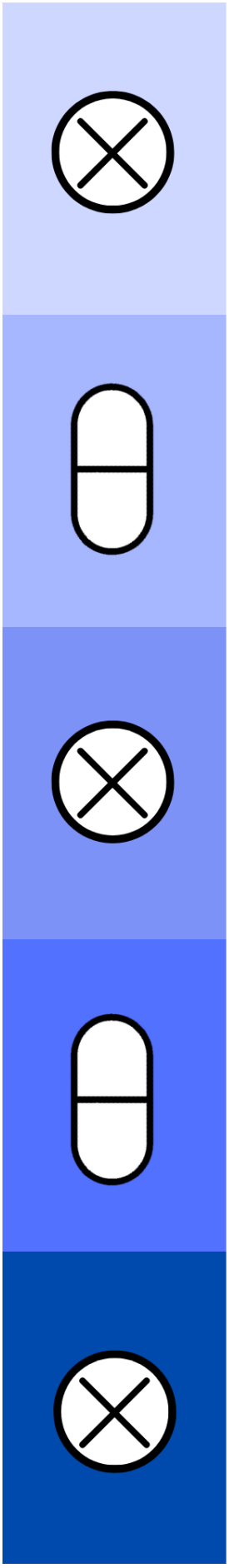

Universitat de Girona
Facultat de Medicina

Efficacy and safety of Apixaban as treatment for left ventricular thrombus after acute ST-elevation myocardial infarction

A MULTICENTRIC, RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY CLINICAL TRIAL

Final degree project - January 2023

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Methodological tutor: Xavier Castells Cervello

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“Hay una vela en tu corazón,

lista para encenderse.

Hay un vacío en tu alma,

listo para ser llenado.

Lo sientes, ¿verdad?”

- Yalāl ad-Dīn Muhammad Rūmī

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ABSTRACT

Background: Left ventricular thrombus (LVT) is a frequent complication associated with ventricular dysfunction following ST-segment elevation myocardial infarction (STEMI). It is estimated to have an annual incidence of 200 cases in Catalonia, whose complications can be life-threatening. Nowadays, surprisingly enough given its remarkable morbidity and mortality, there are still many gaps in research regarding the best anticoagulation regimen. With the introduction of direct oral anticoagulants (DOACs) in clinical practice, doubts about the role it could play in the LVT arsenal are increasing. The better convenience and safety of DOACs, such as Apixaban, in certain clinical settings compared to vitamin K anticoagulant antagonists (VKAs), have motivated multiple studies in this regard, such as the present trial.

Objective: The main aim of this study is to verify if Apixaban has a non-inferior efficacy compared to the use of Acenocoumarol in the echocardiographic resolution of LVT after STEMI, at the 3-month follow-up. Regarding secondary objectives, we will compare complications and safety between the two groups, as well as identify independent predictors of LVT persistence at 6 months.

Design: This study is a multicentric, randomised, controlled, double-blinded, double-dummy, non-inferiority clinical trial.

Participants: Adult patients with a diagnosed LVT up to 3 months after STEMI, visible echocardiographically and without contraindications for anticoagulation nor echocardiographic contrast administration.

Setting: This study is designed to include multiple hospitals from Catalonia having a cardiology department and/or cardiac imaging unit where cardiologist specialised in cardiac imaging techniques and echocardiography equipment are available.

Methods: 264 patients will be consecutively recruited and subsequently randomly assigned to one of two study groups with a 1:1 ratio: control group (A) with Acenocoumarol (n=132), and intervention of interest group (B) with Apixaban (n=132). Once the intervention has started, contrast echocardiographic assessments will be made at baseline, as well as at 3- and 6-month follow-up, as does a record of complications at each control visit. The intervention will last 6 months.

Keywords: Left ventricular thrombus · Apixaban · DOAC · Acenocoumarol · echocardiography

ABBREVIATION LIST

AMI: Acute myocardial infarction

CMR: Cardiac magnetic resonance

CT: Computed tomography

DAPT: Dual antiplatelet therapy

DE-CMR: Delayed enhancement cardiac magnetic resonance

DOAC: Direct oral anticoagulant

DVT: Deep vein thrombosis

FIIa: Factor II activated

FXa: Factor X activated

IL: Interleukin

INR: International normalised ratio

LAA: Left atrial appendage

LAD: Left anterior descending

LV: Left ventricle

LVEF: Left ventricular ejection fraction

LVT: Left ventricular thrombus

MACE: Major adverse cardiovascular events

MI: Myocardial infarction

NOAC: Novel oral anticoagulant

NVAF: Non valvular atrial fibrillation

OAT: Oral anticoagulant therapy

PAI-1: plasminogen activator type 1

PCI: Percutaneous coronary intervention

PET: Positron emission tomography

STEMI: ST-elevation myocardial infarction

TAFI: Thrombin activatable fibrinolysis inhibitor

TEE: Transesophageal echocardiography

TF: Tissue factor

TNF-α: Tumour necrosis factor alpha

TTE: Transthoracic echocardiography

VKA: Vitamin K antagonist

VTE: Venous thromboembolism

1. INTRODUCTION

1.1 LEFT VENTRICULAR THROMBUS AFTER STEMI

1.1.1 DEFINITION

Left ventricular thrombus (LVT) is a well-recognized and **relatively frequent major complication** in patients who have suffered an acute ST-elevation myocardial infarction (STEMI), even in the absence of aneurysm or advanced left ventricle (LV) disfunction (1-7). This clinical syndrome is based on the formation of a thrombus in the LV, favoured by factors explained by Virchow's triad, which can lead to other life-threatening complications such as cerebrovascular accident or systemic embolism (2-7).

1.1.2 PATHOPHYSIOLOGY AND NATURAL HISTORY

The pathophysiology of the LVT is explained by the interrelation of three main factors such as endothelial injury, blood stasis, and hypercoagulability, being described as **Virchow's triad** 150 years ago (2-8). It is important to highlight that the presence of any of these factors can trigger the response of any of the other two, although the concomitance of all the factors of Virchow's triad would not be necessary for the establishment of LVT. Although Virchow's postulates are still valid, some authors propose an updated triad with elements such as abnormal blood flow, abnormal blood constituents (platelets and coagulation and fibrinolysis pathways), and endothelial abnormalities (8).

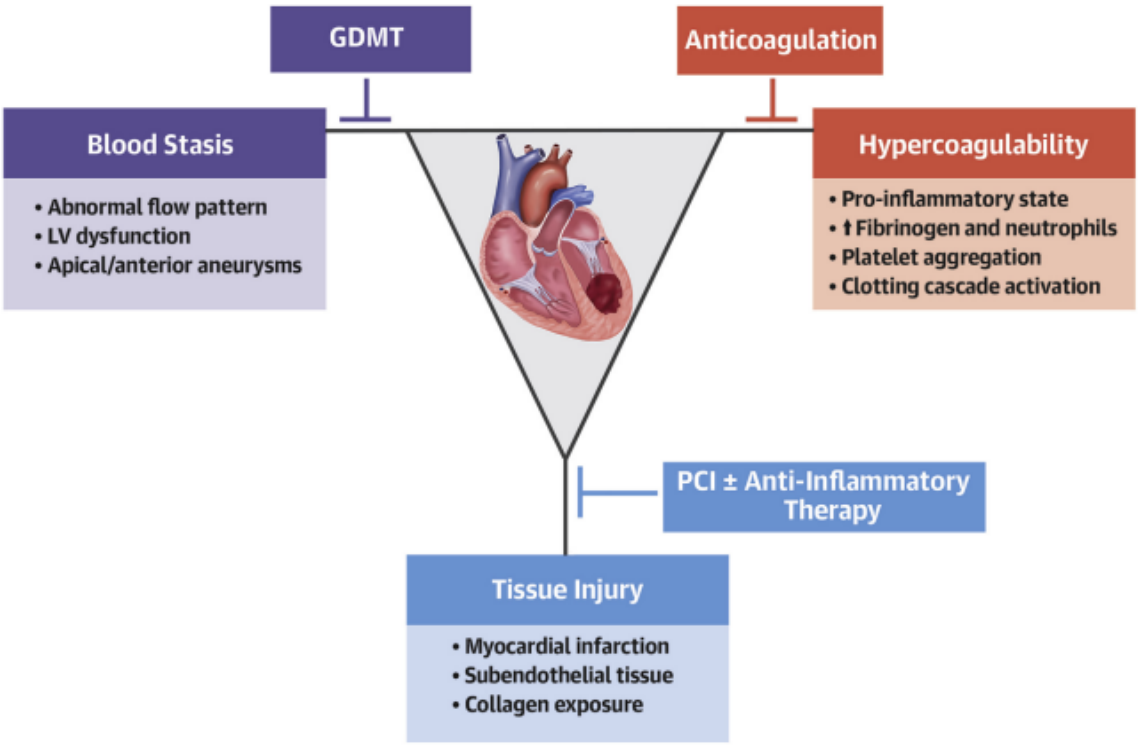

Figure 1. ***Virchow's Triad****: Pathophysiological Basis and Treatment Target*. Extracted from (3).

In the first place, the establishment and expansion of an acute myocardial infarction (AMI) entails a mechanical alteration of the cardiac walls (3). Thinning and dilation of the injured endothelium occurs almost immediately after AMI (2,3,9). Thus, on the one hand, there is an increase in the tension exerted by the blood on the heart wall (favouring the formation of ventricular aneurysms), whereas, on the other hand, it leads to LV dysfunction (3,4,6,9). In this respect, the strong association between a reduced ejection fraction, an apical or anterior akinesia or dyskinesia of the left ventricle and/or a reduced myocardial contractility to **blood stasis** is known, this being a fundamental constituent for thrombus formation, especially during the first 7 days following AMI (2,3,5-7,9). Furthermore, the presence of an abnormal vortex and flow pattern secondary to regional left ventricular dysfunction has been shown to increase the risk of LTV (2,3,5-7).

On the other hand, regarding tissue damage caused by AMI, the exposure of subendothelial tissue and collagen to circulating blood has been shown to promote a prothrombotic state, as well as an **inflammatory state** (3,5). In this context, an association has been shown

between higher levels of cardiac enzymes in larger infarcts with an increased risk of LVT formation, as well as, an elevation of baseline C-reactive protein, fibrinogen, and the neutrophil-lymphocyte ratio with its early formation (3,5,7).

Finally, the third factor that contributes to the formation of the LVT is the **hypercoagulable state**, which **persists for up to 6 months** or longer (2-4,6,7). The coagulation system is activated by the common pathway (increased concentrations of prothrombin, fibrinopeptide A, and von Willebrand factor, decreased concentrations of ADAMTS13, and the accumulation of fibrin via cross-linking), and the intrinsic pathway (platelets) (2,3,9).

Thus, the fresh thrombus is composed of fibrin, red blood cells, and platelets (2,3,7). This **fresh thrombus is more prone to embolize than the persistent thrombus**, due to its lack of anchor to the endocardium, its contribution to a persistent inflammatory reaction and the exposure to the dynamic forces of circulating blood (3). Nevertheless, the formation and embolization of the LVT often appears after the expansion of the infarct zone, with no time for the LVT to organise and prevent aneurysm and myocardial rupture (2,5,7,9).

LVT can befall within the first 24 hours after AMI (2,3,9), forming about **90% of thrombi at a maximum of 2 weeks after the AMI** (2,3,6,9,10). Furthermore, there is some evidence whose findings seem to point out that most of the LVT were detected **within the first week** after acute percutaneous coronary intervention (PCI) (6,10,11).

It should be noted that more than 50% of the thrombi will resolve by 6 months after the AMI, being relatively common the spontaneous resolution in non-anticoagulated patients (2,3). **About 3 months** after the establishment of the LVT, **there is a decrease in the risk of embolization** caused by a process of organisation of the thrombus, in which it becomes a fibrotic mass adherent to the LV wall, leading to what is known as **endothelialization process** (2,5,7,9). In those patients with no resolution beyond this period, the LVT has been speculated to play a positive role in the acutely infarcted myocardium, limiting potential infarct expansion and restoring some of the myocardial thickness, reducing stress on the cardiac wall, limiting aneurysmal development, ultimately improving overall myocardial function (2,3). Nevertheless, persistent thrombus is considered as a marker of LV dysfunction

by some studies, and it was associated with higher risk of major adverse cardiovascular events (MACE), but not necessarily being the cause of death (3).

1.1.3 EPIDEMIOLOGY

Regarding the prevalence, the incorporation of reperfusion therapies in selected AMI patients led to a sharp reduction in the development of LVT as a complication of myocardial infarction (MI) (2-4,7,10).

The first reperfusion therapy, the thrombolytic therapy, was introduced and widely validated throughout the 1980s (4). Early data from the **prethrombolytic era** show the formation of LVT in 7-46% of the patients with STEMI, even reaching 60% in patients with large anterior MI (2-4,10). It should be noted that the incidence of LVT after MI is likely to have been underestimated in the prethrombolytic era due to the limitations of diagnostic techniques, such as transthoracic echocardiography (TTE)(3). With the arrival of **thrombolytic therapy**, the overall prevalence dropped to 26%, but remained high (up to 40%) in patients with large MI (3,12). Some authors explain the reduction in LVT formation with thrombolytic therapy by direct lysis of the thrombus or by limitation of the infarct area, with an improvement in global left ventricular function (13).

It was in the mid-1990s, with the introduction of **primary PCI therapy**, when LVT formation rates declined further. The most recent systematic review in primary the PCI, using the gold standard technique as a diagnostic method (2,7,14) (contrast-enhanced cardiac magnetic resonance), showed an overall prevalence of LVT up to 6,3% in patients with STEMI, 12,2% in those with anterior location, and 19,2% in those with left ventricular ejection fraction (LVEF) less than 50% due to STEMI (3,14). Thus, some authors justify the current decline in LVT prevalence with more aggressive anticoagulation therapies during the acute phase, smaller infarcts and improved left ventricular remodelling (2).

This variation in the incidence of LVT depending on the location of the STEMI acquires great relevance in the follow-up of patients with STEMI, since more extensive and accurate

records show a left anterior descending (LAD) location in 38% of them, and reaching LV dysfunction or heart failure in 42% of them (3).

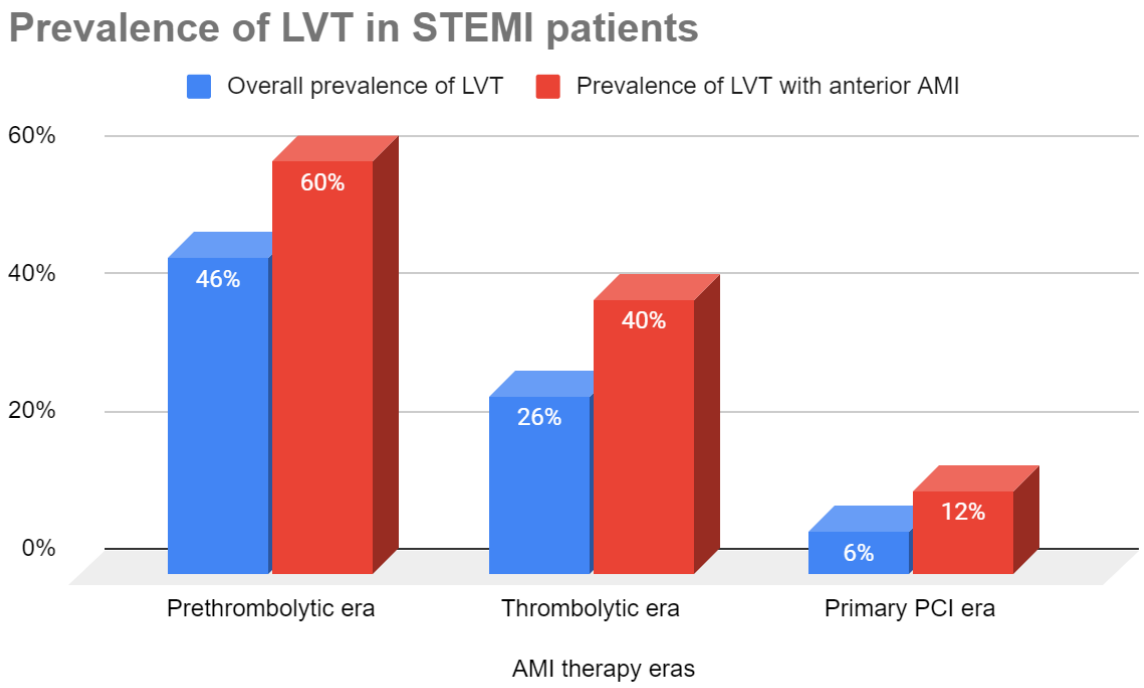

Figure 2. ***Prevalence of left ventricular thrombus in STEMI patients:*** *in the prethrombolytic era, thrombolytic era and primary percutaneous coronary intervention era, separated in overall prevalence and prevalence in patients with anterior acute myocardial infarction.*
Adapted from (2-4,10,12,14)

Therefore, by making an inference from the current rates of AMI complications in the form of LVT (6,3%) and the annual incidence of AMI in Catalonia (420-450/1.000.000 inhabitants/year), we can estimate an annual incidence of about **200 cases of LVT in Catalonia per year** (15).

