).

### 1.6.2. CTO crossing strategies

There are 4 different CTO crossing strategies, classified according to wiring direction (antegrade and retrograde) and whether or not the subintimal space is used (wiring versus dissection and reentry).

#### 1.6.2.1. Antegrade wire escalation

Antegrade wire escalation is the most used CTO crossing technique, and it is performed in approximately 75% of cases. Various guidewires are advanced in the antegrade direction (original direction of blood flow), it is a true-to-true lumen approach (4,14).

Usually a polymer-jacketed, low penetration force, tapered guidewire is used firstly, with subsequent escalation to intermediate and high penetration force guidewires, as required. However, guidewire choice depends on CTO characteristics, it depend if the proximal cap is tapered or blunt.

Stiff, high penetration force guidewires may be required in highly resistant proximal caps or when areas of resistance are encountered within the body of the occlusion. After proximal cap crossing of 1 to 2 mm, however, deescalation to less penetrating guidewires should follow to navigate through the CTO segment.

If the guidewire enters into the distal true lumen, the microcatheter is then advanced into the distal true lumen, and the dedicated CTO guidewire is then exchanged for a workhorse guidewire through the microcatheter to minimize the risk for distal vessel injury and perforation during balloon angioplasty and stenting, it is called wire deescalation (14) (figure 5).

#### 1.6.2.2. Antegrade Dissection and Reentry

Antegrade dissection and reentry involves entering the subintimal space, followed by subintimal crossing of the CTO with subsequent reentry into the distal true lumen. Antegrade dissection and reentry may be intentional or unintentional during antegrade wiring attempts (14) (figure 5).

#### 1.6.2.3. Retrograde approach

The retrograde technique differs from the antegrade approach in that the occlusion is approached from the distal vessel with guidewire advancement against the original direction of blood flow (figure 5), normally through septal branches.

A guidewire is advanced into the artery distal to the occlusion through a collateral channel or through a bypass graft, followed by placement of a microcatheter at the distal CTO cap.

Retrograde CTO crossing is then attempted either with retrograde wiring (usually for short occlusions, especially when the distal cap is tapered) or using retrograde dissection/reentry techniques.

The most commonly used retrograde crossing technique is reverse controlled antegrade and retrograde tracking (CART), it consists on the antegrade introduction of a guide through the CTO, using a retrograde balloon dilation to create a local subintimal dissection to facilitate the passage of the guide to the true distal light (14,15) (figure 6).

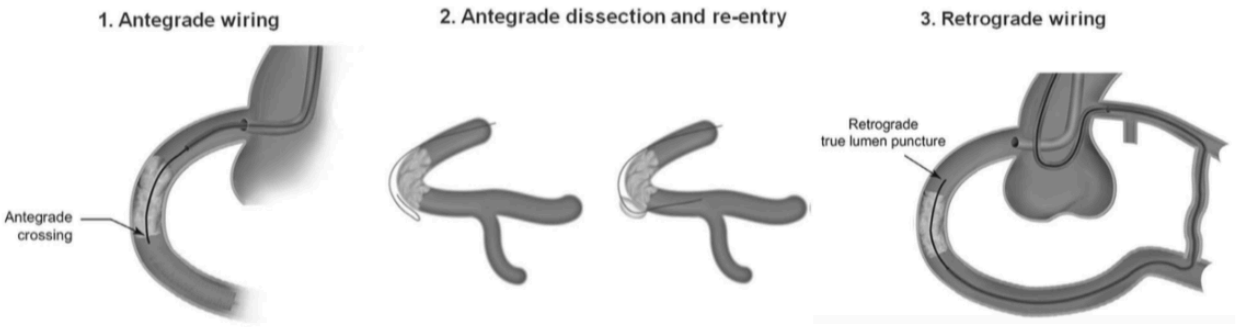


*Figure 5. Illustration of the chronic total occlusion crossing techniques, adapted from (18).*

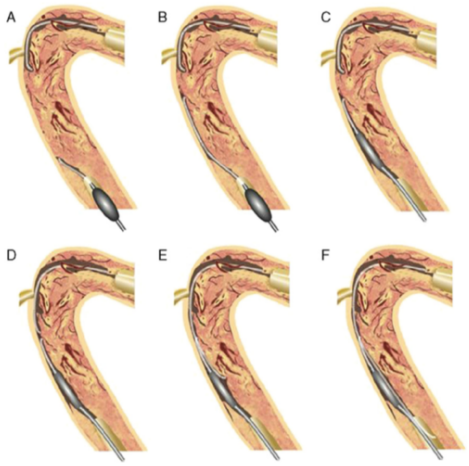


*Figure 6. Concept of CART from (20).*

#### 1.6.2.4. "Hybrid algorithm"

Selecting the initial and subsequent crossing strategies depends on the CTO lesion characteristics and local equipment availability and expertise.

However, flexibility is important for the success, safety, and efficiency of CTO-PCI. If the initial crossing strategy fails to achieve progress, small changes (such as modifying the guidewire tip angulation or changing guidewire) or more significant changes (such as converting from an antegrade to a retrograde approach) should be made (14).

The integration of the techniques mentioned before into a homogeneous strategies has become known as the "hybrid algorithm". This approach was developed by North American operators in 2012 in order to optimize procedural efficienty and is based on the concept of a rapid switch from one approach to another in case of low likelihood of success.

The hybrid algorithm has been shown to be effective (success rates of ~90%), safe (low rate of complications), and efficient (favorable procedural metrics) (4) (ANNEXE 4).

#### 1.6.2.5. Stent implantation

After successful recanalization of CTOs, implantation of drug-eluting stents reduces the rates of major cardiac events, restenosis and stent re-occlusion as compared to bare metal stents. Everolimus-eluting and zotarolimus-eluting stents (second-generation) are currently preferred for CTO interventions as they allow better outcomes compared to the first generation of DES (4).

#### 1.6.2.6. Medical therapy after CTO-PCI

Dual antiplatelet therapy (DAPT) for at least 6 months is currently recommended post-stenting in patients with stable ischemic heart disease (class I recommendation) (4). However, in specific clinical scenarios, this standard DAPT duration can be shortened (<6 months) or extended (>6–12 months) (12).

The algorithm for the use of antithrombotic drugs in patients undergoing PCI done by the European Society of Cardiology is shown in ANNEXE 5.

### 1.6.3. PCI complications

Advances in techniques and devices to treat CTOs have also reduced the rate of complications, where the rate of a major complications (death, emergent coronary artery bypass graft and stroke) is as low as 0.5%. In any case, operators should be aware of the complications that are more common in performing CTO PCI and this include cardiac (coronary and noncoronary) and extracardiac complications (16), showed in figure 7.