1.1.4 RISK FACTORS

- **Baseline risk factors for thrombogenesis**

There are several baseline characteristics that patients may present, which pose an increased risk of intracardiac thrombus formation (especially when they are associated with each other), which are the following:

- **Age:** There is an exponential increase in thrombotic phenomena with age, partly due to the progressive increase of some coagulation factors (factors V, VII, VIII, and IX, fibrinogen), tissue factor (TF) exposure, von-Willebrand factor, fibrinogen, plasminogen activator type 1 (PAI-1) and platelet reactivity with age (16-18). In addition, recent studies have shown a statistically significant association between older age (>50 years) and LVT formation (19).
- **Genetics:** Recent studies have shown a statistically significant association between the presence of a family history of ischaemic heart disease and LVT formation (19).
- **Hypertension or high blood pressure**: There is large evidence that demonstrates the association between hypertension and alteration of coagulation and fibrinolytic pathways (increased plasmatic fibrinogen), as well as platelets and endothelium, thus forming a prothrombotic state which is significantly associated with the formation of LVT (8,19). It is important to highlight that it is part of the metabolic syndrome, which involves a prothrombotic state due to its hypercoagulability and systemic inflammation (16,17).
- **COVID-19:** SARS-CoV-2 infection has been associated with a higher incidence of thrombotic phenomena such as deep vein thrombosis (DVT) (20-23). Furthermore, although a more comprehensive study is required, some authors link COVID-19 with an increased risk of LVT formation (24). This may be partly explained by their systemic hyperinflammation (cytokine storm) and hypercoagulability state (endothelial disruption, platelet activation and

coagulopathy) (21-24), as well as a statistically significant association with reduced function of both ventricles in hospitalised patients (20-22,25).

- **Reperfusion therapy performed:** Judging from the epidemiological data explained above, whether or not reperfusion therapy is received, together with selected reperfusion therapy (thrombolysis or primary PCI), as treatment for STEMI, play a very important role in the risk of developing intraventricular thrombus as a complication (26). However, although some studies have confirmed a significant relationship between thrombolytic given and not given with LVT (19), other studies have not shown significant differences in LVT occurrences in patients treated with thrombolytic therapy and primary PCI, so further research is needed (27).

- **Risk factors in relation to AMI characteristics**

Moreover, there are some other factors related to the clinical and echocardiographic characteristics and complications of the AMI which pose a higher risk of developing a LVT, such as:

- **Infarct size**: Solid evidence claims that the amount of ischaemia-induced myocardial damage plays a major role in LVT formation prediction, due to more pronounced myocardial injury, major probability of wall motion disturbances or aneurysm formation, an increment in inflammatory response, and a more pronounced hypercoagulable state (2,3,10,11). Furthermore, larger AMI with peak creatine kinase levels >4,912 U/L have proven to be associated with an increase in the risk for developing LVT by 12 times (11).
- **Severe apical asynergy (akinesis or dyskinesis)**: LVT has demonstrated to appear earlier when initial LVEF≤40. Thus, the lower the LVEF, the higher the thrombus incidence (2,7,11,28).
- **LV aneurysm**: Starting from plausible reasoning, LV aneurysm has been demonstrated to be associated with an increment in the contribution of at least two of the three components of Virchow's triad, due to major stasis phenomenon and greater area of injured subendocardium (2).

- **Anterior AMI**: Patients with anterior AMI have a higher incidence of LVT, although its formation can be located at the septal or inferoposterior wall, and even in small apical infarcts with good global systolic function (2,7,11). This risk factor is also usually associated with large infarcts and with greater impairment of ventricular function due to occlusion or lesion of the LAD coronary artery (3,9,11,14,28,29).

1.1.5 DIAGNOSIS

Due to the possibility of developing a LVT after STEMI, as well as its high risk of embolic complications (44 times higher during the first month)(30), routine imaging is recommended for all patients after presenting AMI, with the aim of early diagnosis of LVT formation through the following screening techniques, although a proportion of LVT diagnoses are made on the basis of incidental findings (6).

- **Echocardiography**

Transthoracic echocardiography stands out for its greater availability, absence of radiation, test duration, portability and affordability, being the **most used imaging technique to diagnose LVT after AMI**, in addition to being a very useful tool to assess ventricular function and structural abnormalities (3,31). Using TTE seen from at least two views (generally apical and short axis), LVT is distinguished from the surrounding endocardium, as well as from the akinetic, hypokinetic, or aneurysmal region of the LV, where it is usually detected as an intracavitary echodense mass of variable mobility and location (2,3). Whereas acute establishments of the LVT present more protuberant and/or mobile characteristics, in the more chronic phases, it is usually observed as a mural and/or sessile and flat mass (3,7).

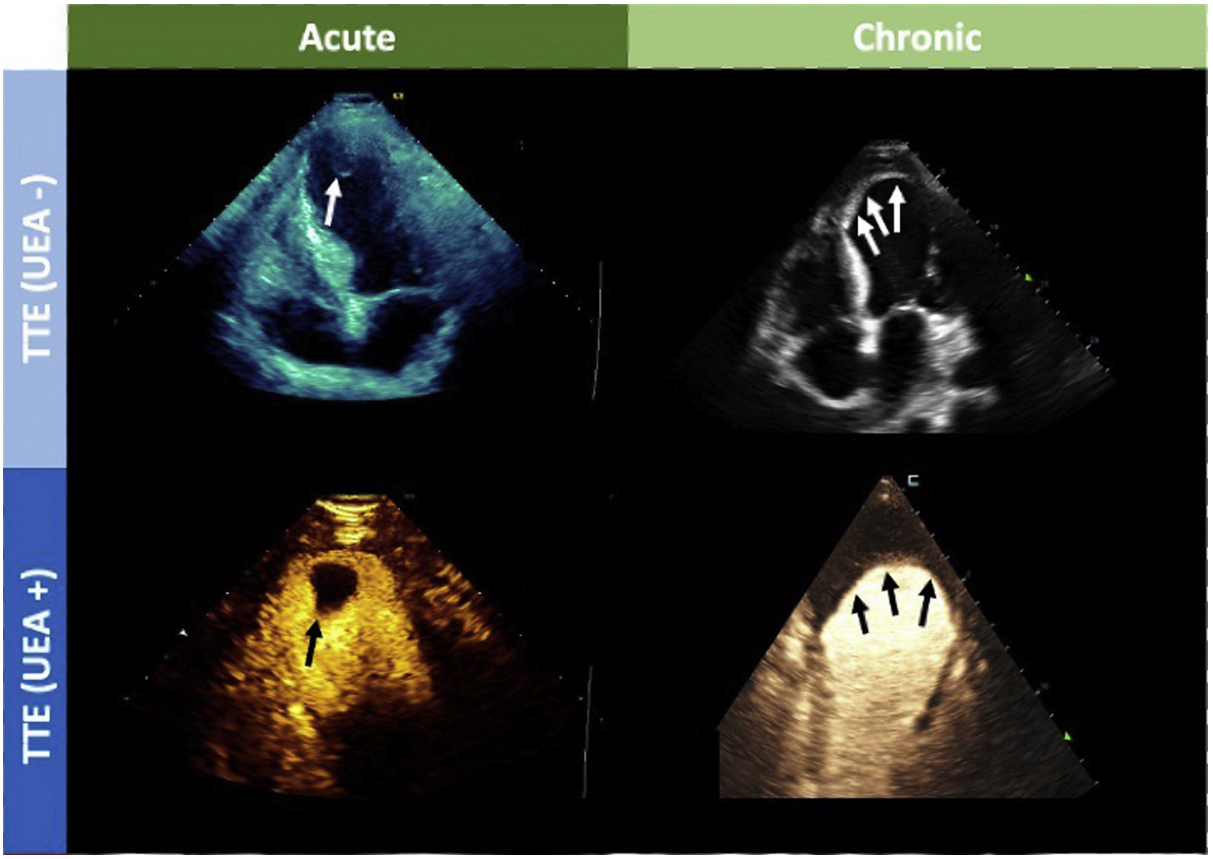

Figure 3. ***Visual representation of acute and chronic left ventricular thrombi****: Acute and chronic left ventricular thrombi as seen by transthoracic echocardiography (TTE) with and without an ultrasound-enhancing agent (UEA). Single arrows (black and white) depict acute thrombus formation characterised as a protruding apical mass. Triple arrows (black and white) show chronic thrombus formation characterised as a smooth, laminar apical mass. Black and white arrows show thrombus detected by TTE with and without the use of a UEA, respectively*. Extracted from (3).

Whereas **routine TTE** is an imaging technique with high specificity (95-98%), its relative low sensitivity in most studies (21-35%) suggests the presence of many LVT that will not be detected through TTE, especially those related to poor acoustic window, reduced size and/or non-protruding thrombus or inadequate apical visualisation leading to inconclusive results (2,3,29). It is important to highlight that some studies have demonstrated an increased sensitivity (60-94%) and positive predictive value (75-94%) for TTE when echo is performed on the **clinical indication of LVT**, compared to unfocused routine TTE, possibly due to the operator-dependent limitation of the test (28,30,31).

Furthermore, the addition of an **intravenous ultrasound-enhancing** (contrast) is capable of improving both specificity (99%) and sensitivity (64%) data in routine TTE, being especially useful in patients with anterior AMI (3,5,29).

Regarding the usefulness of transesophageal echocardiography (TEE), although some data suggest a better display of small LV apical thrombus by TEE compared to TTE, it is a much more limited test due to the poor visualisation offered of a generally foreshortened LV apex, especially in patients with dilated LV or apical dyskinesia (2,3).

- **Cardiac magnetic resonance imaging**

CMR has proven to be the most optimal imaging test, establishing itself as the **gold standard**, yielding very high sensitivity (79-88%) and specificity (99-100%) values with Cine-CMR when compared with surgical and/or postmortem confirmations (7,53,54,55). By using delayed enhancement (DE-CMR) with gadolinium, thrombus detection on a "long T1" sequence can be improved, due to its avascular composition, in contrast to the surrounding infarcted myocardium and blood pool after contrast administration (3,31-33). Thus, DE-CMR allows us to assess, relatively rapidly and very precisely, its presence, size and location, due to tissue characteristics identification rather than anatomical appearance alone (3,31-33). Moreover, CMR not only helps to detect the already established thrombus but also the risk factors that favor its appearance in patients with AMI, such as infarct size or scar burden (3,31,32). Therefore, sensitivity values range from 88-100% and specificity values reach 100% (2,9,29,31,32).

However, CMR disadvantages, such as substantial economic cost, lack of availability, repeated breath-holding, closed space environment, supine position or the duration of the test in critical patients, are some of the features that limit its use in clinical practice, especially if it is used as a first screening test (3,29). Furthermore, DE-CMR use is also limited by the contrast administration in patients with end-stage renal failure (3). That is why, in order to avoid unnecessary DE-CMR tests and to obtain perfect sensitivity and specificity,

some authors propose performing DE-CMR in those patients with high apical wall motion abnormality scores on screening TTE (≥7 with contrast and ≥5 without contrast) (3,29).

Importantly, evidence suggests that **patients with LVT diagnosed by CMR and missed by TTE have similar outcomes** than patients with LVT evident on TTE. The reason behind it is that small mural thrombi that can be detected only by CMR have a smaller impact on the patient's prognosis (3).

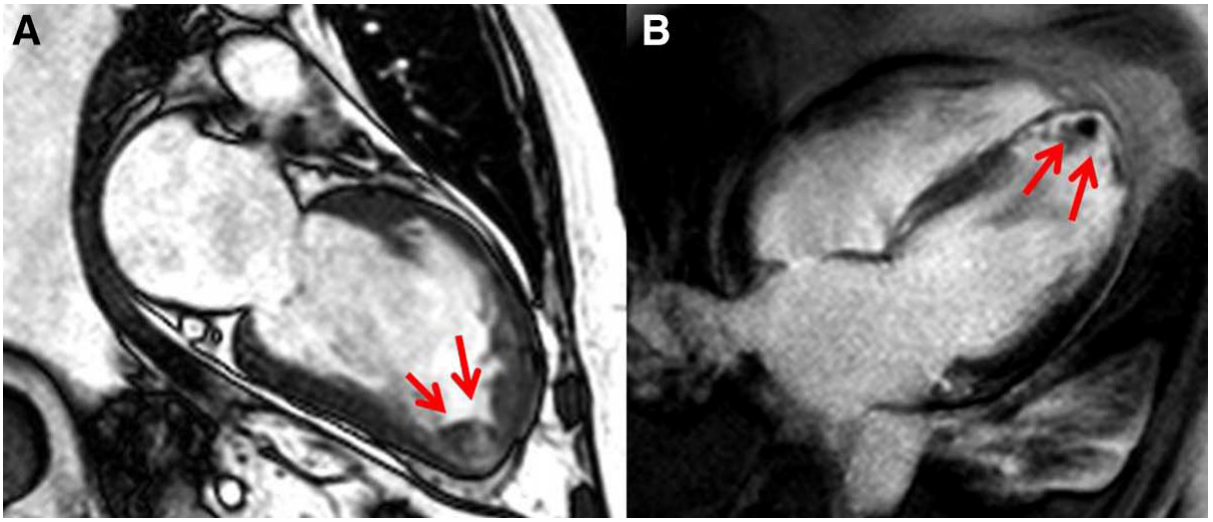

Figure 4. ***Patient with transmural anterior infarction with thrombus in the left ventricular apex*** *(red arrows) in cine cardiac magnetic resonance imaging (A) and contrast-enhanced images (B).* Extracted from (29).

	Sensitivity	Specificity	Accuracy	Positive Predictive Value	Negative Predictive Value
Routine TTE (UEA -)	21-35%	95-98%	82%	57-67%	85-94%
TTE (UEA +)	23-64%	99%	92%	82-93%	91-97%
TTE in LVT indications	60-94%	88-98%	77-97%	75-94%	78-98%
Cine-CMR	79-88%	99-100%	95%	93-100%	95-98%
DE-CMR	88-100%	99-100%	100%	100%	100%

Table 1. ***Performance values of main imaging tests for the diagnosis of LVT****: Routine TTE (transthoracic echocardiography) UEA- (without an ultrasound-enhancing agent), TTE UEA+ (with an ultrasound-enhancing agent), TTE in left ventricular thrombus (LVT) indications, Cine-CMR (Cardiac Magnetic Resonance), delayed enhancement (DE) CMR with gadolinium.*
Adapted from (2,3,7,28-33).

- **Computed Tomography**

Computed Tomography (CT) is currently not considered a routine imaging technique in the detection of LVT, mostly because of requiring intravenous injection of radiographic contrast material (iodine) and unnecessarily exposing the patient to ionising radiation. Although there are few studies on the detection of LVT by CT, it has historically been attributed a similar accuracy to TTE. However, the excellent validity values which this test has shown in recent studies and meta-analyses on the detection of thrombus in the left atrium or in its appendage, open a debate on its potential diagnostic role in the context of LVT (2-4).

As a matter of fact, other CT techniques, such as contrast-enhanced coronary CT angiography or spectral CT, seem to have also a very promising potential in the LVT detection, although further investigation is needed (3).

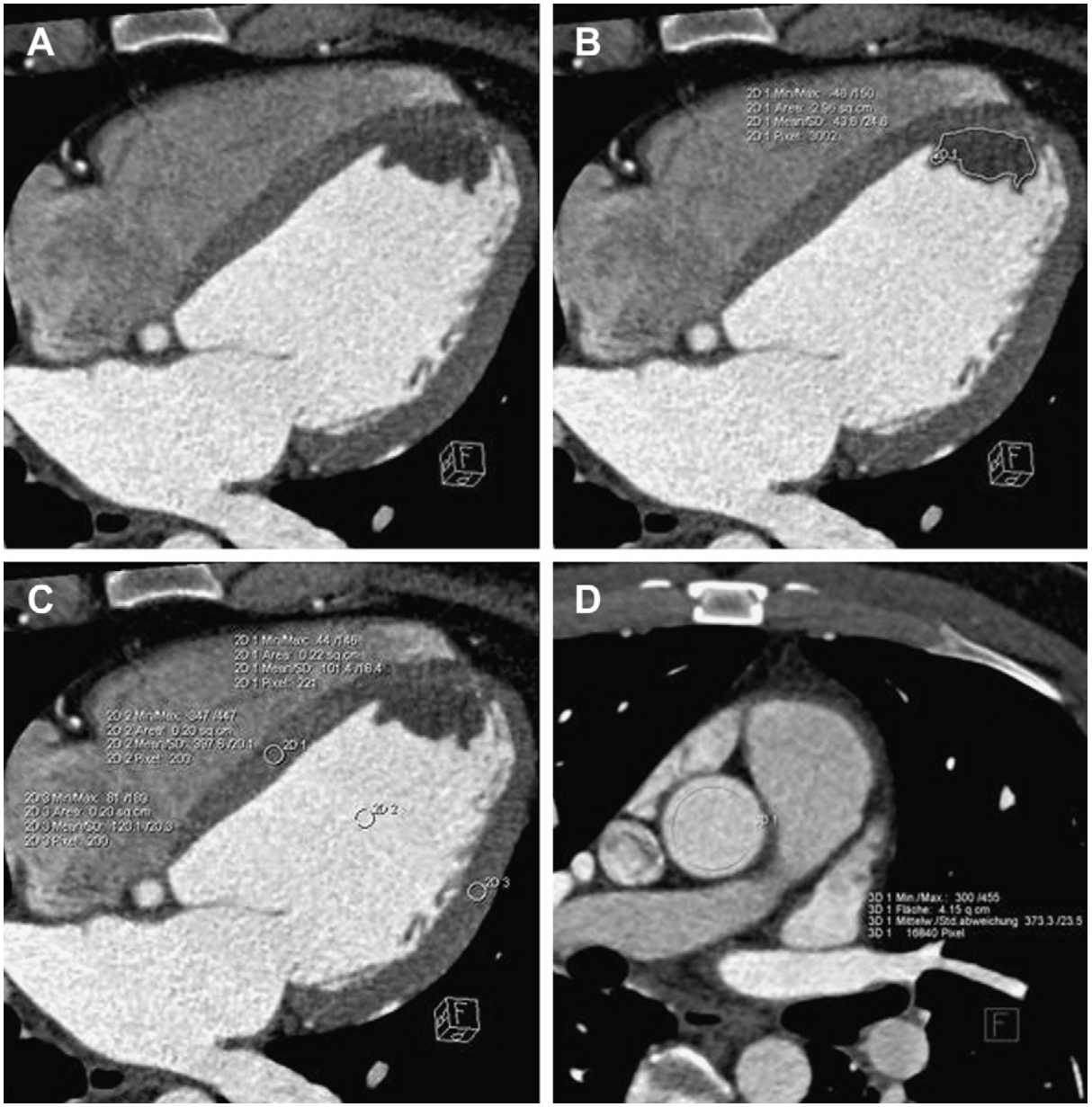

Figure 5. ***Attenuation measures of left ventricular thrombus seen by Computed Tomography imaging.*** Extracted from (34).

- **Radionuclide based techniques**

Emerging molecular imaging techniques, such as positron emission tomography (PET) using the radiotracer ^{18}F-GP1, are capable of targeting active thrombus formation, due to its binding to activated platelet glycoprotein IIb/IIIa receptors. This radionuclide based technique has proved to detect, not only LVT formation, but the location of its potential complications, such as cerebral and coronary thromboembolism (3).

On the other hand, the use of PET with indium-111 labelled platelet have been shown to have a specificity of 95% and a sensitivity of 70% in the detection of LVT compared to TTE, being only applicable at the time of active platelet aggregation on the surface of the LV mural thrombus. In addition, its use is also limited by high time and cost requirements, low availability, necessary exposures to ionising radiation, and artifacted uptake by other organs under some conditions (2).

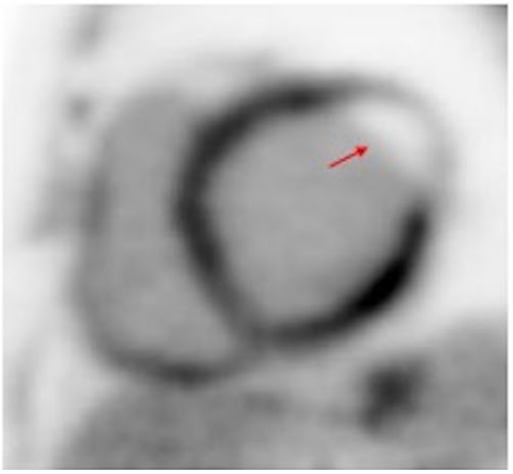

Figure 6. ***Cardiac FDG PET:*** *basal anterolateral wall aneurysm with an organised left ventricular thrombus within the aneurysm, which correlates with the photopenic defect seen on PET (red arrow).* Extracted from (35).

1.1.6 MORBIDITY AND MORTALITY ASSOCIATED TO LVT

The morbidity and mortality associated with the formation of LVT are related to thromboembolic events - systemic, and specifically stroke -, MACE, as well as major bleeding secondary to treatment (2-7,9).

Whereas initially embolic complication rates in prethrombolytic era were about 10%, in thrombolytic era decreased to rates from 2% to 3% in patients with LVT (2,10). However, we dispose of little evidence on the prevalence of embolic complications in LVT patients treated by primary PCI (2). A recent single-centre study revealed, by a 7-year follow-up in patients diagnosed with LVT, **all-cause mortality** rates of 18.9%, **MACE** incidence of 37.1%, **embolic complications** incidence of 22.2% and major bleeding rates of 13.2% (3). The same study demonstrated a **reduction in mortality with the regression of the thrombus**, although no significant differences were not found when comparing the appearance of embolic complications to those patients with persistent thrombi. Furthermore, another recent study with a large cohort of patients showed an annual incidence of embolism of 3,7% in patients with LVT, being more than 3 times greater than in patients with no LVT (0,8%), despite the fact that 89% of LVT patients were treated with contemporary anticoagulation. No significant differences were found in the rate of embolism in patients with LVT detected by TTE compared to those with CMR (3).

There are some features in diagnostic imaging, such as thrombus **mobility** and **protrusion** - defined as the thrombus rejected mainly into the LV cavity, as opposed to mural or laminar thrombus (5) -, which are associated to a **higher rate of embolisation**, being specially important to assess in early diagnose (2-8,28). However, it should be noted that there is some evidence questioning the usefulness of the assessment of these features, showing that 41% of the LVT experienced significant changes in shape, and 29% experienced changes in mobility, thus demonstrating the frequency of its spontaneous time-course variations (2).

Importantly, there is conflicting evidence with respect to the influence of the central echolucency, thrombus size or hyperkinesia of the myocardial segments nearby the thrombus, on the occurrence of embolisms (2,9). However, there are other conditions which

indeed increase the risk of systemic embolisation, which are diffuse LV dilatation, LV systolic dysfunction, severe congestive heart failure, atrial fibrillation, previous embolisation, and advanced patient age. Regarding aneurysms, they are suggested to be less likely to embolize, since the contraction near the location of the intracavitary thrombus is reduced (2).

1.1.7 TREATMENT AND PROPHYLAXIS

Regarding the treatment and prophylaxis of LVT, several recommendations have been developed over the last 10 years in Europe and the United States with varying, but all low, grades of recommendation and levels of evidence (1,3,4,9,36), summarised in **Table 2**. In addition, definitions of each strength of recommendation and level of evidence are provided in the ***Annex 1***.

Firstly, the 2012 ***American College of Chest Physicians*** guidelines advised, with a grade 2c recommendation, that oral anticoagulant therapy (OAT) with vitamin K antagonists (VKA) in addition to dual antiplatelet therapy (DAPT) should be given for 3-6 months among patients with anterior MI associated to some of the risk factors for developing LVT, such as LVEF <40% and anterior-apical wall motion abnormality. As a matter of fact, the addition of oral anticoagulation therapy to the patient's ongoing DAPT is known as *triple therapy* (3,36).

Similarly, the 2013 ***American College of Cardiology/American Heart Association*** guidelines provide a Class 2b, Level of Evidence: C recommendation for prophylactic anticoagulant therapy in patients with STEMI and anterior apical akinesis or dyskinesis, advising targeting a lower international normalised ratio (INR: 2,0-2,5) in patients with STEMI concomitantly receiving DAPT. Regarding treatment once the thrombus has been diagnosed, with level of recommendation Class 1, Level of evidence: C, the 2014 ***American Heart Association/American Stroke Association*** advise treatment with VKAs (target INR: 2.5; range: 2.0-3.0) for 3 months in patients with ischaemic stroke or transient ischaemic attack as a consequence of an AMI or prophylactically with apical akinesis or dyskinesis in the context of anterior STEMI (Class 2b and a Level of evidence: C). Furthermore, *American Heart Association/American Stroke Association*, introduced a new recommendation (Class

2b, Level of evidence: C) as an alternative to VKA treatment, if not tolerated, in the above-mentioned prophylactic and therapeutic indications, with low molecular weight heparin, dabigatran, rivaroxaban or apixaban for 3 months (3,4,7,9,36).

Otherwise, according to the 2017 ***European Society of Cardiology*** guidelines, once the mural thrombus is diagnosed - and not as a prophylactic therapy -, OAT ought to be considered for up to 6 months, based on a Class 2a, Level of Evidence: C recommendation. Therefore, echocardiographic controls via TTE, as well as assessments of the risk of bleeding and the need for concomitant DAPT inherent to AMI, will be required. According to these guidelines, DAPT consists of indefinite antiplatelet therapy with acetylsalicylic acid and therapy with *P2Y12 inhibitors* for up to 12 months (1,3,9,36).

Importantly, all guidelines agree that an **echocardiographic control should be performed at least 3 months** after initiating treatment, although in some guides the periodicity of the rest of the image monitoring may vary or not be specified (6).

Moreover, It is important to know that while the most prescribed VKA drug in Anglo-Saxon countries is Warfarin, in Europe (and more specifically in Spain), Acenocoumarol has gained greater impact in the prevention of thromboembolic complications in different clinical settings. Although the two drugs are not exactly equivalent and the available studies have some limitations, to date no significant differences have been demonstrated in terms of efficacy, safety, anticoagulation control or clinical characteristics (37,38).

It should be noted that in both European and American recommendations, **the strength of recommendations and the level of evidence** regarding the treatment and prophylaxis of LVT **are low** and require further studies to be able to determine precisely the type of OAT indicated, target and INR range, antiplatelet combination, duration of *triple therapy*, benefits of long-term anticoagulation, the most appropriate therapeutic approach for those patients with LV aneurysm or persistent LVT, target population for preventive treatment or the superiority of the therapeutic approach once diagnosed (1,3,4,36).

Regarding the use of direct oral anticoagulants (DOACs) for the treatment of LVT, despite presenting a safer profile in some groups of patients in reducing intracardiac thrombotic risk - without the need for serial analytical controls and increasing overall quality of life -, the scientific evidence yields contradictory results. Therefore, its implementation and role in the LVT therapeutic arsenal is still controversial and poorly defined, and further investigation is needed with ongoing clinical trials prior to its routine use for LVT (1,3-5,7,9,36,39-41).

	Level of evidence, strengh of recommendation	OAT	Months of duration of OAT	DAPT	TTE controls
The American College of Chest Physicians	2c	**VKA:** *Prophylactic*, if anterior MI associated to some of the risk factors for developing LVT	3-6	Concomitantly	At 3 months
American College of Cardiology / American Heart Association	C, 2b	**VKA:** *Prophylactic,* if STEMI with anterior apical akinesis or dyskinesis	-	Concomitantly	At 3 months
American Heart Association / American Stroke Association	C, 1	**VKA:** *Once diagnosed* LVT with ischemic stroke or TIA in the setting of AMI	3	Concomitantly	At 3 months
	C, 2b	**Low molecular weight heparin or DOACs:** *Once diagnosed* LVT with ischemic stroke or TIA in the setting of AMI and VKA not tolerated	3	Concomitantly	At 3 months
	C, 2b	**Low molecular weight heparin or DOACs:** *Prophylactic,* if ischemic stroke or TIA in the setting of STEMI with anterior apical akinesis or dyskinesis and VKA not tolerated	3	Concomitantly	At 3 months
European Society of Cardiology	C, 2a	**VKA:** *Once diagnosed* LVT	6	Concomitantly	Periodically (at 3 months)

Table 2. ***European and American recommendations of treatment and prophylaxis for LVT.***

OAT= Oral anticoagulant therapy; DAPT= ; TTE= Dual antiplatelet therapy; VKA= Vitamin K antagonist; DOACs =Direct oral anticoagulants; MI= Myocardial infarction.

Adapted from (1,3,4,9,36).

1.2 ORAL ANTICOAGULANTS AS THROMBUS TREATMENT AND PROPHYLAXIS

In recent years, there have been profound changes and advances in the treatment of heart patients with the introduction of novel oral anticoagulants (NOACs) or DOACs, which have progressively displaced the use of VKAs, such as Acenocoumarol or Warfarin, as their properties were better studied and they were included in the clinical practice within the therapeutic arsenal (4,39,40,42,43).

Illustrated in **Figure 7**, while VKAs (44) reduce the synthesis of functional vitamin-K-dependent enzymes (factors II, VII, IX, X, as well as protein C and protein S), the mechanism of action of DOACs is specifically directed against activated clotting factor, factor II (thrombin or FIIa) for Dabigatran (45), or factor Xa (FXa) for Rivaroxaban (46), Edoxaban (47) and Apixaban (48). Therefore, it has been possible to **overcome the limitations associated with the use of VKA** (variation in doses, low onset-offset of activity, abundant monitoring and considerable food and drug interactions), maintaining its same effectiveness with even a safer profile in some clinical settings (4,5,36,40,42). In addition, with the introduction of **reversion agents for DOACs** (Idarucizumab for Dabigatran; Andexanet alfa for Apixaban, Edoxaban, and Rivaroxaban; and PER977 for Edoxaban), one of their classic limitations was eventually surmounted (49).

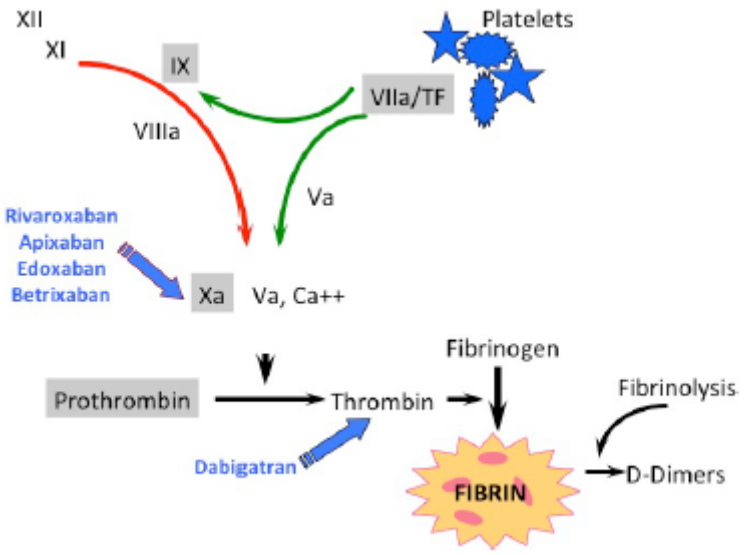

Figure 7. ***Classical scheme of the coagulation cascade with direct oral anticoagulants (DOAC) and vitamin K antagonists (VKA) attack points.*** *(XII= Factor XII; XI= Factor XI; IX= Factor IX; VIIa= Factor VII activated; VIIIa= Factor VIII activated; Va= Factor V activated; Xz= Factor X activated; TF= Tissular factor; Ca++= Calcium).* Extracted from (42).

Moreover, although some authors had theorised about a possible decrease in adherence to treatment due to lack of monitoring (42), most recent evidence has shown **greater satisfaction and better adherence in patients treated with DOACs** versus VKA, regardless of which DOAC they were taking (43).

Despite the fact that all DOACs indications are almost identical, there are some pharmacodynamic and pharmacokinetics differences between each one, collected in the next table (**Table 3**):

DOAC	Rivaroxaban	Edoxaban	Apixaban	Dabigatran
	Xarelto ®	Lixiana ®	Eliquis ®	Pradaxa ®
Target	FXa	FXa	FXa	FIIa
t ½	7–13 h	10–14 h	8–15 h	12–17 h
Cmax	2–4 h	2–4 h	2–4 h	1–2 h
Renal clearance	33% active 33% inactive	50%	25%	80%
Bioavailability	80%	62%	50%	6%
Dosing scheme	OD	OD	BID	BID
Interaction	CYP3A4, CYP2J2, P-gp	P-gp	CYP3A4 P-gp	P-gp
Interference with food	Increases AUC to 39%	None	None	Prolongs Cmax to 2 h
Antidote	Andexanet alfa	Andexanet alfa	Andexanet alfa	Idarucizumab
Allowed in pregnancy	No	No	No	No
Induces HIT II	No	No	No	No

Table 3. ***Pharmacodynamics and pharmacokinetics of DOAC:*** *once daily (OD); twice daily (BID); P-glycoprotein (P-gp); area under the curve (AUC); heparin induced thrombocytopenia (HIT); maximum drug concentration in plasma (Cmax).* Extracted from (42).

1.2.1 DIRECT ORAL ANTICOAGULANTS IN OTHER HEART CONDITIONS

Some of the currently approved anticoagulation indications of use of DOACs includes the treatment for non valvular atrial fibrillation (NVAF), venous thromboembolism (VTE) and recurrent VTE prophylaxis and DVT prophylaxis in Europe and the USA, although its off-label use in valvular atrial fibrillation, heart failure, LVT, superficial vein thrombosis (SVT) or pulmonary hypertension is still controversial and need further study (4,7,42,43).

Importantly, DOACs in general have contributed to a significant **reduction in thromboembolic events** in recent years, while maintaining very similar rates of major bleeding, and even reducing them in some clinical settings by the use of certain DOACs (50).

More precisely, among all the DOACs, the one that has presented a **safer profile** in its approved indications on indirect comparisons, has been **Apixaban** (51,52). For NVAF

treatment, Apixaban has shown, in systematic reviews and meta-analyses, significant **reduction in stroke, systemic embolism** (**Figure 8**) and **major bleeding** (**Figure 9**) - with similar efficacy - compared to warfarin, the latter especially in patients with chronic kidney disease or end stage renal disease compared to warfarin and in elderly patients compared to all oral anticoagulants (50,53,54).