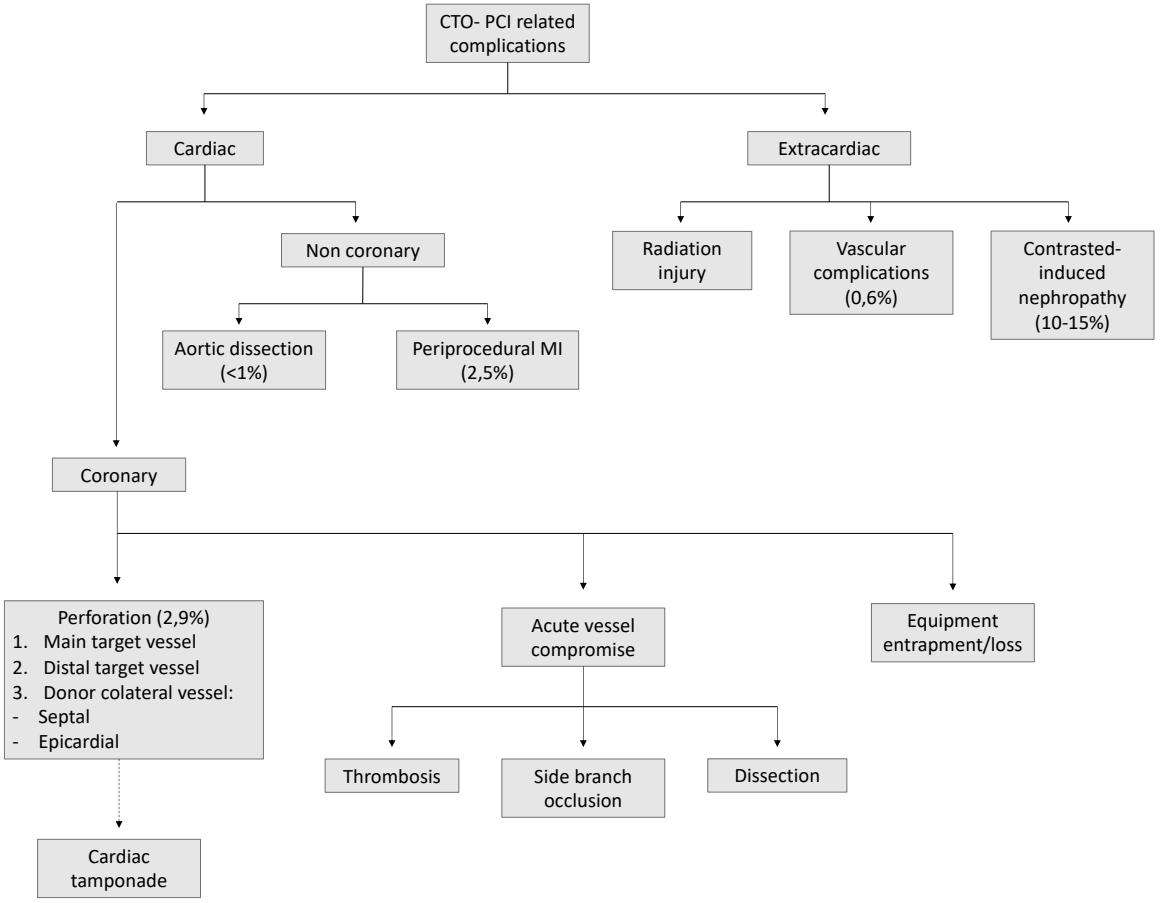


*Figure 7. Complications of percutaneous coronary intervention of chronic total occlusions adapted from (16).*

### 1.6.4. Current role of PCI in CTO patients

The role of percutaneous revascularization in patients with CTO has long been a subject of controversy due to two main factors; 1) lack of robust level of evidence A supporting treatment indications of CTO by PCI in clinical guidelines, and 2) CTO PCI is considered to be a technically challenging and costly procedure, and has been associated with a higher rate of complications (17).

For these reasons clinicians have been reluctant to refer a patient for CTO PCI, and the revascularization rate is only a 10-15% of all patients with CTO. Patients are normally treated with optimal medical therapy (17,18).

Despite that, in the lasts years the interest of the interventional community in CTOs has exponentially grown due to important developments in equipment and techniques. High rates of success and low rates of complications are now achieved by expert operators, even in complex cases (17).

Nowadays, current European guidelines recommended PCI of CTOs in patients with angina resistant to medical therapy or with a large area of documented ischaemia in the territory of the occluded vessel (Class IIa B) (12).

Nevertheless, several studies has reported improvement in quality of life and symptoms, including angina, heart failure and fatigue, LVEF, but there aren't enough randomized CTO clinical trials to wider adoption of CTO recanalization.

To supply this absence of robust evidence, some randomized clinical trials have been carried out and published recently (4).

The EXPLORE trial randomized patients with STEMI treated with primary PCI with a non-infarct-related CTO to be treated with PCI of the CTO or assigned to conservative treatment. Primary outcome were LVEF and left ventricular end diastolic volume (LVEDV) on CMR imagine after 4 months. It didn't find benefits for CTO PCI in terms of LVEF or LVEDV, despite that, it found in the left anterior descending coronary artery subgroup a significant higher LVEF. But this fact still needed further investigation (19).

The EUROCTO trial randomized CTO patients to CTO PCI plus OMT and OMT alone. Primary outcome was a change in health status subscales as assessed by Seattle Angina Questionnaire between the treatment groups at 12 months. A greater improvement was observed in the PCI group (20).

The IMPACTOR trial randomized patients with isolated of the right coronary artery to either PCI or OMT. Primary outcome was the change in myocardial ischemia burden at 12 months. It find a higher decrease in the primary outcome in the PCI group. Similarly, functional status and quality of life only improved in the PCI group, confirming the findings of EUROCTO trial in the setting of single-vessel disease CTO patients (21). Differences between this 3 clinical trails are shown in ANNEXE 6.

The DECISION trial randomized patients with CTO to OMT vs. CTO PCI. Primary outcome was a composite of death, myocardial infarction, stroke and any revascularization. Health quality was assessed at baseline and at 1, 6, 12, 24 and 36 months. Critical points in trial design include the fact that revascularization of non-CTO lesions was allowed in both groups and observed in more than 70% of patients (thus diluting the real impact of CTO recanalization on patient outcomes), extremely low enrolment even from high-volume centres (it suggests a strong selection bias), an high crossover rate. Not surprisingly, this trial did not find any difference in the primary endpoint (4,22).

Even though there are some published trials, clinical trials still remain a scientific gap.

# 2. JUSTIFICATION

Cardiovascular disease continues to cause a huge proportion of deaths and disability in Europe and within this group ischemic heart disease (IHD) is the most common cause, representing 20% of all deaths in 2015, followed by stroke. This fact represents an important burden on the health care systems and economies in Europe (23).

Within this population of patients with IHD, 20% undergoing a coronary angiography have a CTO. This fact reflects that CTO involves a significant amount of population.

However, treatment of CTO lesions has been a matter of controversy and revascularization rates have historically been low. Most of the patients are treated with a conservative strategy (OMT). PCI is performed only 10-15% of the patients with CTO (17), due to the fact that there isn't a robust level of evidence, as well as the complexity and high rate of complications associated with the techniques.