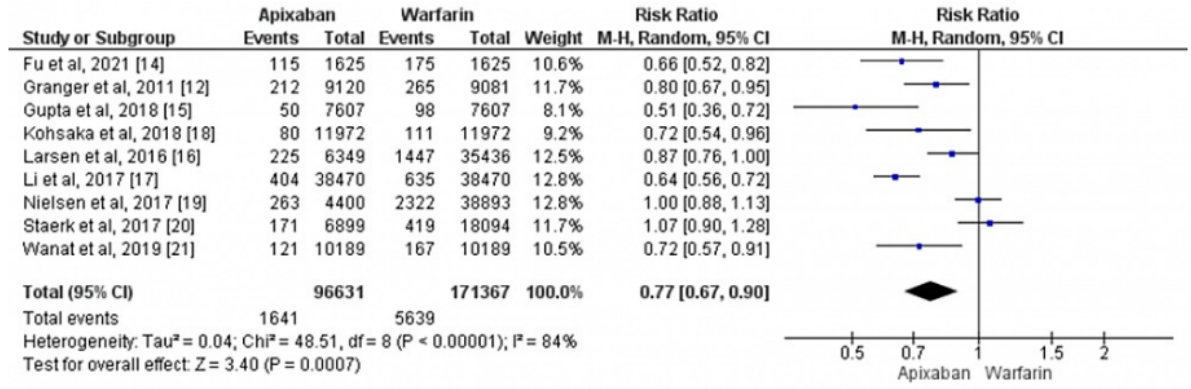

Figure 8. ***Comparison of the effect of apixaban and warfarin on the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.***

Extracted from (54).

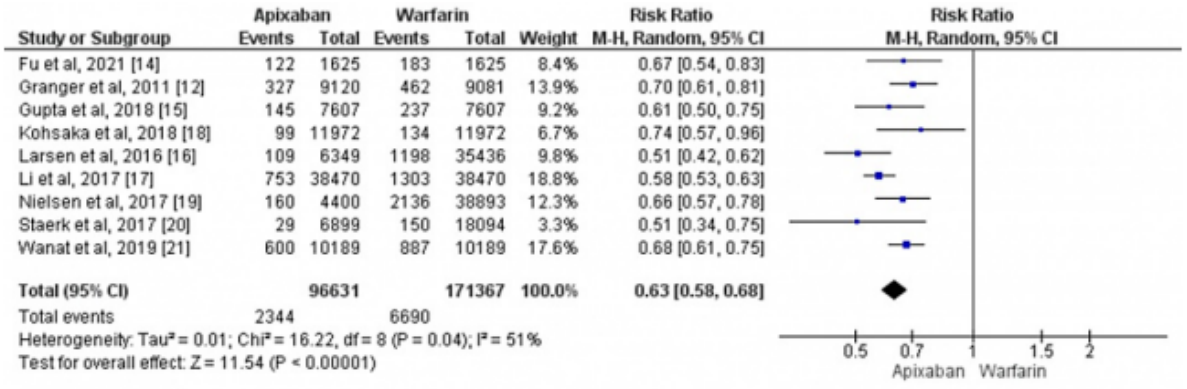

Figure 9. ***Comparison of the effect of apixaban and warfarin on the risk of major bleeding events in patients with non-valvular atrial fibrillation.***

Extracted from (54).

Besides, in VTE indications, **significant reduction in major or clinically relevant non-major bleeding** - with similar efficacy - compared to the rest of DOACs has been demonstrated in systematic reviews and meta-analyses (**Figure 10**), specially in patients with chronic kidney disease or end stage renal disease compared to warfarin (53,55,56).

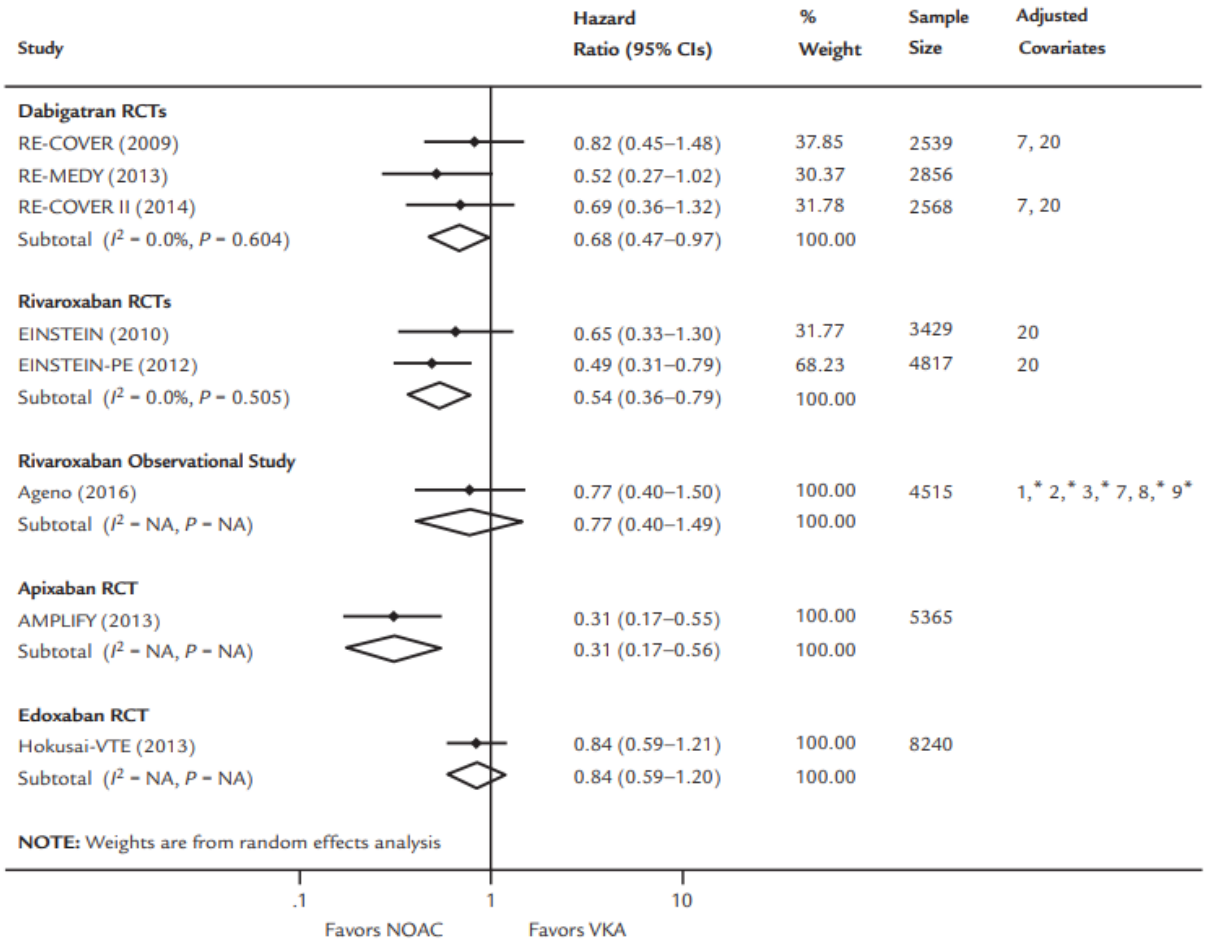

Figure 10. ***Forest plot for the risk of major bleeding in patients with venous thromboembolism (VTE):*** *non-vitamin K antagonist oral anticoagulants (NOACs) versus vitamin K antagonist (VKAs).* Extracted from (56).

Furthermore, it was shown that Apixaban offered a **better global satisfaction** for the patients, compared to other DOACs (43), as it is represented on **Figure 11**.

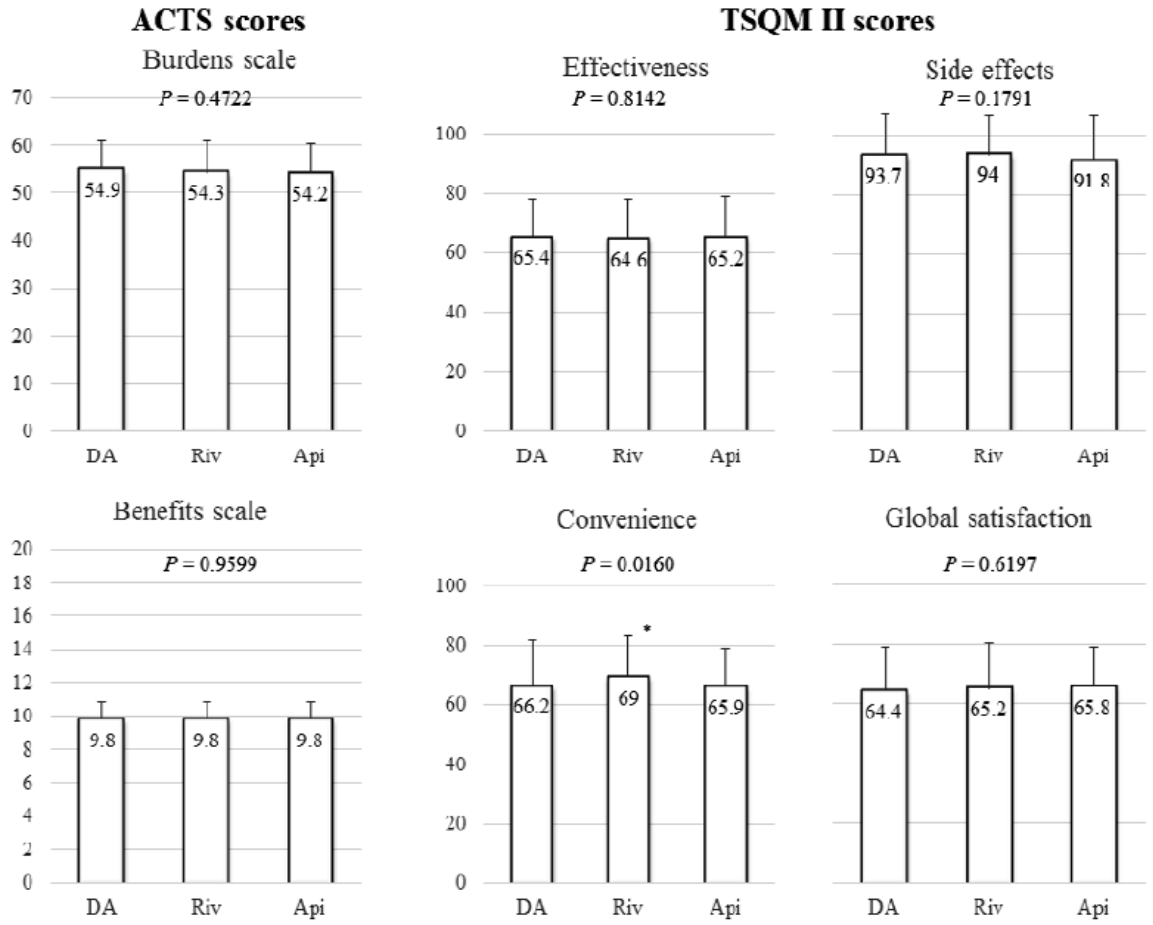

Figure 11. ***Anti-clot treatment scale (ACTS) scores and treatment satisfaction questionnaire for the medication version II (TSQM II):*** *scores of the dabigatran (DA; n = 241), rivaroxaban (Riv; n = 331), and apixaban (Api; n = 81) users. *P < 0.05 versus dabigatran by Kruskal-Wallis test plus Steel-Dwass post hoc test.* Extracted from (43).

Otherwise, although they are a great starting point, we cannot directly extrapolate efficacy and safety data for DOACs in approved on-sheet indications for the treatment of LVT. In the case of NVAF, for example, the pathophysiological basis of thrombotic formation in the left atrial appendage (LAA) is based on low LAA emptying velocities associated with blood stasis, whereas in the setting of LVT it is based on hypercoagulability and endocardial changes in addition to stasis (***see 1.1.2 Pathophysiology and natural history***). These pathophysiological differences could explain differences in anticoagulation response, so we cannot assume the same OAT of choice and regime without conducting adequately powered randomised control trials, specific to the LVT setting (4).

1.2.2 DIRECT ORAL ANTICOAGULANTS IN LEFT VENTRICULAR THROMBUS

Since the beginning of the 2010s, several observational studies have been conducted on the efficacy and safety of DOACs in patients with LVT (36,39-41,57,58). However, only three clinical trials have been conducted in this regard during the last few years. While one study compares Rivaroxaban with VKAs (59), two other small clinical trials have comparatively studied Apixaban in this respect (30,60).

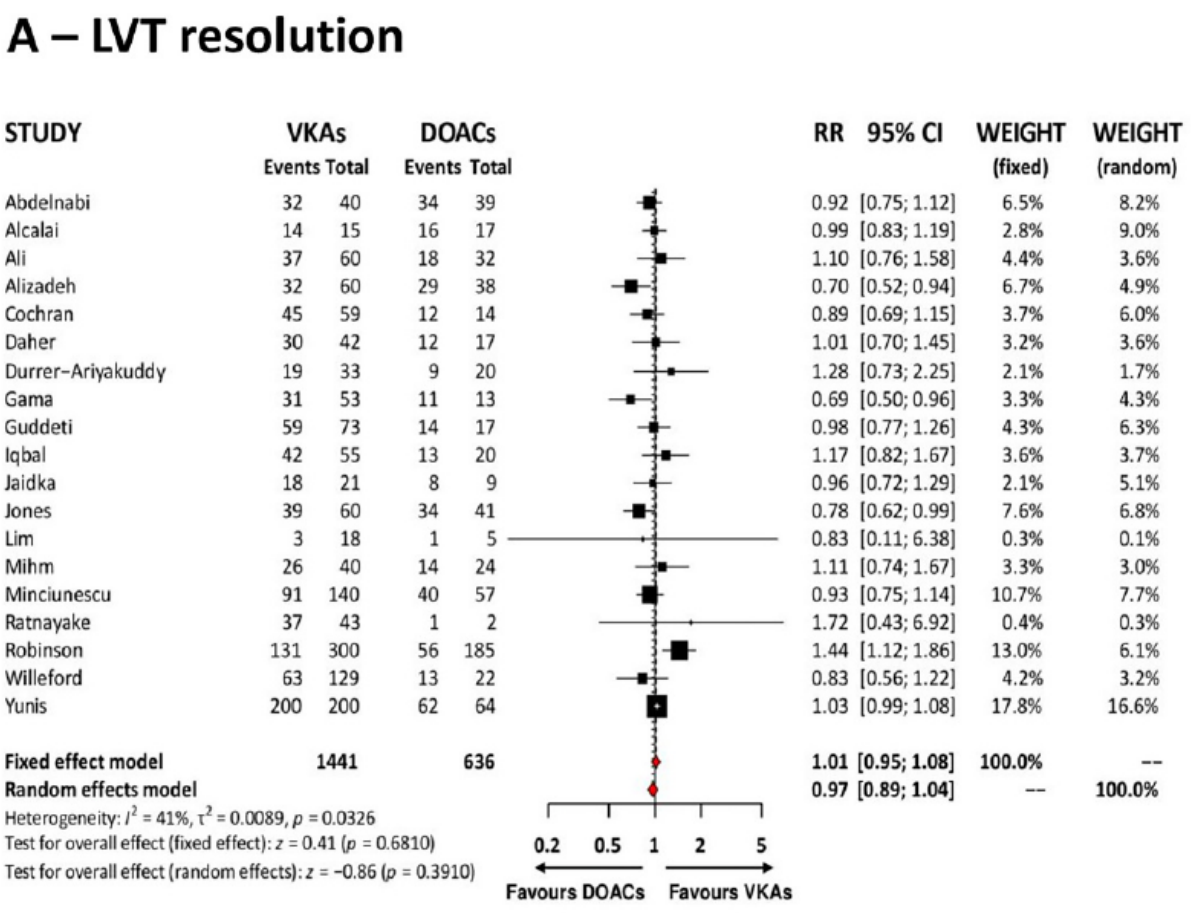

Figure 12. ***Forest plot showing the RR with 95% CI for LVT resolution with VKAs or DOACs****: as calculated by means of a random effects model due to high heterogeneity. (RR = Risk ratio; CI = Confidence interval).* Extracted from (40).

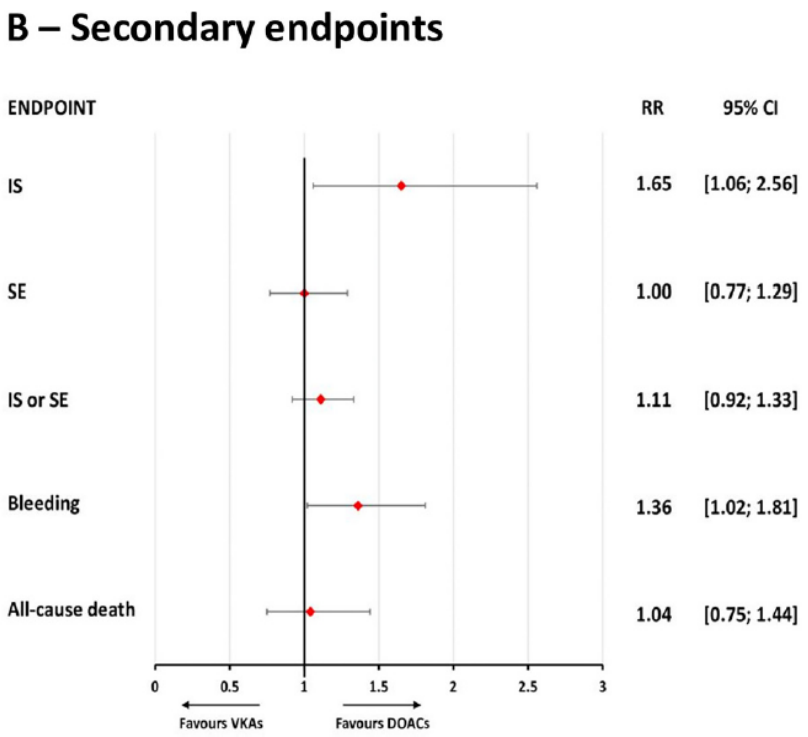

Figure 13. ***Forest plot showing the RR with 95% CIs for the secondary endpoints****: as calculated using a fixed effect model due to low heterogeneity. (DOAC = Direct oral anticoagulant; IS = Ischaemic stroke; LVT = Left ventricular thrombus; RR = Risk ratio; SE = Systemic embolism; VKA = Vitamin K antagonist; CI = Confidence interval).* Extracted from (40).

Systematic reviews and meta-analyses of the retrospective studies collected to date (40,41) **report similar results regarding the effectiveness and safety of DOACs over VKAs** in the treatment of LVT, as can be interpreted from **Figures 12 and 13**. However, although the results of these analyses suffer from the limitations of the included non-randomised retrospective studies (which may lead to significant selection bias), it is important to highlight that one study showed an increased risk of systemic embolism in the case of DOACs (39).

With respect to the clinical trial comparing the use of Rivaroxaban (59), this particular DOAC demonstrated non-inferiority in LVT resolution over warfarin, and corroborated preliminary results from retrospective analyses (57) that also showed faster thrombus resolution in those patients treated with DOACs. Otherwise, in this clinical trial, patients had too few thromboembolic events to make meaningful comparisons in this regard.

Similarly, the two **randomised clinical trials conducted to evaluate the efficacy and safety of Apixaban also demonstrated its non-inferiority in thrombus resolution compared to VKA**. Due to the design of both studies, neither were sufficiently powered to obtain significant results for thromboembolic, cardiovascular, haemorrhagic and mortality events. Other limitations include the relatively small sample size (due to previous overestimation of thrombus resolution with OAT) and large margin of non-inferiority, the need to conduct open-labelled studies, and possible lack of sensitivity of non-contrast TTE diagnosis (30,60).

As stated by many authors, including those responsible for clinical trials, although much evidence has been provided over the last few years, in order to include the use of DOACs as treatment in clinical practice in the setting of LVT, **further research is required** that can **overcome the limitations of the studies** presented to date (1,3,4,7,9,30,36,39-41,59,60).

Furthermore, although the evidence available so far is limited, a recent multicenter study estimated that 43.9% of patients with LVT were treated with DOACs, and it is expected to increase in the next few years while physicians are becoming more comfortable with prescribing it for other off-label use indications (39). Thus, **the need for adequately powered randomised clinical trials is imperative** to provide more safety for medical doctors and patients in clinical practice (1,3,4,7,9,36,39-41).

2. JUSTIFICATION

Left ventricular thrombus is a frequent complication associated with ventricular dysfunction following ST-segment elevation myocardial infarction (1). It is currently estimated to occur in about 6% of STEMI, which would mean an annual incidence of about 200 patients throughout Catalonia (14,15). Moreover, its early management is of vital importance since the embolic potential of LVT is a major source of morbidity and mortality (2-7,9).

Its most widespread diagnostic screening after AMI is routine TTE, due to its wide availability, affordability and portability, as well as it is a rapid and radiation-free test (3,31). According to European guidelines, once diagnosed, it should be treated with VKA anticoagulants for 6 months, in addition to the patient's ongoing DAPT inherent to the AMI, giving rise to what is known as *triple therapy* (1). However, this recommendation does not have great strength, nor a high level of evidence, so there are still many unknowns regarding the best anticoagulation regimen for the treatment of LVT.

With the introduction of DOACs in clinical practice, which offer greater patient convenience, with similar efficacy and better safety profiles in some clinical settings - especially Apixaban -, doubts about the role it could play in the LVT arsenal are increasing (4,5,43,51,52). In order to justify their emerging off-label use, numerous retrospective studies have been conducted since the 2010s (36,39-41,57,58), but it is only in recent years that some clinical trials have been conducted to evaluate the efficacy and safety of DOACs compared to VKAs (30,59,60). However, their own limitations (small sample size, large margin of non-inferiority, absence of double-blinding and possible lack of sensitivity of TTE without contrast) have prevented the inclusion of DOACs within the European and American recommendations, thus requiring studies with sufficient statistical power to overcome these limitations.

Therefore, with this protocol, we offer a multicentre, controlled, double-blind, double-dummy, adequately powered clinical trial to demonstrate the non-inferiority of Apixaban, compared to Acenocoumarol in the resolution of LVT.

For this purpose, we will select those patients with recent STEMI whose thrombus can be visualised ultrasonographically and, after excluding those patients in whom we could cause greater harm and signing the informed consent of those who wish to participate, they will be randomly assigned to either of the two intervention groups, carried out by a blinded statistician. Half of the patients will be assigned to the control group with standard LVT treatment with Acenocoumarol for 6 months, and the other half will be assigned to the experimental group with Apixaban for 6 months. We have chosen Apixaban because it is the most studied DOAC in this setting, has proven to be the safest of them in many of its indications, as well as offering higher overall patient satisfaction (43,50-56). For the first time in a clinical trial in this setting, patients will not know which anticoagulant they are receiving. To achieve this, it will be necessary to carry out a double simulation that resembles the external characteristics of both interventions.

Taking advantage of the echocardiographic equipment and expert personnel in most hospitals in Catalonia, we propose an echocardiographic follow-up with contrast by blinded echocardiographers for the assessment and measurement of LVT, being a procedure already contemplated within routine clinical practice. By doing so, we can overcome the lack of sensitivity of routine echocardiography, as the indication for LVT and the administration of the ultrasound-enhancing agent itself have been shown to considerably improve its sensitivity and positive predictive value (28,31). At each follow-up, in addition to LVT assessment, the occurrence of complications and length of hospitalisation will be recorded as well in order to adequately assess the safety profile that Apixaban may offer compared to Acenocoumarol. Furthermore, in order to individualise medical practice identifying predictors of thrombus persistence, as well as to identify possible confounding factors, at the start of the study we will record a series of demographic, clinical and echocardiographic baseline risk factors of the patients.

For these reasons, a study of the characteristics of our project is necessary in order to safely include the use of Apixaban in the guidelines for the treatment of LVT, and to incorporate it into routine clinical practice, thus improving the quality of life of patients.

3. HYPOTHESIS

Our hypothesis is that the use of Apixaban is not less effective than the use of Acenocoumarol as treatment for echocardiographic resolution of left ventricular thrombus after acute myocardial infarction with ST segment elevation.

4. OBJECTIVES

4.1 PRIMARY OBJECTIVE

The main objective of this study is to verify if Apixaban has a non-inferior efficacy compared to the use of Acenocoumarol as treatment for echocardiographic resolution of left ventricular thrombus after acute myocardial infarction with ST segment elevation.

The primary endpoint, the complete LVT resolution, is defined by the disappearance of LVT on all 2-dimensional transthoracic echocardiography views with ultrasound-enhancing agent at the 3 month follow-up.

4.2 SECONDARY OBJECTIVES

- To compare the effectiveness between Acenocoumarol and Apixaban arms, measured by the occurrences of the following LVT complications:
    - Ischaemic stroke in a time frame of 3 and 6 months.
    - Acute peripheral artery emboli in a time frame of 3 and 6 months.
    - Congestive heart failure in a time frame of 3 and 6 months.
    - Myocardial reinfarction in a time frame of 3 and 6 months.
    - Thrombus persistence at 6 months.

- To compare, in both Acenocoumarol and Apixaban arms, the *late* thrombus resolution in a time frame of 6 months.

- To compare, in both Acenocoumarol and Apixaban arms, the partial thrombus area regression in a time frame of 3 and 6 months.

- To compare the safety between Acenocoumarol and Apixaban arms, measured by the occurrences of major bleeding, in a time frame of 3 and 6 months.

- To compare, in both Acenocoumarol and Apixaban arms, the time of re-hospitalisation in a time frame of 3 and 6 months.

- To compare all-cause mortality occurrences between Acenocoumarol and Apixaban arms, in a time frame of 3 and 6 months.

- To identify independent predictors of LVT persistence at 6 months.

The variables that form part of each primary and secondary objective are fully defined below (***see 5.5.2 Dependent variable***).

5. METHODOLOGY AND MATERIALS

5.1. STUDY DESIGN

This study is a multicentric, randomised, controlled, double-blinded, double-dummy, non-inferiority clinical trial.

5.2. STUDY SETTING

The protocol of this study is designed to be multicentric, including all public hospitals from Catalonia having a cardiology department and/or cardiac imaging unit where cardiologists specialised in cardiac imaging techniques and echocardiography equipment are available. All these participating hospitals belong to the *Institut Català de la Salut* (ICS), being the main public company dedicated to the provision of health care, attached to the *Department of Health of the Generalitat de Catalunya* in Spain. However, in order to be able to include some reference hospitals from the *Central Catalonia Health Region*, we will have reference centres that have formalised alliances with the ICS through agreements within a framework of collaboration.

A *Contract Research Organization* (CRO) project manager will contact the reference hospitals from each *Health Region* in Catalonia, which, if they finally decide to participate, will likewise contact other regional hospitals within their *Health Region* to invite them to take part in this study. The *Health Regions* and their reference hospitals, contacted in the first instance, will be the following:

- **Girona Health Region:** *Hospital Universitari Doctor Josep Trueta* (Girona).
- **Barcelona Health Region:**
    - **Northern Metropolitan Area:** *Hospital Universitari Germans Trias i Pujol* (Badalona).
    - **Barcelona City:** *Hospital Universitari Vall d'Hebron* (Barcelona).

    - **Southern Metropolitan Area:** *Hospital de Viladecans* (Viladecans), *Hospital Universitari de Bellvitge* (L'Hospitalet de Llobregat)
- **Central Catalonia Health Region:** *Althaia* (Manresa), *Consorci Sanitari de l'Anoia* (Igualada), *Hospital San Bernabé* (Berga) and *Consorci Sanitari de Vic* (Vic).
- **Alt Pirineu, Arran and Lleida Health Region:** *Hospital Universitari Arnau de Vilanova* (Lleida).
- **Camp de Tarragona Health Region:** *Hospital Universitari Joan XXIII* (Tarragona).
- **Terres de l'Ebre Health Region:** *Hospital de Tortosa Verge de la Cinta* (Tortosa).

For this clinical trial, the main coordinator of the study will be the principal investigator from *Hospital Universitari Doctor Josep Trueta* (HUDJT) in Girona, together with the assistance of the CRO project manager. With the aim of creating good communication and coordination between all participating centres, a group coordinator will be chosen in each participating hospital (***see 8. Work plan and chronogram***).

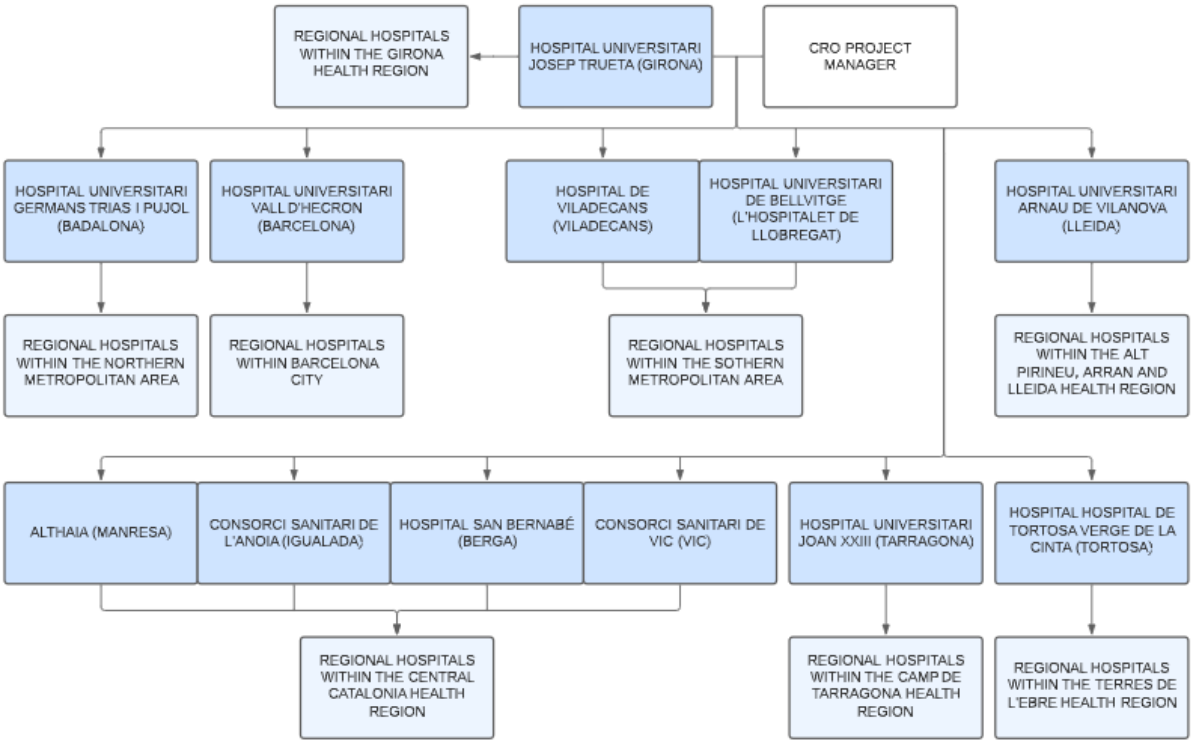

Figure 14. ***Study setting flow chart.*** Own creation.

5.3. STUDY POPULATION

Our study will include patients diagnosed with left ventricular thrombus by TTE after a STEMI at all participant hospitals from Catalonia (***See 5.2 Study Setting***), meet the inclusion criteria and do not meet exclusion criteria of the study.

5.3.1. INCLUSION CRITERIA

- Patients of both sexes, aged 18 years or older.
- Patients diagnosed with left ventricular thrombus by transthoracic echocardiography (with or without ultrasound-enhancing agent) by two cardiologist specialised in cardiac imaging techniques. LVT is defined as an echodense mass distinct from the endocardium with well-defined edges adjacent to a region of abnormal wall motion. It must be visible in at least two views during the cardiac cycle.
- Patients with an acute myocardial infarction in the last 3 months prior to recruitment.
- All patients must have signed the *informed consent* (***see Annex 3***).

5.3.2. EXCLUSION CRITERIA

- Contraindications to anticoagulation therapy (44,48,62,63), such as:
    - Hypersensitivity to the active substance of Acenocoumarol, Apixaban and/or Heparin/Enoxaparin sodium, substances of porcine origin or to any of their excipients (***see Annex 5***).
    - Active bleeding, increased risk of bleeding due to altered haemostasis or organic lesions susceptible to bleeding.

    - Haemorrhagic diathesis, haemorrhagic blood dyscrasia or injury or pathology considered to pose a significant risk of major bleeding (***see Annex 5***) or to pose a risk of bleeding greater than the clinical benefit.
    - History or suspicion of immunologically-mediated heparin-induced thrombocytopenia.
    - Disseminated intravascular coagulation attributable to heparin-induced thrombocytopenia.
    - Pregnancy.
    - Severe liver function disorder or hepatopathy associated with coagulopathy and with clinically relevant bleeding risk.
    - Damage or surgical interventions on the central nervous system, eyes and ears.
    - Endocarditis.
    - Uncooperative patients (e.g. alcoholic patients, patients with psychiatric disorders or unsupervised senile patients).
- Contraindications to contrast echocardiography (sulphur hexafluoride microbubbles) (64), such as:
    - Hypersensitivity to sulphur hexafluoride or to its excipients (***see Annex 5***).
    - Patients with very recent AMI whose doctor considers not to perform the contrast test due to clinical instability.
    - Very severe pulmonary hypertension (>90 mmHg).
    - Right-to-left shunts.
    - Uncontrolled systemic hypertension.
    - Adult respiratory distress syndrome.
- Hypersensitivity to the placebo excipients (***see Annex 5***).
- In case of disagreement by the two experienced echocardiographers on the existence of the LVT at enrollment.
- Concomitant treatment with any other anticoagulant drug, indicated by any other medical condition.
- Patients with severe renal failure (CrCl< 15 ml/min).
- Lack of understanding of *informed consent* (***see Annex 3***).
- Participation in other clinical studies that may affect patient management.