In recent years the techniques and success rate have been exponentially improved in specialized centers. That fact helps to try to establish percutaneous revascularization as valid treatment option for CTOs.

In addition, despite the low rate of revascularization, there are many observational studies that have reported clinical benefits of successful CTO-PCI as well as clinical practice (17), but only four clinical trial are published until now, as it has already been exposed. For that reason is still a need to carry out more randomized clinical trials.

Of the four studies previously mentioned, only one has evaluated LVEF and they have done it in a very specific population of patients with CTO, who are those who have suffered a STEMI, with a monitoring period of only 4 months, and no significant differences were found between the two branches.

Despite this results, clinical practices and observational studies show that there is an improvement on ventricular function, for that reason this study propose to analyse objective outcomes, therefore LVEF and GLS are chosen, because represents a strong predictor of left ventricular function and it can be translate to clinical outcomes. In other scenarios GLS has been used to assess the ventricular function, and non of the recent trials value it, so it would be another way to evaluate the possible improvement on the left ventricular muscle.

Moreover, the published clinical trials always include a selected patient group, so new registers including all-comers are important for the assessment of trends in treatment (4). For that reason the study pretend to include a larger population than not only a select patient group, since it is not the only clinical presentation in patients with CTO. Also it will not include patients with a previous STEMI.

To finish, the other trials that have a larger follow-up period and a wider sample of patients do not look at the ventricular function, and only evaluate more subjective outcomes such as change in health status.

# 3. HYPOTHESIS AND OBJECTIVES

## 3.1. HYPOTHESIS

A successful PCI in patients with CTO will improve their LVEF and/or GLS values compared to patients treated only with OMT strategy.

## 3.2. OBJECTIVES

Primary objective:

The aim of the study is to compare the change in LVEF and GLS values between the two groups of treatment after 4 and 12 months. Group A will be treated with PCI plus OMT, and the group B will be treated with OMT alone.

Secondary objective:

To evaluate major adverse cardiovascular and cerebrovascular events (MACCE) occurrence during follow-up in both groups.

# 4. METHODS

## 4.1. STUDY DESIGN

It will be a phase IV, prospective, multi-centric, open-label, randomized, controlled clinical trial with parallel groups.

Patients diagnosed with a CTO will be randomly assigned with a ratio 1:1 to receive a PCI in the CTO plus OMT, or OMT alone.

Considering the difficulty of recruiting the sample in its entirety in Hospital Universitari Dr Josep Trueta (HUDJT), it will be a multi-centric study, and data will be collected in different reference hospitals of Catalonia where CTO percutaneous intervention is done routinely, which are the following:

- Hospital Clínic de Barcelona, Barcelona
- Hospital Universitari de Bellvitge, Hospitalet de Llobregat
- Hospital Universitari Dr. Josep Trueta, Girona
- Hospital Universitari Joan XXIII, Tarragona
- Hospital Universitari Vall d'Hebron, Barcelona
- Hospital del Mar, Barcelona
- Hospital de Santa Creu I Sant Pau, Barcelona

## 4.2. STUDY POPULATION

The population of the study will be patients with an age over 18 years old diagnosed with at least one CTO in the 3 main coronary arteries (Left anterior descending coronary artery, Left circumflex coronary artery or Right coronary artery), in reference hospitals of Catalonia.

All patients must meet inclusion and exclusion criteria.

### 4.2.1. Inclusion criteria

- Patients $\geq$ 18 years old
- A chronic total occlusion with TIMI 0 flow of a coronary artery.
- Evidence of myocardial viability and ischemia by magnetic resonance
- Target artery diameter $\geq$ 2,5 mm
- Acceptance of informed consent
- Patients able to pursue the follow-up

#### 4.2.2. Exclusion criteria

- Patients <18 years old
- Hemodynamic instability
- Malignant neoplasm during the previous 5 years
- Concomitant diseases with life expectancy <1 year
- ACS <12 months before baseline
- Very restricting angina
- Contraindication for PCI or high procedural risk
- Several valvular heart disease requiring cardiac operation within 4 months
- Indication for CABG
- Non-acceptance of informed consent
- Pregnancy

### 4.3. SAMPLE

#### 4.3.1. Sample size

The online free application Calculadora de Grandària Mostral (GRANMO) has been used to calculate the sample size (24).

Accepting an alpha risk of 0,05 and beta risk of 0,2 in a two-sided test, 157 subjects are necessary per arm to recognize as statistically significant a difference greater than or equal to 4% in LVEF. Standard deviation is assumed to be 12% (19). It has been anticipated a drop-out rate of 10%.

It has been also calculated for GLS values and the sample obtained was smaller. For this reason, it has been decided to take LVEF as reference since it includes a higher number of patients.

#### 4.3.2. Sample selection

A non-probabilistic consecutive sampling method will be performed in patients diagnosed with at least one CTO. This is a multi-centric trail and different reference hospitals in Catalonia will be involved. The recruitment will be carried out in the cardiology department of each center. Once is guaranteed that patients meet the inclusion and exclusion criteria, they will be proposed to participate in the study and the informed consent (ANNEXE 7) will be given. Only those who sing it after reading the information can be enrolled in the study. Patients will be randomly assigned to one of the two treatment groups, avoiding, this way, the selection bias.

## 4.4. STUDY VARIABLES

### 4.4.1. Independent variables

The independent variables of this study are the administration of two different therapies to treat coronary CTO. The first group will be treated with **percutaneous coronary intervention** of the CTO associated to OMT. The second group receive a **OMT strategy;** symptoms will be treated only with the optimal medical treatment for each patient. These are defined as dichotomous qualitative variables.

### 4.4.2. Dependent variables

#### 4.4.2.1. Main dependent variables

This study will assess the function of the left ventricle using two different variables.

- LVEF: it measures how much end-diastolic volume is ejected from LV with each contraction, is the most well accepted expression of global LV function and a strong predictor of clinical outcomes and long term survival. It will be measured in a percentage. Normal values are $\geq$ 55% (25). It is a continue quantitative variables. It will be evaluated by echocardiogram.
- Strain (deformation): it measures the change in length during myocardial contraction and relaxation.

  Two-dimensional speckle tracking echocardiography has recently emerged as a novel technique for the objective and quantitative evaluation of general and regional myocardial function, and has been related to the systolic function of LV. The strain values are modified before those of the LVEF if there exist a dysfunction in myocardial contractibility.

  This study will measure the LV global longitudinal strain and it will be expressed as a percentage. Normal values of GLS will be -21,5 % (26). It is a continue quantitative variable. It will be evaluated by echocardiogram.

#### 4.4.2.2. Secondary dependent variables

- MACCE occurrence, defined as: cardiac death, myocadiac infarction, unplanned revascularization in the target vessel and stroke. It will be assessed during follow-up. It is a nominal qualitative variable.