5.4. SAMPLE

5.4.2. SAMPLE SIZE

We expect, based on the evidence available to date (30,49,59,60), a 75% LVT resolution with OAT at the 3-month follow-up. We have designed a **two-sided test**, with an **alpha risk** value equal to 0.05, **beta risk** value equal to 0.2, assuming a **dropout rate** of 5% and a 10% of **absolute margin of non-inferiority** (δ), in which we require a total sample size of **264 patients** (**132 patients for each arm**).

We have set an absolute non-inferiority margin of 10%, as this is the value established in another clinical trial with Rivaroxaban (59), and with this, we will be able to overcome some of the limitations of prospective studies with Apixaban (30) which determined absolute margins of 20%.

As this is a study with a relatively short total follow-up time (6 months), we assume a minimal dropout rate, which is included in the sample size calculation. Thus, we do not consider it necessary to apply any imputation method for the processing of missing data.

Computations were carried out based on the package 'pwr' of the free statistical environment R (version 4.2.2) (61).

5.4.1. SAMPLE SELECTION

The selection will be made using a consecutive, non-probabilistic sampling method of patients attending the cardiology department and/or cardiac imaging unit of any of the participant hospitals in Catalonia indicated above. Patients who meet inclusion criteria and do not meet any of the exclusion criteria will be offered to participate in the clinical trial.

Patients finally included in the sample from each hospital will be proportional to the eligible patients in each of them.

5.4.3. ESTIMATED TIME OF RECRUITMENT

Taking into account the annual incidence of AMI in Catalonia (420-450/1,000,000 inhabitants) and the current incidence of complications in the form of LVT (6,3%), we can assume an annual incidence of LVT in the general population of Catalonia of approximately 2,6/100.000 inhabitants per year. This means an approximate number of 200 patients per year in all hospitals from Catalonia (7.794.749 reference inhabitants according to the *Servei Català de Salut*), so the estimated duration of the recruitment to be able to enrol the required number of participants (n=264) will be about **2 years**.

We consider this incidence inference to be a valid approximation, since it is able to correctly calculate the actual annual incidence at the *HUDJT*, which corresponds to about 20 episodes per year.

5.4.4. RANDOMISATION

Once patients who meet inclusion criteria and do not meet any of the exclusion criteria have signed the informed consent form, they will be randomly assigned to one of the following two groups:

- **Group A - Control group:** The patient will be treated with Acenocoumarol for 6 months, explained in detail below (***see 5.5.1 Independent variable***).
- **Group B - Intervention of interest group:** The patient will be treated with Apixaban for 6 months, explained in detail below (***see 5.5.1 Independent variable***).

Patient assignment will be performed by a blinded statistician who, using dedicated software (https://www.randomizer.org/) in order to avoid selection biases such as bias of the selection procedure, will randomly separate patients into two groups (1:1 ratio), without knowing the treatment that corresponds to each group.

5.4.5. MASKING TECHNIQUES

This is a randomised **double-blind double-dummy** controlled clinical trial, so neither the patients nor the echocardiographers will be aware of the intervention group in which the patients have been included. In order to maintain the double-blind masking technique, patients will be administered drugs or placebos with external characteristics equal to those of the opposite intervention arm, as some forms of presentation and dosing regimens were initially different between the experimental and control group. Therefore, all tablets administered in both groups will be encapsulated, with the aim of homogenising the form of presentation in both arms of the trial. Blinding patients is a way to prevent bias such as compliance bias or bias due to behavioural change influenced by knowledge about the drug received (e.g. increased or decreased risk behaviour that may eventually lead to a haemorrhage).

In those patients who are assigned to the Acenocoumarol group, they will receive this once-daily encapsulated tablet together with a once-daily **encapsulated placebo tablet** (spaced about 12 hours apart) with identical external features to Acenocoumarol, in order to emulate the double Apixaban intake of patients in the other group. Initially, these patients will receive simultaneous anticoagulation induction with two subcutaneous injections of Enoxaparin per day for about 4-5 days, or parenteral administration of Heparin if hospitalised. Once this *bridge* therapy is completed, treatment with Acenocoumarol and placebo is maintained for 6 months. Periodic blood tests will be necessary to assess whether the INR values are within the therapeutic range, as explained in more detail below (***see 5.5.1 Independent variable***).

In contrast, the Apixaban group will receive a double daily dose of encapsulated Apixaban, spaced about 12 hours apart each. However, to maintain the blind, a series of simulations should be performed. At the start of treatment, 0.9% saline (**placebo "Enoxaparin"**) should be administered via subcutaneous injections twice daily for 4-5 days, or parenteral administrations if hospitalised. During the study, periodic **simulated "INR tests"** will be performed, where the minimum amount of blood will be extracted in order to emulate the periodic blood tests corresponding to the control group. In order not to break the blinding,

patients assigned to the Apixaban group will be **paired** with patients in the Acenocoumarol group, so that the periodicity of blood tests and drug handling will be identical in both groups. In case of drop-out or death of any patient from the Acenocoumarol arm, the previously matched patient from the Apixaban group will undergo randomised frequency of blood tests and drug handling (one to four weeks).

Regarding echocardiographers, by making them unaware of the patient's intervention group, we will be able to reduce measurement biases such as procedural bias, whereby the investigator who is aware of the experimental intervention group may show greater observational acuity than with the control group.

This double simulation could only be possible with the help of not-blinded cardiologists, haematologists, nurses, hospital Pharmacy Service and other health personnel involved, who know the real intervention that must be performed on the patient in order to administer the appropriate drug, modify doses if required, carry out the corresponding tests or, if not, the simulations and placebo administrations necessary to avoid breaking the patient's blind.

Furthermore, the analyst will also not know the intervention of each group when separating the two groups as this procedure will be performed by dedicated software, as well as matching patients between both groups and when analysing their results.

5.5. VARIABLES

5.5.1. INDEPENDENT VARIABLE

The independent variable of our study will be the type of intervention being performed. As patients in the study can only belong to one of the following two trial arms, taking Acenocoumarol or Apixaban, it is a dichotomous nominal qualitative variable. As explained above (***see 5.4.4. Randomisation***), patients will be randomly assigned to one of the two study arms.

The Acenocoumarol intervention arm (**Group A - Control group**) will consist of:

- Taking adjusted doses of Acenocoumarol daily orally (encapsulated tablets) for 6 months. The dose administered should be individually adjusted with the aim of maintaining an INR value between 2.0 and 3.0. For this purpose, it will be necessary to carry out periodic INR controls:
    - Monthly if the last value was within the therapeutic range (2.0-3.0).
    - In 2-3 weeks if the last value was between 3.0 and 3.5.
    - In 1 week if the last value was between 1.5 and 2 or 3.5 and 5.
    - In 4 days if the last value was less than 1.5 or more than 5.

  Due to the delayed anticoagulant action of Acenocoumarol, administration of Enoxaparin will be necessary for at least 4-5 days only at the start of the study, as a *bridging* therapy. In order to obtain INR values within the therapeutic range, once the patient is assigned to the Acenocoumarol group, they will be given simultaneously 1 mg/kg of subcutaneous Enoxaparin twice daily (or an intravenous infusion of Heparin if hospitalised).

  As explained above (***see 5.4.5. Masking techniques***), patients in this control arm will receive a daily placebo drug, with similar external features, to be spaced about 12 hours apart from taking Acenocoumarol.

The Apixaban intervention arm (**Group B - Intervention of interest group**) will consist of:

- Taking Apixaban 5 mg twice daily orally (encapsulated tablets) for 6 months

  Or
- Taking a dose reduction of 2.5 mg of Apixaban administered twice daily orally (encapsulated tablets), only performed in the following patients:
    - Age ≥ 80 years,
    - body weight ≤ 60 kg,
    - serum creatinine ≥ 1.5mg/dl (133 micromoles/l) or
    - advanced renal failure (CrCl between 15 ml/min and 29 ml/min).

As explained above (***see 5.4.5 Masking techniques***), patients in this intervention arm will receive a double daily subcutaneous administration of "Enoxaparin" placebo for 4-5 days, while monthly "INR" simulations will be performed where the minimum amount of blood will be taken. A “Heparin” placebo will be administered intravenously if the patient is hospitalised.

5.5.2 DEPENDENT VARIABLE

Main outcome:

- *Complete resolution of thrombus rates:*
  It is defined as the absence of a previously recognized left ventricular thrombus, using all 2-dimensional transthoracic echocardiography views with ultrasound-enhancing agent at the 3 month follow-up. This is a dichotomous nominal qualitative variable, as anticoagulated patients at 3-month follow-up can only show two types of echocardiographic image: complete resolution of the thrombus or persistent LVT. This primary objective will be assessed by two cardiologist specialised in cardiac imaging techniques, but only in case of disagreement on the complete resolution of LVT at follow-up, a third expert echocardiographer will be added in order to seek consensus.

Secondary outcomes:

- *Ischaemic stroke occurrence:* this is a dichotomous nominal qualitative variable. It is defined as the occurrence of any ischaemic stroke, according to the *Catalan Society of Neurology* guidelines. Its incidence will be assessed in our study in a frame of time of 3 and 6 months.

- *Acute peripheral artery emboli occurrence:* this is a dichotomous nominal qualitative variable. It is defined as the occurrence of any acute peripheral artery emboli,

according to the *European Society of Cardiology* guidelines. Its incidence will be assessed in our study in a frame of time of 3 and 6 months.

- *Major bleeding occurrence:* this is a dichotomous nominal qualitative variable. It is defined as the occurrence of any major bleeding rates, according to the *International Society on Thrombosis and Haemostasis* definition (fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 20 g/l or more, or leading to transfusion of two or more units of whole blood or red cells). Its incidence will be assessed in our study in a frame of time of 3 and 6 months.

- *Myocardial reinfarction occurrence:* this is a dichotomous nominal qualitative variable. It is defined as the occurrence of any STEMI, according to the *European Society of Cardiology* guidelines. Its incidence will be assessed in our study in a frame of time of 3 and 6 months.

- *Congestive heart failure occurrence:* this is a dichotomous nominal qualitative variable. It is defined as the occurrence of any congestive heart failure, according to the *European Society of Cardiology* guidelines. Its incidence will be assessed in our study in a frame of time of 3 and 6 months.

- *All-cause mortality rates:* this is a dichotomous nominal qualitative variable. It is defined as the occurrence of death from any cause. Its incidence will be assessed in our study in a frame of time of 3 and 6 months.

- *Late thrombus resolution occurrence:* this is a dichotomous nominal qualitative variable. It is defined as the resolution of the LVT at the 6-month follow-up by TTE (and not at the 3-month follow-up). In case of disagreement on the complete resolution of LVT at follow-up, a third expert echocardiographer will be added in order to seek consensus.

- *Persistent thrombus occurrence:* this is a dichotomous nominal qualitative variable. It is defined as an increased, stable thrombus or a thrombus whose reduction does not reach complete resolution at the 6-month follow-up by TTE (and not at the 3-month follow-up). In case of disagreement on the persistence of LVT at follow-up, a third expert echocardiographer will be added in order to seek consensus.

- *Time of re-hospitalisation*: this is a continuous quantitative variable, but distributed asymmetrically. It is defined as the *days* of re-hospitalisation for cardiovascular reasons and for non-cardiovascular reasons. It will be measured in our study in a frame of time of 3 and 6 months.

- *Partial thrombus area regression:* this is a continuous quantitative variable, but distributed asymmetrically. It will be assessed through the TTE by comparing the size of the thrombus at baseline with the 3-month and 6-month controls. It will be expressed in *percentage units*. For this, it will be necessary to assess the area (cm^2) of the LVT at each echocardiographic examination by two-dimensional visualisation of the thrombus' major diameters.

5.5.3 COVARIATES

This study will record numerous demographic, clinical and echocardiographic baseline characteristics in order to identify confounding variables and independent predictors for LVT persistence at 6 months. These are as follows:

- *Age*: this is a continuous quantitative variable. It will be expressed with numerical values in *years*.

- *Sex*: this is a dichotomous nominal qualitative variable (*MALE / FEMALE*).

- *Personal or family history of STEMI*: this is a dichotomous nominal qualitative variable (*YES / NO*).

- *Hypertension*: this is a dichotomous nominal qualitative variable (*YES / NO*). The hypertension status is defined according to the *WHO* definition.

- *COVID-19 active infection*: this is a dichotomous nominal qualitative variable (*YES / NO*). Active COVID-19 infection is defined according to "*Estrategia de detección precoz, vigilancia y control de COVID-19*" definitions, addressed by the *Ministry of Health* of the *Government of Spain*.

- *Treatment of STEMI*: this is a polytomous nominal qualitative-categorical variable (*PRIMARY PCI / FIBRINOLYSIS / NONE*), according to the *European Society of Cardiology* guidelines definitions.

- *Vessels affected in STEMI*: this is a dichotomous nominal qualitative variable (*SINGLE-VESSEL DISEASE / MULTI-VESSEL DISEASE*), according to the *European Society of Cardiology* guidelines definitions.

- *Apical asynergy*: this is a dichotomous nominal qualitative variable (*YES / NO*). It is defined as akinesis or dyskinesis of the apical segments visualised through TTE.

- *Apical aneurysm*: this is a dichotomous nominal qualitative variable (*YES / NO*), assessed through TTE.

- *LVEF*: this is an ordinal qualitative variable (*PRESERVED*: >50%; *MILD*: 40-50%; *MODERATE*: 30-39.99% or *SEVERE DYSFUNCTION*: <30%), assessed by TTE (Simpson biplane method).

- *Location of STEMI*: this is a polytomous nominal qualitative-categorical variable (*ANTERIOR / POSTERIOR / INFERIOR / LATERAL*), according to the *European Society of Cardiology* guidelines definitions.

- *Appearance of the thrombus*: this is a dichotomous nominal qualitative variable (*PROTRUDING* / *LAMINAR*), assessed through TTE.

- *Mobility of the thrombus*: this is a dichotomous nominal qualitative variable (*MOBILE* / *IMMOBILE*), assessed through TTE.

- *Hospital*: This is a polytomous qualitative-categorical nominal variable. The registry of the hospital which enrolled each patient in the study sample is included in order to control for inter-hospital variability (possible information bias) in the multivariate analysis.

	VARIABLE	DESCRIPTION	CATEGORIES
INDEPENDENT VARIABLE	*Intervention (oral anticoagulant therapy performed)*	Qualitative nominal dichotomous	Acenocoumarol / Apixaban
MAIN OUTCOME	*LVT resolution at 3-month follow up*	Qualitative nominal dichotomous	Yes / No
SECONDARY OUTCOME	*Ischaemic stroke at 3- and 6-month follow up*	Qualitative nominal dichotomous	Yes / No
	Acute peripheral artery emboli at 3- and 6-month follow up	Qualitative nominal dichotomous	Yes / No
	Major bleeding at 3- and 6-month follow up	Qualitative nominal dichotomous	Yes / No
	Myocardial reinfarction at 3- and 6-month follow up	Qualitative nominal dichotomous	Yes / No

	Congestive heart failure at 3- and 6-month follow up	Qualitative nominal dichotomous	Yes / No
	Late thrombus resolution at 6-month follow up	Qualitative nominal dichotomous	Yes / No
	Persistent thrombus at 6-month follow up	Qualitative nominal dichotomous	Yes / No
	Time of re-hospitalisation at 3- and 6-month follow up	Quantitative continuous, asymmetrically distributed	Days
	Partial thrombus area regression at 3- and 6-month follow up	Quantitative continuous, asymmetrically distributed	%
COVARIATES	*Age*	Quantitative continuous	Years
	Sex	Qualitative nominal dichotomous	Male / Female
	Personal or family history of STEMI	Qualitative nominal dichotomous	Yes / No
	Hypertension	Qualitative nominal dichotomous	Yes / No
	COVID-19 active infection	Qualitative nominal dichotomous	Yes / No

	Treatment of STEMI	Qualitative - categorical nominal polytomous	i. Primary PCI ii. Fibrinolysis iii. None
	Vessels affected in STEMI	Qualitative nominal dichotomous	Single-vessel disease / Multi-vessel disease
	Apical asynergy	Qualitative nominal dichotomous	Yes / No
	Apical aneurysm	Qualitative nominal dichotomous	Yes / No
	LVEF	Qualitative ordinal	i. Preserved Ii. Mild iii.Moderate iv. Severe dysfunction
	Location of STEMI	Qualitative - categorical nominal polytomous	i. Anterior ii. Posterior iii. Inferior iv. Lateral
	Appearance of the thrombus	Qualitative nominal dichotomous	Protruding / Laminar
	Mobility of the thrombus	Qualitative nominal dichotomous	Mobile / Immobile
	Hospital	Qualitative - categorical nominal polytomous	Name of the participant hospital

Table 4. ***Variables assigned in the clinical trial.*** *LTV = Left ventricular thrombus; STEMI = ST-elevation myocardial infarction; PCI = Percutaneous coronary intervention; LVEF = Left ventricular ejection fraction*. Own creation.

5.5.4 STUDY CIRCUIT

According to standard clinical practice, all patients with STEMI undergo routine echocardiographic assessment during hospital stay to assess ventricular function and detect early mechanical complications, as well as to exclude the presence of LVT and perform prognostic stratification. After discharge, patients with LVEF≤40% undergo another echocardiogram 6-12 weeks after MI to assess the potential need for implantation of a cardioverter-defibrillator. Therefore, based on the inclusion criteria established in this study, any patient found to have LVT detected by such echocardiographic assessments (contrast or non-contrast) within 3 months after STEMI will be invited to participate in the study, once the trial procedure has been explained and all inclusion criteria and no exclusion criteria have been met.

Exclusion and Apixaban dose reduction criteria based on renal or hepatic function will be assessed through the blood tests performed during admission and hospital stay, so no additional blood tests will be necessary. The remaining exclusion criteria based on medical contraindications and concomitant treatments will be assessed through the patient's clinical history and direct consultation.

Once the study procedure has been explained to the patient, the *information form* (***see Annex 2***) and *informed consent* form (***see Annex 3***) will be given to he/she, leaving enough time to read and decide. With the willingness to participate and the signed *informed consent*, the patient will finally be included in the study. Later, a numerical code will be assigned to each patient in order to preserve the patient's anonymity throughout the study procedure.

A blinded research echocardiographer will then perform a baseline contrast TTE, whose results will be analysed by two blinded cardiologist specialised in cardiac imaging techniques, or three if needed. In addition, they will record all patient covariates using this echocardiographic assessment, the patient's clinical history, and the patient's direct consultation, respectively for each covariate. Once all these data have been recorded, a

blinded statistician will randomly assign the patient to an intervention group, without the statistician's nor the patient's knowledge of the assigned drug.

Independently of the intervention group, and with the intention of not breaking the patient blind, an unblinded multidisciplinary team formed by cardiologist, haematologists and nurses will be in charge of carrying out an education programme for the anticoagulated patient, where they will explain the foods they can eat, the drug intake hours and the INR monitoring through periodical blood tests (real or simulated). All patients will be advised of possible changes in the frequency of blood tests (usually monthly) and drug handling. As this process is part of routine clinical practice, no additional procedure on patient OAT education will be necessary. The patients will maintain treatment at least until the end of the 6-month follow-up. In order not to break the blinding in case of variation in frequency of blood tests and drug handling between the two groups (due to dose adjustment in patients on Acenocoumarol with the aim of maintaining INR values within the target range), patients in the Apixaban group will be matched with those in the Acenocoumarol group. Therefore, we will achieve a total homogenisation of blood tests and drug handling between both groups. However, in case of death or withdrawal of patients from the Acenocoumarol group, the blood test and drug handling frequency of the previously matched Apixaban patients will be randomised between one and four weeks.

This study will consist of two follow-ups, one at 3 months (90 days) and another at 6 months (180 days) after the start of the intervention. At each follow-up visit, the patient will undergo an echocardiographic examination via TTE with contrast, the results of which will be evaluated by two blinded echocardiographers, or three if needed. With these results, it will be possible to evaluate the main dependent variable with the resolution of the thrombus at 3 months, and other secondary variables such as the partial regression of the thrombus area, the persistence of the thrombus at 6 months or the *late* reabsorption of the thrombus at 6 months. In addition, in order to assess other secondary variables, complications and days re-hospitalised during the three months prior to each follow-up will be consulted. This echocardiographic and complication monitoring is already included in clinical practice for patients diagnosed with LVT, so no additional follow-up visits are necessary.

The following table (**Table 5**) and flowchart (**Figure 15**) are intended to summarise the circuit of the study.

	First visit	Baseline	3-month follow up	6-month follow up
Information form	✔			
Informed consent	✔			
Intervention assignment		✔		
Drug administration		B.I.D.		
Contrast TTE assessment		✔	✔	✔
Apical asynergy		✔		
Apical aneurysm		✔		
LVEF		✔		
Appearance of the thrombus		✔		
Mobility of the thrombus		✔		
Thrombus total area		✔	✔	✔
Complete resolution or persistence of thrombus			✔	✔
Complications assessment			✔	✔
Ischaemic stroke			✔	✔
Acute peripheral artery emboli			✔	✔
Major bleeding			✔	✔
Myocardial reinfarction			✔	✔
Congestive heart failure			✔	✔
Time of re-hospitalisation			✔	✔
Exitus			✔	✔

Table 5. ***Schedule of assessments.*** *B.I.D = bis in die (twice a day)*. Own creation.

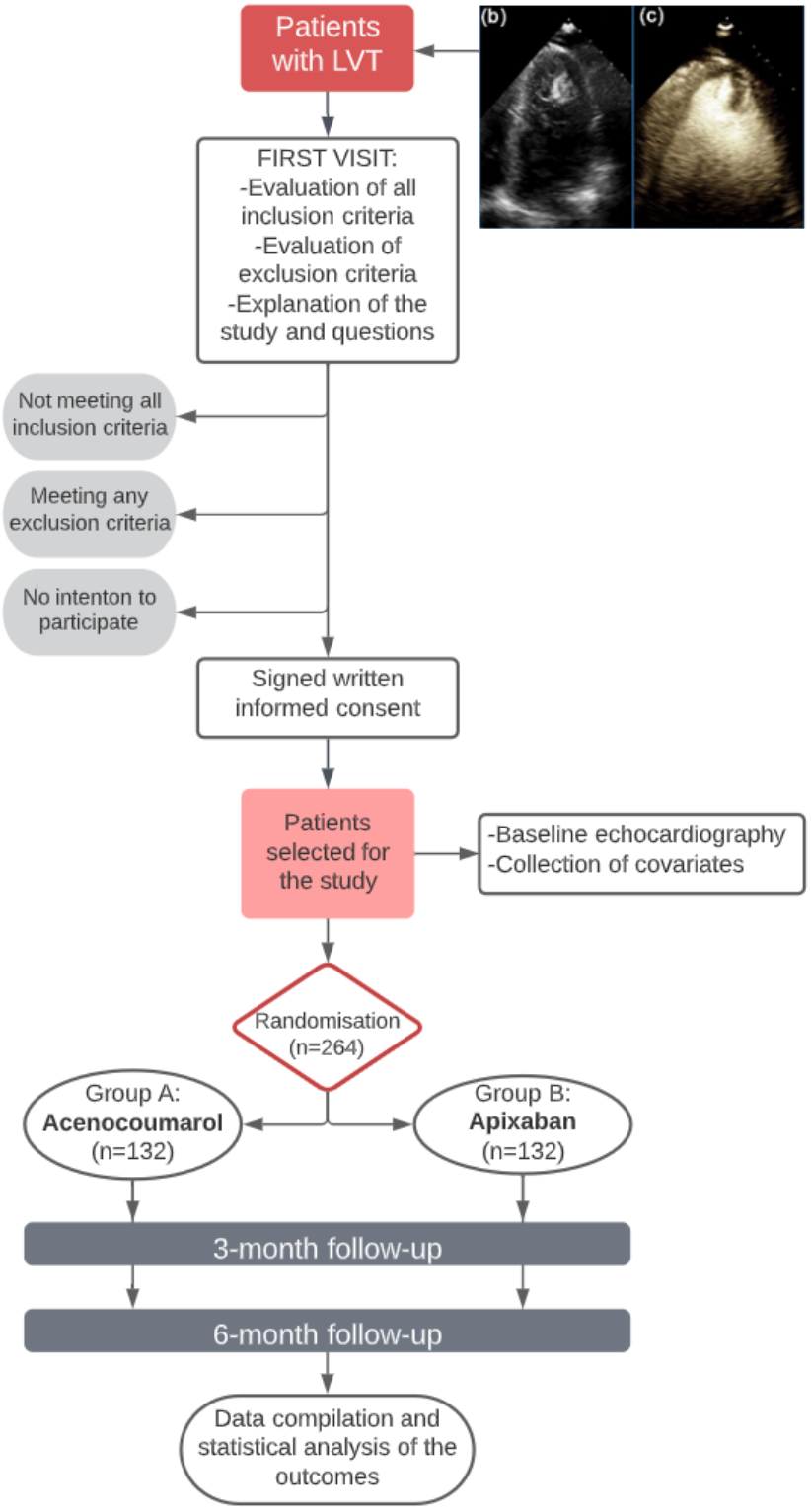

Figure 15. ***Patient flow in the study.*** Echocardiographic images extracted from (7).

5.5.5 DATA COLLECTION

The data collected, at baseline and during the follow-up at 3 and 6 months, will be recorded in an online database developed specifically for this purpose. Each researcher participating in the study will have a unique account and password to access the website and complete the data corresponding to the numerical code associated with each patient, thus ensuring confidentiality.

Once the data collection and follow-up stage of the study has been completed, all recorded data will be organised and analysed by a blinded statistician with access to the database.

5.7. STATISTICAL ANALYSIS

Our study will include three levels of statistical analysis of the data obtained: univariate, bivariate and multivariate analysis. Due to the masking of our study, the statistical analysis will be carried out by a blinded statistician, using the version 28.1 Statistical Package for Social Sciences (SPSS Windows®). For all results, we will assume statistical significance at a value of $p<0.05$, defining a 95% confidence interval. We will compute the non-inferiority p-value (one-side) and the two-side p-value.

5.7.1 DESCRIPTIVE UNIVARIATE ANALYSES

Descriptive analysis will be carried out for all variables in the study. Qualitative variables will be summarised using **percentages (proportions)**, while quantitative variables (either continuous or discrete) will be summarised using **median** and **interquartile range**, as they are not expected to follow a normal distribution.

These analyses will be stratified by the intervention (independent variable), although they will be additionally stratified by the covariates. Age will be categorised in **quartiles**.

5.7.2. BIVARIATE INFERENCE

Regarding bivariate analysis, the difference in *complete thrombus resolution rates* at 3 months (main dependent variable) in the two intervention groups (independent variable) will be analysed by the **chi-squared test**. Likewise, the occurrences of *ischaemic stroke*, *acute peripheral arterial embolism*, *congestive heart failure*, *myocardial reinfarction*, *major bleeding*, *all-cause mortality* at 3 and 6 months, as well as *late thrombus reabsorption* and *thrombus persistence* at 6 months in the two intervention groups (independent variable) will be analysed by the **chi-squared test** or the **Fisher's exact test** (in case in any of the cells the expected number of cases were lower than 5).

However, the difference of medians of *time of re-hospitalisation* and *partial thrombus area regression* at 3 and 6 months, between the groups defined by our independent variable (type of intervention) will be tested using the **Mann-Withney's U test**.

We will estimate the **Kaplan-Meier curves** for *time of re-hospitalization* between the intervention and the control group, while the differences between the curves will be tested using the **Log-Rank test**.

These analyses will be additionally stratified by the covariables. Using the results obtained from these bivariate analyses, we will fulfil all objectives except the last secondary objective (***see 4. Objectives***). The main outcome of the study will be assessed using **relative risk**.

5.7.3. MULTIVARIATE ANALYSES

As this is a randomised clinical trial, it is unlikely that there will be differences between the covariates in the two groups. However, we will also perform a multivariate analysis in order to detect any covariate that may play a role as a confounding variable.

The effect of the intervention (independent variable) on the *complete resolution of the thrombus* at 3 months (main dependent variable) will be estimated by controlling for the

effect of third factors that could act as confounders, such as *baseline clinical and echocardiographic characteristics* (covariates), through **logistic regression**. Likewise, to analyse the effect of the intervention (independent variable) on the rest of the qualitative dependent variables (the occurrences of *ischaemic stroke*, *acute peripheral arterial embolism*, *congestive heart failure*, *myocardial reinfarction*, *major bleeding*, *all-cause mortality* at 3 and 6 months, as well as *late thrombus reabsorption* and *thrombus persistence* at 6 months), we will perform also a **logistic regression** controlling for all covariates.

Using the results obtained from the logistic regression between the intervention and *thrombus persistence* at 6 months, controlling for all the covariates, we will fulfil the last secondary objective (*to identify independent predictors of LVT persistence at 6 months*).

To analyse the effect of the intervention (independent variable) on the quantitative continuous, but asymmetrically distributed, *partial thrombus area reduction* at 3 and 6 months, controlling for all variables, it will be necessary to use **Poisson regression**.

To assess the effect of the intervention on the *time of re-hospitalisation* we will estimate a **Cox regression**, again controlling for the covariates.

6. ETHICAL AND LEGAL CONSIDERATIONS

This clinical trial, motivated by the basic ethical principles of Beauchamp and Childress (65), will be conducted in accordance with the human rights and ethical principles guaranteed by the World Medical Association Declaration of Helsinki (66) of "*Ethical Principles for Medical Research Involving Human Subjects*", first adopted in 1964 at the 18th World Medical Assembly in Helsinki (Finland) and last amended in 2013 at the 64th General Assembly in Fortaleza (Brazil).

Among all the medical ethical principles respected in this study, the principle of **justice** will be guaranteed by avoiding any kind of discrimination between those patients who meet the inclusion criteria and do not meet the exclusion criteria, inviting all of them to participate in our study.

On the other hand, in order to preserve the principle of **patient autonomy**, the signature of the informed consent form will be required as compulsory to participate in our study, as well as free enrolment with necessary time for the patient to assess his/her participation. Therefore, lack of oral and written comprehension of the informed consent, as assessed by the physician, will be included as a criterion for exclusion from the study. We consider that all these measures fall within the legal framework in Spain of the "*Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de los derechos y obligaciones en materia de información y documentación clínica*".

As explained in the introduction (***1.2.2 Direct oral anticoagulants in left ventricular thrombus***), systematic reviews and meta-analyses have shown that Apixaban has very similar efficacy to Acenocoumarol treatment in patients with left ventricular thrombus. Therefore, no lower efficacy is expected in the experimental arm of the study (Apixaban) compared to the control group (Acenocoumarol), thus respecting the principle of **non-maleficence**. Moreover, patients with characteristics that confer a higher risk of receiving more harm than benefit have been included in the exclusion criteria. In addition, in order to maintain double-blinding in our study, it will be necessary to perform double

simulations with placebos or simulated tests that pose no or minimal harm (e.g. minimal blood draw in the simulated "INR" tests) on the patients.

As Apixaban seems to be a safer anticoagulant than VKAs in some clinical settings, and - like the other DOACs - is more convenient for the patient than Acenocoumarol treatment, resulting in an improvement of the patients' quality of life, this study will be conducted according to the principle of **beneficence**.

The development of this protocol was carried out in accordance with the Spanish legal framework, as it will respect the precepts of "*Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos*" and the "*Ley 14/2007, de 3 de julio, de Investigación Biomédica*".

Furthermore, respect for Spanish laws on patient confidentiality, such as the "*Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos*" and the "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*", they will be guaranteed by assigning a numerical code to each patient participating in the study, with the aim of preserving their anonymity when storing all the data collected.

In order for the study to commence, the protocol must be evaluated by the "*Comité d'Ètica d'Investigació Clínica*" (CEIC) of the *Hospital Universitari Doctor Josep Trueta* from Girona, the coordinating hospital of the study. Once it has been approved by the ethics committee, and its recommendations have been assessed and implemented in the final protocol, this document will be sent to the coordinator of each participating hospital. The clinical trial will only be carried out in those centres that have approved it, and the signature of all participating investigators in each hospital will be required to formalise their support for the final protocol and their ethical declarations regarding the research.

Importantly, in order to avoid publication bias and to promote transparency in our study, all data will be published, so records of unfavourable data or events will not be hidden.

Finally, we declare **no conflict of interest** of any kind.

7. STRENGTHS AND LIMITATIONS

Strengths:

- This is the first clinical trial with sufficient power to demonstrate non-inferiority efficacy and safety of Apixaban in the treatment for LVT resolution, compared to standardised treatment with Acenocoumarol. This is due to a more rigorous preliminary estimate of thrombus resolution rates with OAT at 3 months and a smaller margin of non-inferiority applied, compared to recent small unpowered clinical trials, resulting in a higher estimate of the sample size needed to demonstrate significant differences.
- This is a randomised controlled clinical trial, the results of which will provide high-quality scientific evidence in the therapeutic approach to LVT with Apixaban. This avoids procedural selection bias, and confusion bias by multivariate analysis as well.
- This is the first double-blind double-dummy clinical trial in this regard, as neither the patients nor the echocardiographers will know which intervention group patients are in. This will minimise measurement biases such as procedural bias caused by unblinded investigators, or compliance bias caused by unblinded patients.
- In our study, LVT detection and measurement will be performed by contrast-enhanced TTE with preliminary indications of LVT, which significantly increases its sensitivity, compared to the use of non-contrast TTE in those few recently published clinical trials. This is intended to avoid measurement biases such as bias due to lack of sensitivity of an instrument. In addition, the determination of a single detection and measurement technique for the study in all follow-ups in all participating hospitals is intended to reduce detection bias.
- As this is a multicentre study, the results of the study will have high external validity (high representativeness), allowing greater extrapolation to the general population.
- This is a feasible clinical trial because the participation of the reference hospitals has been calculated based on their reference population and the estimated sample size to carry out our study.