#### 4.4.3. Co-variables

- Age: is a discrete quantitative variable. It will be expressed in years.
- Sex: is a dichotomous nominal qualitative variable. It will be assessed by male or female.
- Body mass index: is a continue quantitative variable and it will be measured in $kg/m^2$. Patients will be classified into four groups; <18,5 (underweight group), 18,5-24,9 (normal weight group), 25-29,9 (overweight group) and >30 (obese group).
- Hypertension: is a dichotomous nominal qualitative variable (yes/no). We will consider hypertension, blood pressure values $\geq$ 140/90 mmHg.
- History of smoking: is a nominal qualitative variable and it will be defined as; never smoker, past smoker (>1 year without smoking) or smoker (at least 1 cigarette/day/month).
- Hypercholesterolaemia: is a dichotomous nominal qualitative variable (yes/no). It will be defined as LDL-cholesterol >130 mg/dL. We will also count patients receiving statin therapy.
- Chronic kidney disease: is a dichotomous nominal variable (yes/no). It will be defined as Glomerular filtration rate of <60mL/min/1,73m2, calculated using CKD-EPI (27).
- Previous myocardial infarct: is a dichotomous nominal qualitative variable (yes/no). It will be assessed by clinical history of the patient or by ECG (pathologic Q waves).
- Previous CABG: is a dichotomous nominal qualitative variable (yes/no). It will be assessed by clinical history.
- Number of disease vessel: is a discrete quantitative variable. It will be expressed as 1 vessel disease, 2 vessel disease or 3 vessel disease.
- Target vessel: is a nominal qualitative variable. It will be categorized as Left anterior descending coronary artery, Left circumflex coronary artery or Right coronary artery.
- Visual diameter of the vessel: is a continue quantitative variable. It will be measured in mm.
- Visual length of the vessel: is a continue quantitative variable. It will be measured in mm.
- J-CTO score: is an ordinal qualitative variable. It will be measured with the J-CTO score sheet (28).
- SYNTAX score: is an ordinal qualitative variable. It will be calculated by a computer program consisting of sequential and interactive self-guided questions (29).

## 4.5. PROCEDURE

Once the patients will be enrolled in the study, the following steps will be taken:

1. **Data collection:** the collection of the variables of interest will be done through the notebook of data collection (ANNEXE 8). Once all the variables are assessed, those patients with multi vessel disease will be evaluated to verify if the revascularization of non-CTO arteries is necessary.
   If so, they will be revascularized 4 weeks prior to randomization and initial evaluation.
2. **Patient randomization:** Each patient will be included in one of the two groups:
   - Group A: Percutaneous coronary intervention plus medical therapy.
   - Group B: Conservative strategy with medical therapy.
3. **Basal assessment:** All patients, regardless of the group, will be assessed by basal echocardiography to collect values of LVEF and GLS, prior to any intervention related to the study.
4. **Intervention:** Patients assigned to the intervention group will be practiced percutaneous revascularization in less than 4 weeks after the initial evaluation. The revascularization technique will be left to the operator choosing the best technique taking into account the characteristics of the patient and the lesion.
5. **Follow-up:** it will be made to all patients at 4 and 12 months. Each time an echocardiography will be made to collect the data of LVEF and GLS.
   A record of MACCE that may appear during the follow-up will also be made.

## 4.6. METHODS OF MEASUREMENT

The cardiologist that will carry out the follow-up of the patients will be in charge of performing the transthoracic echocardiography. Each time the following measures will be done:

### 4.6.1. Left ventricular ejection fraction

One of the simplest ways to evaluate the ventricular function is obtaining the LVEF. For that porpoise it is necessary to calculate the diameters and the volumes of the left ventricle.

The calculation of these volumes will be carried out using two-dimensional echocardiography based on the Simpson technique, which calculates it automatically. It is the most accurate and widely method used in the routine

Once the volumes are obtained, the ejection fraction is calculated based on the following formula (25,30):

LVEF (%) = ( ( LVEDV – LVESV ) / LVEDV ) x 100

LVEDV: Left ventricular end-diastolic volume

LVESV: Left ventricular end-systolic volume

### 4.6.2. Global Longitudinal Strain

It will be measured using two-dimensional echocardiography and an special technique called speckle tracking will be performed. It analyses the movement of the myocardium following the ventricular speckles (acoustic markers) of the ultrasonic image, during the cardiac cycle.

With this technique different values related to contractibility can be obtained, but this study will be based only on the GLS (31).

# 5. STATISTICAL ANALYSIS

## 5.1. DESCRIPTIVE ANALYSIS

Descriptive analyses will be performed using different statistical analysis measures.

Quantitative variables will be summarized by measures of central tendency (mean and median) and dispersion (standard deviation and interquartile range (IQR)).

Qualitative variables will be summarized using absolute frequencies and proportions.

Kolmogorov-Smirnov test will be used to identify whether continuous variables are normally distributed.

## 5.2. UNIVARIATE INFERENCE

Major adverse cardiovascular and cerebrovascular events will be summarized descriptively.

Other variables will focus on descriptive analysis.

## 5.3. BIVARIATE INFERENCE

The changes in LVEF and GLS between PCI and conservative strategy at baseline and 4 and 12 months will be compared using unpaired T-test or Mann-Whitney (where appropriate).

To asses changes in LVEF and GLS before and after each treatment at 4 and 12 months will be used an analysis of variance (ANOVA) for repeated measures (paired data).

P values <0,05 will be considered statistically significant. Analyses will be performed using IBM SPSS (Statistical Package for the Social Sciences). An intention-to-treat analysis will be performed.

# 6. ETHICAL CONSIDERATIONS

The study will be performed following the declaration of Helsinki “Ethical principles for medical research involving human subjects” developed by the World Medical Association (1964, last revision October 2013).

Before the study begins, the protocol will be sent to the Clinical Research Ethics Committee (CEIC) from Hospital Universitari Dr Josep Trueta. All the recommendations will be considered and relevant modifications will be made to gets its approval. Once the CEIC has approved the protocol, it must be authorized by all the centers participating in the study.

An information sheet with all the important aspects of the study will be given to each participant. Once they read and understand the information a written informed consent will be provided. Only those who have signed the consent will be enrolled in the study.

The clinical trial will be performed following the “Ley 14/2007, de 3 de julio, de Investigación Biomédica” which regulates invasive procedures. As this study includes invasive techniques an insurance policy will be contracted.

All data collected will be treated anonymously in order to guarantee and protect the confidentially of the patient according to “Ley orgànica 3/2018, de diciembre, de Protección de Datos Personales y garantía de los derechos digitales”.

The research team will assert that all the results will be published with transparency and clarity.

All investigators involved in the study will have to declare no conflict of interest.

# 7. LIMITATIONS

- It is a clinical trial and this implies a high economic cost, compared to other types of studies such as observational ones. However, most of the techniques carried out in this study are done in clinical practice, therefore they will not be an added cost.

- As explained before, exclusion criteria leave out patients with restrictive angina, hemodynamic instability, severe valve disease with need for surgery, etc. Therefore the results obtained from the study will not be applicable to high risk population.

- It is a multi-centric study that involves the collaboration of many hospitals and staff, so more errors in data collection or protocol execution could be done. In order to avoid these errors there will be a coordinator of the study in each center that will ensure that everything is carried out in a proper manner, as well as periodic meetings between the entire research team. Nevertheless, a multi-centric study provide a more representable sample than an uni-centric study.

- The techniques used in this study, both PCI and echocardiography, are operator-dependent, therefore the results can be affected depending on who performs them. Due to the fact that it is a multi-centric study, in each hospital the procedures will be carried by different specialist. Nevertheless, all will be qualified professionals and a protocol with all the guidelines to follow will be provide.

- It is not a double-blind study, due to the difficulty of blinding a treatment that is not pharmacological. To solve part of this limitation the expert statistician will not know which treatment was assigned to each patient.

- A non-probabilistic sample method it will be used, so not all the population have the same chance to enter the study. Although, a consecutive sampling will be used, and it is one of the best non-probabilistic methods to reduce this bias.

# 8. WORK PLAN AND CHRONOGRAM

**MEMBERS OF THE TEAM:**

**Main investigator (MI):** responsible for bibliographic research and protocol elaboration, study supervising, result interpretation, writing of the conclusions and result publication and dissemination.

**Collaborator:** it will be formed by:

- Cardiologist (C): in charge of selection patients for the study, collect data, and carry out the follow-up of the patients. It will be one in each hospital and it has to be done always by the same professional.
- Interventional cardiologist (IC): in charge of the PCI. It has to be a trained cardiologist who knows how to carry out the procedure and has a high experience in it. The procedure has to be done always by the same professional.
- Nurse staff (NS): trained in interventionism procedures.

**Expert statistician (S):** responsible for the statistical analysis.

**Study coordinators (SC):** responsible for overseeing the study (according to the protocol) and the coordination of the team. It will be one in each hospital. It will be necessary to coordinate and control the quality of data collect and procedures in each hospital, since is a huge study with a lot of centers implicated. For that reason we need an extra support to avoid mistakes that could decrease the value of the study.

The study will last 3 years and 10 month, but it will depend on the time it takes each phase to be developed (CEIC approbation, sample collection, statistic analysis and final article elaboration).

It will be divided in the following phases:

**PHASE 0: Protocol design**

Protocol design will be in the charge of the main investigator. Following, it will be presented to the Ethics Committee (CEIC) who will revise it and approve.

**PHASE I: Preparation and initial coordination**

At the beginning a chorogram will be prepared with all the detailed phases and procedures and a general coordination meeting will be performed. This meeting will include all the coordinators from each hospital. After it, every coordinator will have to transfer all the information provided to their hospital team.

Meetings will be held every 4 months between the main investigator and each hospital collaborating team (cardiologist, interventional cardiologist, and coordinator) to clarify any doubts and keep the information updated.

**PHASE II: Patients recruitment, follow-up visits and data collection**

The main investigator as well as the other collaborating cardiologist will select the patients that meet the inclusion and inclusion criteria. Subsequently they will be proposed to be part of the study and will be included once they sign the informed consent.

A baseline visit will be carried out at the beginning with a detailed medical history and echocardiography to measure de LVEF and GLS. The following controls will be at 4 and 12 months.

In the intervention group revascularization will be programmed in a period of $\leq$ 4 weeks.

Each cardiologist will be responsible for data collection from their hospital, and it will be included in a common data base.

**PHASE III: Data analysis and interpretation**

Once data collection is complete, the statistician will analyse the data and present the results to all the research team. A final meeting with all the team will be held for the analysis and interpretation of the data.

**PHASE IV: Results publication**

The main investigator will elaborate the final article. It will be published in a cardiologist journal in order to properly disseminate the results of the study. Moreover, the results will be exhibited in national and international congress of specialists.

The chronogram is showed in figure 8.

| Year | | 2019 | | 2020 | | | 2021 | 2022 | | | | 2023 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Months | | NOV | DEC | GEN | FEB | MAR - DEC | JAN-DEC | JAN - MAR | APL - JUN | JUL - SEP | OCT - DEC | JAN | FEB | MAR | APL | MAY | JUN | JUL | AUG | SEP |
| ACTIVITY | STAFF | | | | | | | | | | | | | | | | | | | |
| PHASE 0: STUDY DESIGN | | | | | | | | | | | | | | | | | | | | |
| Protocol elaboration | MI | | | | | | | | | | | | | | | | | | | |
| Protocol approbation | CEIC | | | | | | | | | | | | | | | | | | | |
| PHASE I: STUDY COORDINATION | | | | | | | | | | | | | | | | | | | | |
| Coordination meeting | All team | | | | | | | | | | | | | | | | | | | |
| Chronogram elaboration | MI, SC | | | | | | | | | | | | | | | | | | | |
| PHASE II: PATIENTS RECRUITMENT, FOLLOW-UP VISITS AND DATA COLLECTION | | | | | | | | | | | | | | | | | | | | |
| Sample collection | C, NS | | | | | | | | | | | | | | | | | | | |
| Intervention | IC, NS | | | | | | | | | | | | | | | | | | | |
| Follow-up | C | | | | | | | | | | | | | | | | | | | |
| Data collection | C | | | | | | | | | | | | | | | | | | | |
| PHASE III: DATA ANALYSISI AND INTERPRETATION | | | | | | | | | | | | | | | | | | | | |
| Statistical analysis | S | | | | | | | | | | | | | | | | | | | |
| Interpretation | S, MI, C, IC | | | | | | | | | | | | | | | | | | | |
| PHASE IV: RESULT PUBLICATION | | | | | | | | | | | | | | | | | | | | |
| Finale article elaboration | MI | | | | | | | | | | | | | | | | | | | |
| Result publication | MI | | | | | | | | | | | | | | | | | | | |
| Dissemination | MI | | | | | | | | | | | | | | | | | | | |

*Figure 8. Chronogram.*

# 9. IMPACT OF THE STUDY

CTOs are a frequent finding in patients with coronary artery disease and are likely to have an important role in ventricular function.

A few years from now, percutaneous coronary revascularization has begun to be incorporated as a possible treatment for all of these patients. But due to the lack of scientific evidence has not yet been established as a valid optimum treatment and is carried out only in very selected patients.

If the study presented proves a significant benefit, there would be a significant evidence in order to give a more meaningful role to percutaneous coronary revascularization and it will imply an important change to clinical practice. PCI will be another valid strategy to keep in mind while treating a patient with CTO and the patient will achieve a significant clinical improvement as well as a decrease in long-term mortality.

# 10. BUDGET

All research team and personnel are employees of the hospital. So it will not be necessary to hire any worker for clinical functions. Moreover, the procedures made in this study are done by routine in the hospitals included, so extra money will not be needed. For other functions, the cost will be the following:

*Table 2: Budget needed for the study*

| | CONCEPT | AMOUNT | COST | SUBTOTAL |
|---|---|---|---|---|
| **STAFF COST** | Expert statistician | 80 hours | 35€/h | 2.800 € |
| | Study coordinators | 3h/year, 7 coordinators | 20€/h | 1.820 € |
| **COORDINATION MEETINGS** | Diets | 22 people | 15€/person | 4.290 € |
| **MATERIAL** | Printing and papers | 300 units | 1,00 € | 300 € |
| **INSURANCE** | Insurance that covers damage | 300 units | 50,00 € | 15.000 € |
| **FOLLOW-UP** | Echocardiography | 600 units | 58 € | 34.800 € |
| **PUBLICATION AND DISSEMINATION** | English correction | 1 | 300 € | 300 € |
| | Publishing cost | 1 | 2.000 € | 2.000 € |
| | National congress | 1 | 1.500 € | 1.500 € |
| | International congress | 1 | 2.000 € | 2.000 € |
| | | | **TOTAL COST** | 64.810 € |

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# 12. ANNEXES

## 12.1. ANNEXE 1. TIMI GRADE FLOW (32)

| | |
|---|---|
| **Grade 0 (no perfusion)** | There is no antegrade flow beyond the point of occlusion. |
| **Grade 1 (penetration without perfusion)** | The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiography filming sequence. |
| **Grade 2 (partial perfusion)** | The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel – e.g., the opposite coronary artery or the coronary bed proximal to the obstruction. |
| **Grade 3 (complete perfusion)** | Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery. |

## 12.2. ANNEXE 2. SYNTAX SCORE (29)

**Table 3. The SYNTAX score algorithm**

**1. Dominance**

**2. Number of lesions**

**3. Segments involved per lesion**

*Lesion Characteristics*

**4. Total occlusion**

i. Number of segments involved
ii. Age of the total occlusion (>3 months)
iii. Blunt Stump
iv. Bridging collaterals
v. First segment beyond the occlusion visible by antegrade or retrograde filling
vi. Side branch involvement

**5. Trifurcation**

i. Number of segments diseased

**6. Bifurcation**

i. Type
ii. Angulation between the distal main vessel and the side branch <70°

**7. Aorto-ostial lesion**

**8. Severe tortuosity**

**9. Length >20mm**

**10. Heavy calcification**

**11. Thrombus**

**12. Diffuse disease/small vessels**

i. Number of segments with diffuse disease/small vessels

## 12.3. ANNEXE 3. J-CTO SCORE SHEET (28)

# J-CTO SCORE SHEET

Version 1.0

**Variables and definitions**

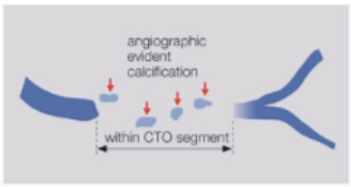
### Tapered / Blunt

Entry with any tapered tip or dimple indicating direction of true lumen is categorized as "tapered".

**Entry shape**
☐ Tapered (0)
☐ Blunt (1)

point

### Calcification

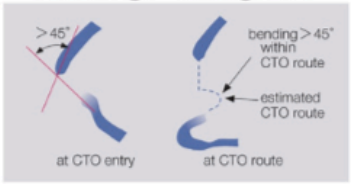



Regardless of severity, 1 point is assigned if any evident calcification is detected within the CTO segment.

**Calcification**
☐ Absence (0)
☐ Presence (1)

point

### Bending > 45degrees

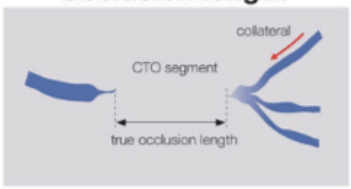



One point is assigned if bending > 45 degrees is detected within the CTO segment. Any tortuosity separated from the CTO segment is excluded from this assessment.

**Bending > 45°**
☐ Absence (0)
☐ Presence (1)

point

### Occlusion length




Using good collateral images, try to measure "true" distance of occulusion, which tends to be shorter than the first impression.

**Occl.Length**
☐ <20mm (0)
☐ ≥20mm (1)

point

### Re-try lesion

Is this Re-try (2nd attempt) lesion ? (previously attempted but failed)

**Re-try lesion**
☐ No (0)
☐ Yes (1)

point

Category of difficulty (total point)
☐ easy (0) ☐ Intermediate (1)
☐ difficult (2) ☐ very difficult (≥3)

Total _____ points

## 12.4. ANNEXE 4. HYBRID ALGORITHM (33)

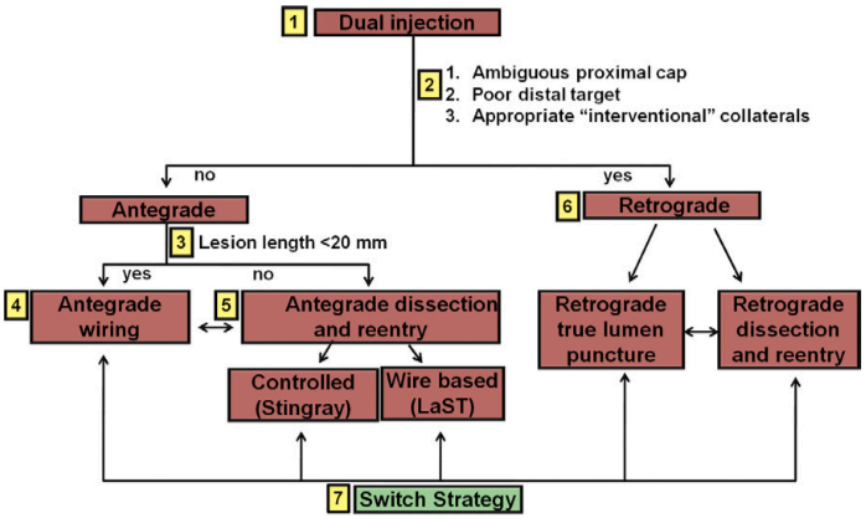
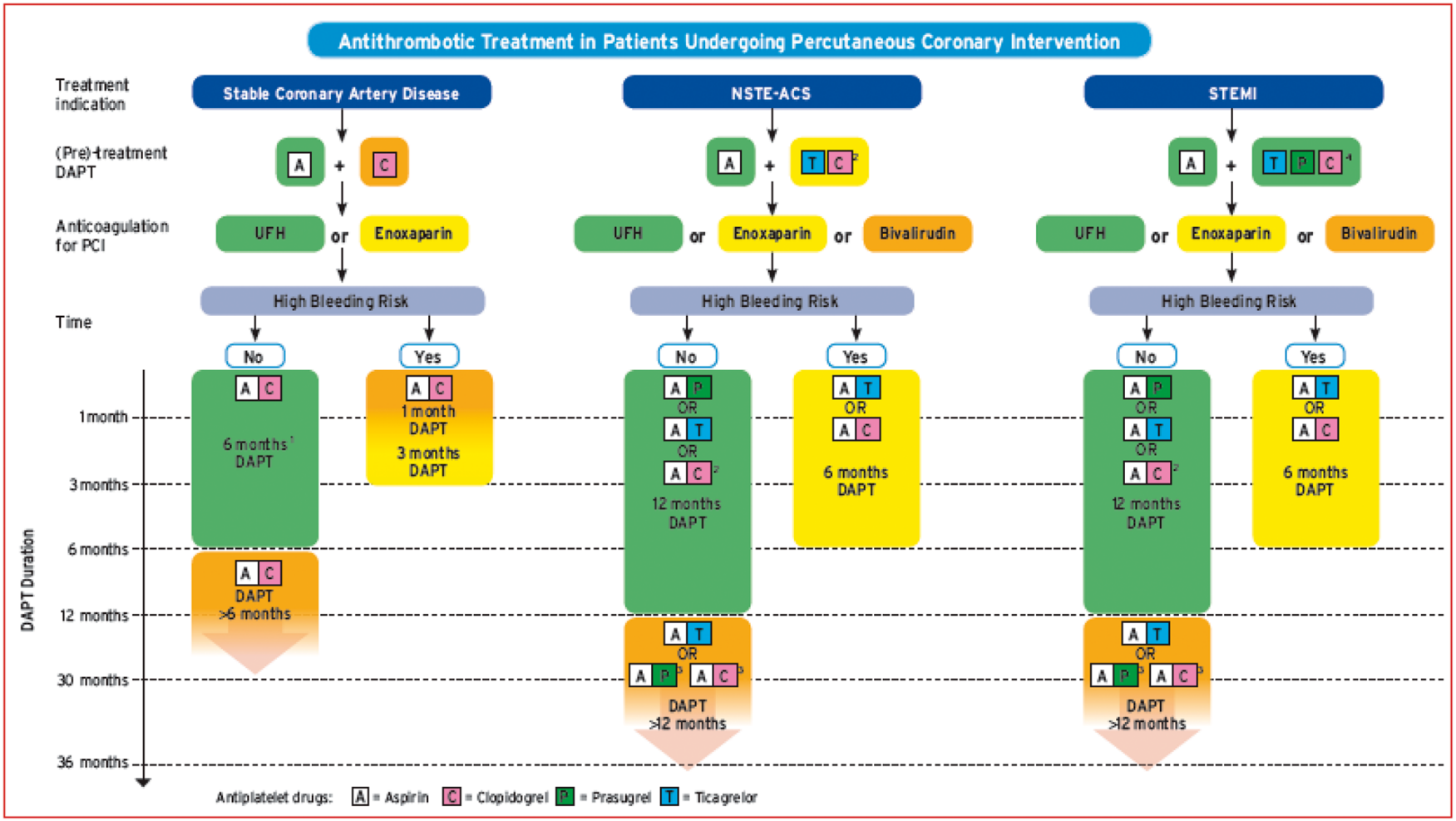



**Figure 1. Algorithm for Crossing CTOs**

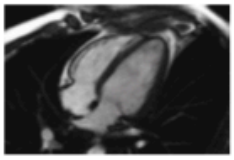
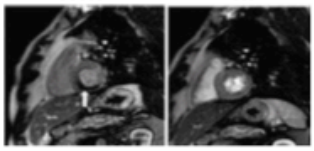
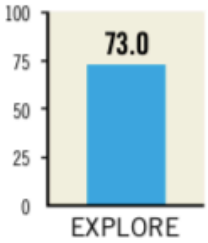
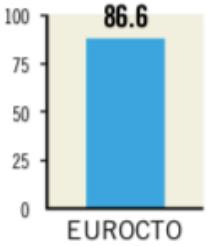
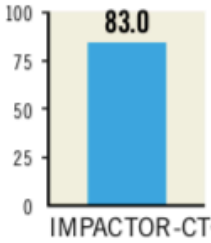
The algorithm starts with dual coronary injection **(box 1)** to allow assessment of several angiographic parameters **(box 2)** and allow selection of a primary antegrade **(boxes 3 to 5)** or primary retrograde **(box 6)** strategy. Strategy changes are made **(box 7)**, depending on the progress of the case. CTO = chronic total occlusion; LaST = limited antegrade subintimal tracking.

## 12.5. ANNEXE 5. ALGORITHM FOR THE USE OF ANTITHROMBOTIC DRUGS IN PATIENTS UNDERGOING PCI (34)




DAPT = dual antiplatelet therapy; DCB = drug-coated balloon; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STEMI = ST-elevation myocardial infarction; UFH = unfractionated heparin.
Colour-coding refers to the ESC classes of recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).
[1]After PCI with DCB 6 months DAPT should be considered (class IIa) - [2]Clopidogrel if patient is not eligible for a treatment with prasugrel or ticagrelor; or in a setting of DAPT de-escalation (Class IIb).
[3]Clopidogrel or prasugrel if patient is not eligible for a treatment with ticagrelor - [4]Pretreatment before PCI (or at the latest at the time of PCI); clopidogrel if potent P2Y12 inhibitors are contraindicated or not available.
(For scores see Supplementary Table 4.).
High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25)

## 12.6. ANNEXE 6. PCI CTO CLINICAL TRIALS (4)

| | EXPLORE | EUROCTO | IMPACTOR-CTO |
|---|---|---|---|
| Location & design | Europe & Canada  Multicentre RCT (14 centres) | Europe  Multicentre RCT (28 centres) | Russia  Single-centre RCT |
| N patients | 304 | 407 | 72 |
| Study population | Patients with STEMI treated with PCI with a non-infarct-related CTO | SCAD CTO patients with symptoms and/or ischaemia and viability | Patients with isolated dominant RCA CTO and stable angina |
| Primary endpoint |  LVEF and LVEDV by CMR |  QoL (SAQ, EQ-5D) | Stress Rest  ΔMIB by adenosine stress CMR |
| Follow-up period | 4 months | 1 year | 1 year |
| Mean J-CTO score | 2±1 | 1.82±1.07 | 1.92±0.86 |
| Success rate |   |   |   |
| Positive/negative RCT | − | + | + |
| Major findings | PCI OMT<br>MACE: No difference<br>QoL: N/A<br>Ischaemia reduction: N/A<br>LVEF and LVEDV: No difference<br>PCI of a CTO located in the LAD may improve LVEF and clinical outcome | PCI OMT<br>MACE: No difference<br>QoL: Better<br>Ischaemia reduction: N/A<br>LVEF and LVEDV: N/A | PCI OMT<br>MACE: No difference<br>QoL: Better<br>Ischaemia reduction: Better<br>LVEF and LVEDV: N/A |

## 12.7. ANNEXE 7. INFORMATION SHEET AND INFORMED CONSENT

### HOJA DE INFORMACIÓN AL PACIENTE

**TÍTULO DEL PROYECTO**: Beneficios en la fracción de eyección del ventrículo izquierdo y el strain longitudinal global de la intervención coronaria percutánea contra la terapia médica optima en pacientes con oclusiones coronarias crónicas.

**INTRODUCCIÓN**

Nos dirigimos a usted para informarle sobre un estudio de investigación que lleva a cabo el servicio de Cardiología del Hospital Dr. Josep Trueta de Girona, al que se le invita a participar. El estudio ha sido aprobado por el Comité Ético de Investigación Clínica del Hospital Universitario de Girona Dr. Josep Trueta.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda evaluar si quiere o no participar en este estudio. Antes de decidir si quiere participar o no, le rogamos lea detenidamente este documento que incluye la información sobre este proyecto. Puede formular todas las preguntas que le surjan y solicitar cualquier aclaración sobre cualquier aspecto. Puede consultar la decisión con las personas que considere oportunas.

**Participación voluntaria**

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que ello altere la relación con su médico ni se produzca ningún perjuicio en su atención sanitaria.

**Descripción del estudio**:

El motivo del estudio que le queremos proponer participar, es para evaluar la eficacia del tratamiento de intervencionismo percutáneo en relación a la mejoría de la función del ventrículo izquierdo en aquellos pacientes que presenten una oclusión crónica de alguna arteria coronaria y a pesar de tratamiento médico.

El objetivo y la intención primordial del estudio es la mejora del tratamiento de estos enfermos, cuando se hayan analizado los resultados se propondrá una validación para estandarizar los parámetros si los resultados son favorables.

**PROCEDIMIENTOS DEL ESTUDIO**

La valoración diagnóstica y tratamiento médico será el habitual para los pacientes con oclusión crónica, como son la historia clínica así como pruebas complementarias entre las que se puede requerir de una coronariografía y un intervencionismo coronario percutáneo. En este estudio se dividirán los pacientes en dos grupos de forma aleatoria, un grupo se tratará con intervencionismo coronario percutáneo sobre la oclusión crónica juntamente con tratamiento médico, y otro grupo será únicamente tratado con tratamiento medico óptimo.
Le solicitamos permiso para realizar controles de forma personal para realizar una ecocardiografía basal, y otras seguidamente a los 4 y 12 meses.

**BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO**

Pretendemos conseguir una mejora del tratamiento en pacientes que presenten una oclusión crónica coronaria.

Cualquier hallazgo que se pueda aplicar el curso de su enfermedad le será indicada.
Aunque también es posible que los conocimientos adquiridos con la investigación no lo beneficien a usted personalmente, sino a futuros pacientes que padezcan la misma enfermedad.

Usted tiene derecho a conocer los resultados de los estudios que se obtengan. Y también tiene derecho a la no información de estos resultados.

**CONFIDENCIALIDAD**

Los datos recogidos serán estrictamente confidenciales. Sólo se autorizará para la recogida de datos de su historial médico a personas sometidas al secreto profesional siempre con el previo conocimiento del investigador principal.

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustará a la Ley de confidencialidad 03/2018, de protección de datos de carácter personal. De acuerdo a lo establecido en la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, por eso se ha de dirigir a su médico del estudio. Los datos recogidos por el estudio estarán identificados mediante un código y sólo su médico del estudio / colaboradores podrán relacionar estos datos con usted y con su historia clínica.

En ningún caso su nombre aparecerá en la publicación de los resultados. Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos y, exigir la destrucción de toda la información personal obtenida.

**CONTACTO CON EL INVESTIGADOR**

Para cualquier duda o información adicional que precise, o sobre sus derechos como participante en un ensayo clínico, debe contactar con el investigador.

**CONSENTIMIENTO INFORMADO**

Yo (nombre y apellidos) .....con DNI .....

- He leído la hoja informativa que se me ha entregado sobre el estudio.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con: (nombre del investigador) .....
- Comprendo que mi participación es voluntaria.
- Comprendo que los resultados obtenidos serán guardados para mantener la confidencialidad de mis datos de acuerdo con la Ley de Biomedicina de 2018 (ley 03/2018 de Investigación Biomédica).
- Comprendo que puedo revocar mi consentimiento en cualquier momento, sin tener que dar explicaciones y sin que ello altere mi asistencia sanitaria.

Accede a que los investigadores principales del proyecto puedan contactar con usted en un futuro si lo consideran oportuno.

☐ Sí ☐ No

Doy libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

Firma del paciente:

Fecha: ____ / _____ / _____

Firma del investigador:

Fecha: _____/ _____/_____

Firma del representante legal, familiar o persona vinculada de hecho
Fecha: ____/_____/_____

Firma del investigador

Fecha: ____/_____/_____

## 12.8. ANNEXE 8. NOTEBOOK OF DATA COLLECTION

## HOJA DE RECOGIDA DE DATOS

**ESTUDIO:** Beneficios en la fracción de eyección del ventrículo izquierdo y el strain longitudinal global de la intervención coronaria percutánea contra la terapia médica optima en pacientes con oclusiones coronarias crónicas.

| Etiqueta identificativa paciente |
|---|

| | |
|---|---|
| **Grupo de intervención** | ☐ A ☐ B |
| **Edad** | _____ |
| **Sexo** | ☐ Mujer ☐ Hombre |
| **Fracción de eyección del ventrículo izquierdo (FEVI) (%)** | _____ |
| **Strain Longitudinal Global (%)** | _____ |
| **Índice de masa corporal** | ☐ < 18,5 ☐ 18,5 – 24,9 ☐ 25 - 29,9 ☐ > 30 |
| **Hipertensión** | ☐ Si ☐ No |
| **Consumo de tabaco** | ☐ No fumador ☐ Ex-fumador (>1 año si fumar) ☐ Fumador (<1 año sin fumar) |
| **Hipercolesterolemia** | ☐ Si ☐ No |
| **Insuficiencia Renal Crónica** | ☐ Si ☐ No |
| **Infarto de miocardio previo** | ☐ Si ☐ No |

| | |
|---|---|
| **Bypass coronario previo** | ☐ Si ☐ No |
| **Número de arterias coronarias afectadas** | ☐ 1 ☐ 2 ☐ 3 |
| **Arteria afecta** | ☐ Arteria descendiente anterior<br>☐ Arteria circunfleja<br>☐ Arteria coronaria derecha |
| **Diámetro del vaso afecto** | _____ |
| **Puntuación J-CTO** | ☐ Fácil (0) ☐ Intermedio (1)<br>☐ Difícil (2) ☐ Muy difícil (≥ 3) |
| **Puntuación SYNTAX** | ☐ Bajo (≤ 22) ☐ Intermedio (23-32)<br>☐ Alto (≥ 33) |
| **Complicaciones** | ☐ Muerte cardíaca<br>☐ Infarto de miocardio<br>☐ Revascularización no planeada<br>☐ Ictus |