Limitations:

- As this is a clinical trial, the cost of the study is high due to the sample size, the duration of the study, the administration of drugs and the performance of simulated medical tests or administration of placebo drugs outside the usual clinical practice in the treatment of LVT. However, we will apply for various Catalan, Spanish and European grants in order to obtain sufficient funding to carry out the study.
- Favourable results in this study could change the treatment guidelines for LVT with the inclusion of Apixaban in its therapeutic arsenal, which although it is much more convenient and possibly safer for the patient compared to the use of Acenocoumarol, would mean a doubling of annual costs according to the estimates of *Servei Català de Salut*. Fortunately, once generic DOACs become available, the expense of INR monitoring will be greatly reduced.
- As this is a multicentre study where the main dependent variable is measured by an operator-dependent technique (TTE), there will be inter- and intra-hospital variability intrinsic to the characteristics of our study. Otherwise, we consider that echocardiographic training together with teaching of data collection methods before starting the recruitment stage are procedures aimed to homogenise and standardise results. Furthermore, all echocardiographic findings will be assessed by two expert echocardiographers (or three if required), while a CRO project manager will be contracted in order to assist in inter-centre coordination and ensure the quality and validity of the study and statistical analysis. Moreover, in order to control for inter-hospital variability (possible information bias), the registry of the hospital which enrolled each patient in the study sample will be included as a covariate for the multivariate analysis, in addition to proportional admission of patients in the sample in every hospital, according to the reference patients for each centre.
- As this is a clinical trial with a non-probability sampling method, there is an intrinsic risk of selection bias that may provide us with a sample that is unrepresentative of the general population. However, by using a consecutive sampling method, we believe that we will be able to mitigate this bias.
- This is a clinical trial whose primary dependent variable is measured by an instrument other than the gold standard (DE-CMR), so we do not have perfect sensitivity in our study. However, detection of LVT with ultrasound contrast-enhanced

TTE with preliminary indications of LVT may considerably increase the sensitivity of the test performed simply with routine TTE without contrast, as in previous studies. Considering this good but not perfect sensitivity of the test, which is likewise an inclusion criterion, we have estimated a slightly longer recruitment time than initially calculated to ensure that we detect all patients who are likely to be included in our study.

- As in all prospective studies, there is always a risk of patient dropout. As in our study collection of variables will be performed at day 0, month 3 and month 6, we expect relatively low dropout rates. Therefore, the sample size calculation was performed assuming a withdrawal rate from the study.
- Although the clinical trial is designed to be double-blinded and double-simulated, it would be possible for the blinding to break due to variation in drug dosage and blood tests and drug handling frequency between both groups, as Acenocoumarol dosing and monitoring is highly fluctuating. Because of that, we will impair blood tests and drug handling frequency between patients in the Apixaban and Acenocoumarol group. Furthermore, the encapsulation of all administered tablets will make changes in the dose received imperceptible. While we are aware of the logistical complications that this method of study may entail, we believe it is necessary to provide high quality evidence while eliminating the biases associated with open-label trials.
- Additional time investment will be required for explaining the study, obtaining informed consent and data recording by research echocardiographers, as well as randomisation by statisticians, compared to standard clinical practice. Unfortunately, these are insurmountable elements in most clinical trials.

8. WORK PLAN AND CHRONOGRAM

8.1. RESEARCH TEAM

The research team will be composed of:

- The **principal investigator** and the **main research group** of this study will be cardiologist specialised in cardiac imaging techniques from the *Cardiac Imaging Unit* at the *Hospital Universitari Doctor Josep Trueta*. The principal investigator will be in charge of conducting the literature search, preparing the protocol, contracting the services of a qualified statistician, managing the online meetings and follow-ups and coordinating the project with the help of a *Contract Research Organization* (CRO) project manager, whose services had been previously contracted by he/she. Before the recruitment stage, the main research group will be in charge of giving an echocardiographic and data collection training course to all participating researchers. During the study, like the other investigators, they will be in charge of patient recruitment, and echocardiographic and complication monitoring for the next 6 months from the start of the intervention. The principal investigator group will also be blinded for the intervention groups. Finally, the principal investigator will be in charge of interpreting the results of the statistical analyses, writing the discussion and conclusion of the study, publishing the article in scientific journals and attending and presenting at Catalan, Spanish or European cardiology congresses, together with other selected investigator.
- **Investigators** from each participating hospital will be cardiologist specialised in cardiac imaging techniques from cardiology departments or cardiac imaging units. They will be responsible for internally selecting a coordinator, attending echocardiographic and data collection training, and conducting patient recruitment, and echocardiographic and complication follow-up for the next 6 months from the start of the intervention. All investigators will be blinded for the intervention groups. In addition, the coordinators of each participating centre will be responsible for maintaining communication with the principal investigator and the CRO project manager, attending the first face-to-face meeting, attending the three-monthly

online follow-ups during the study, and interpreting the results of the statistical analyses obtained together with the principal investigator and the CRO project manager.

- The **CRO project manager** will be in charge of contacting the CEIC and the Spanish Agency for Medicines and Health Products (*AEMPS: Agencia Española de Medicamentos y Productos Sanitarios*), contracting the civil liability insurance and facilitating communication between the participating hospitals, organising regular meetings and assisting in the coordination of the project, and ensuring the quality and validity of the study and the final statistical analysis.
- The **statistician**, blinded for the intervention groups, will be responsible for randomly assigning the intervention group of patients, patient matching and statistically analysing the data obtained in the study.

To carry out this clinical trial while maintaining the double-blind double-dummy, it will be necessary to count on the help of not blinded **cardiologists**, **haematologists**, **nurses**, **Pharmacy Service** of each hospital and **other health personnel** involved, who know the real intervention that must be performed on the patient in order to encapsulate and handle the appropriate drug, modify doses if required, carry out the corresponding blood tests or, if not, the simulations and placebo administrations necessary to avoid breaking the patient's blind.

8.2. STUDY STAGES

The clinical trial relevant to this protocol consists of a series of activities organised in the following phases:

STAGE 0: STUDY DESIGN (November 2022 - January 2023)

- ***1st step:*** In order to develop the protocol, the main investigator will first conduct a literature search on LVT, its diagnostic management and therapeutic recommendations.

- ***2nd step:*** Preparation of the protocol will be carried out with the detailed wording of objectives, hypotheses, variables and methodology. In order to ensure the quality of the study, optimise coordination and communication between the participating centres and professionals, manage patient information and the data obtained, the principal investigator will subcontract the services from a *Contract Research Organization* (CRO) company, which will assign a project manager to the study.

STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL (February 2023 - March 2023)

- ***3rd step:*** The protocol will be submitted to the CEIC of *HUDJT* in Girona for evaluation and approval. All suggestions will be taken into consideration and pertinently added to the final study protocol. The CRO project manager will be responsible for submitting the initial application to the ethics committee, as well as communicating with them and the *AEMPS*. Once we have the final protocol, the CRO project manager will send it to the departments and direction of the centres likely to participate in our study, with the aim of formalising the support and participation of these hospitals.
- ***4th step:*** The CRO project manager will also be responsible for contracting liability insurance.

STAGE 2: COORDINATION (March 2023 - April 2023)

- ***5th step:*** Once the participant centres of the study have been defined, the research group in each participating hospital will internally select a group coordinator responsible for communicating with other centres, the principal investigator and with the CRO project manager during the conduct of the study.
- ***6th step:*** The CRO project manager together with the principal investigator of the *HUDJT* will set up a first meeting in Girona between all the coordinators of each participating hospital. At this point, the tasks to be performed by each participating hospital will also be clearly defined, as well as all study due dates.
- ***7th step:*** In order to standardise and homogenise the results of the study, it will be necessary to carry out an echocardiography training in Girona, led by the *HUDJT* research echocardiographers, to define and practise the imaging planes necessary to assess the presence and size of the LVT. During the course, the procedure for data

collection and recording as well as the information that will be orally and in writing given to the patient will also be taught.

STAGE 3: DATA COLLECTION AND FOLLOW-UP (May 2023 - November 2025)

- ***8th step:*** Patients will be recruited using a consecutive method in each participating hospital. A pre-established proportional number of admissions per centre will be set. Only patients who meet the inclusion criteria, do not meet the exclusion criteria, and decide to participate and sign informed consent, will be included in the clinical trial sample. The duration of this step is estimated to be two years. They will be randomly assigned by a contracted blinded statistician, to either of the two intervention arms of the clinical trial.
- ***9th step:*** Once baseline echocardiogram is performed (assessed by two echocardiographers, three if needed), the intervention will start. As this is a double-blind, double-dummy study, patients will not know which intervention group they belong to. To achieve this masking (with the help of unblinded cardiologists, haematologists, nurses, hospital Pharmacy Service and other health personnel involved), it will be necessary to perform several simulated tests and administer different placebos, depending on the intervention group. Due to patient matching, patients from both groups will undergo the same number of tests and be administered the same number of drugs. Although covered more extensively in the variables section (***see 5.5.1 Independent variable***), patients assigned to the control group will receive anticoagulant treatment with Acenocoumarol for LVT resolution, while those assigned to the intervention of interest arm will receive Apixaban.
- ***10th step:*** Patients will be followed up at 3 and 6 months, where two blinded cardiologist specialised in cardiac imaging techniques will ultrasonographically visualise the presence and size of the LVT, if it still persists. At each visit, complications and re-hospitalisation time in the respective time periods will also be consulted and recorded together, in the database, with the echocardiographic findings. The duration of this step will be two years plus an additional follow-up period of six months for the last patients enrolled. The research group of each participant hospital will be the main responsible, working throughout the study according to *Good Clinical Practice* standards.

All processes included in this stage will be evaluated by the CRO project manager to ensure the quality of the study. During this stage, three-monthly online meetings led by the principal investigator and the CRO project manager will be held with the rest of the research group coordinators of each participating hospital, with the aim of facilitating communication between centres, assessing compliance with deadlines, notifying problems that have occurred during this time and being able to solve them as quickly as possible. At the end of the clinical trial, the CRO project manager will notify both the *CEIC* and the *AEMPS* of the end of the clinical trial.

STAGE 4: DATA ANALYSIS AND INTERPRETATION (December 2025 - February 2026)

- ***11th step:*** All data recorded in the database will be statistically analysed by a masked statistician for the intervention groups. In order to preserve patient confidentiality, each patient will be assigned a numerical code associated with their recorded data. The CRO project manager will also ensure the quality of this phase by carrying out several controls.
- ***12th step:*** The analysed data will then be interpreted by the principal investigator, CRO project manager and each research group coordinators of all participating hospitals, thus adding final sections of the study such as discussion and conclusion.

STAGE 5: PUBLICATION AND DISSEMINATION OF THE RESEARCH FINDINGS (March 2026 - June 2026)

- ***13th step:*** The findings of the study will be published, by the principal investigator, in various scientific journal articles and reports. In order to maximise the dissemination of the results obtained, they will be presented at national and international conferences and congresses of cardiology specialists.
- ***14th step:*** The final report will be presented to the *Societat Catalana de Cardiologia* (SCC), *Sociedad Española de Cardiología* (SEC) and to the *European Society of Cardiology* (ESC).

8.3. CHRONOGRAM

2022		2023										2024									2025									2026	
TASKS		N-D	J	F	M	A	M- 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	A	S-O	N	D	J-F	M-Jn
STAGE 0	Protocol elaboration																														
	CRO recruitment																														
STAGE 1	Presentation and approval from CEIC																														
	Liability insurance																														
STAGE 2	Coordinators' designation																														
	1st meeting																														
	Training of research groups																														
STAGE 3	Patient recruitment																														
	Baseline echocardiogram and data collection																														
	Intervention																														
	Follow-up visits and data collection																														
	Online follow-up meetings																														
	Quality controls																														
STAGE 4	Statistical analysis																														
	Data interpretation																														
	Quality controls																														
STAGE 5	Publication and dissemination																														

Table 6. ***Chronogram.*** Own creation.

9. BUDGET

The budget for this study consists of different sections:

- **Services expenses:** During the first stage of the study, a CRO company will be contacted to contract the services of a project manager, for 40.000€, to carry out the communication with the *CEIC* and the *AEMPS*, to assist in the coordination of the study among different participating centres and to perform various quality and validity controls of the clinical trial and statistical analysis. Later on, the services of a statistician will be contracted to randomise the patients participating in the study, to patient matching and to perform the statistical analysis of the data collected, being masked for the intervention groups. With an estimated workload of 200 hours (30€/h), he/she would be hired for 6.000€. As the echocardiographers who will perform the echocardiographic imaging will be part of the research team, they cannot charge a fee in order to avoid any conflict of interest.
- **Journey expenses:** A first meeting will be held at the *Hospital Universitari Doctor Josep Trueta* in Girona and will be attended by the coordinating investigators from each participating hospital, followed by an echocardiography course at the same hospital attended by all the investigators participating in this study. Travel expenses are estimated at 350€ for the first meeting and 1000€ for the echocardiographic training. The three-monthly meetings will be held online, so no extra costs will be incurred.
- **Insurance:** If the *CEIC* considers our study to be an invasive clinical trial, liability insurance will be contracted to cover potential harms and adverse events attributable to the intervention due to participation in the trial. We estimate a cost of approximately 80.000€.
- **Execution expenses:** In order to carry out the study, simulated tests or placebos and drugs that are not included in standard clinical practice must be paid for. For example, the double daily administration of encapsulated (0,02€ each capsule) Apixaban (Eliquis®: 1,51€ each dose) and the subcutaneous injection of 0.9% saline (approximately 0,01€ per administration) as placebo "Enoxaparin" for the Apixaban intervention group are additional costs that must be included in the budget.

Likewise, although the administration of Acenocoumarol (Sintrom®) is covered by the *National Health System*, its encapsulation (0,02€ each capsule), as well as the placebo tablet (0,07€ each dose) encapsulation (0,02€ each capsule) to maintain masking on patients, will also must be paid for. Medicines costs have been calculated on the basis of the prices offered by the *Servei Català de Salut* and the hospital *Pharmacy Service*. As usual, the composition of the placebo tablets consists of microcrystalline cellulose and sugar alcohol. However, as all other interventions are already included in standard clinical practice to treat LVT (hepatic and renal profile by blood tests on hospital admission, echocardiographic diagnosis and monitoring, administration of Enoxaparin/Clexane® or Heparin as *bridging* therapy, daily Acenocoumarol/Sintrom® administration and regular blood tests to assess INR), they do not involve additional costs. Finally, other expenses as office consumables must be included in the budget. We estimate a total cost of 17,27€ in printouts (0,0109€ per black and white print) of *information form* (5 pages) and *informed consent* (1 page) to be signed by every patient in order to participate in our study.

- **Publication and dissemination:** The results of this research will be published in international medical journals with high impact factor at an estimated cost of 2.000€, including both translations and revisions of the text. In order to disseminate the results, 2 study investigators will be in charge of attending and presenting at congresses organised by the *Societat Catalana de Cardiologia* (SCC), *Sociedad Española de Cardiología* (SEC) and *European Society of Cardiology* (ESC), with an estimated total cost of 6.000€, including registration fees, travel costs, accommodation and diets.

The total cost of the project amounts to **210.733,99€**

In order to finance this clinical trial, grants will be requested from the *Ministerio de Ciencia e Innovación del Gobierno de España*, *Societat Catalana de Cardiologia* (SCC), *Sociedad Española de Cardiología* (SEC) and *European Society of Cardiology* (ESC).

	Unit cost	*Amount*	*Subtotal*
Services expenses: 46.000€			
CRO project manager	40.000€	1	40.000€
Statistician	30€/h	200 hours	6.000€
Journey expenses: 1.350€			
First meeting	350€	1 meeting	350€
Echocardiography training	1000€	1 training	1000€
Insurance: 80.000€			
Liability insurance	80.000€	1	80.000€
Execution expenses: 75.383,99€			
Apixaban (Eliquis® 5 mg or 2,5 mg)	1'51€	2 intakes x 132 patients x 180 days = 47.520	71.755,2€
Placebo "Enoxaparin" (0,9% saline solution)	0,01€	2 intakes x 132 patients x 4 days = 1056	10,56€
Placebo tablets	0,07€	1 intake x 132 patients x 184 days = 24.288	1.700,16€
Capsules	0,02€	2 intakes x 264 patients x 180 days = 95.040	1.900,8€
Photocopies	0,0109€	6 paper sheets x 264 patients = 1.584	17,27€
Publication and dissemination: 8.000€			
English correction	500€	1	500€
Publication costs	1.500€	1	1.500€
Congress costs	3.000€	2 researchers	6.000€
		TOTAL	**210.733,99€**

Table 7. ***Budget summary.*** Own creation.

10. FEASIBILITY AND PROJECT IMPACT

10.1. FEASIBILITY

We consider our protocol to be a feasible multicentric clinical trial. By making an inference on the annual incidence of AMI in Catalonia, its complication in LVT rates in the pPCI era, the annual incidences of LVT in some of the reference hospitals and the reference population for each centre, we have estimated a recruitment time of approximately 1,5 years. As we are aware that we do not use the gold standard imaging technique for LVT patients to be included in our study, but with a very sensitive but not perfect test, we have considered preliminarily lengthening the recruitment time to 2 years. If it is not possible to reach the required sample size (264 patients) in the estimated time, we could extend the recruitment time to complete it.

The fact of holding three-monthly online meetings between the coordinators of each participant hospital facilitates communication between centres and the resolution of study problems, as well as a possible readjustment of the chronogram if it is not possible to reach the objectives set during the initially estimated deadlines. Importantly, the CRO project manager that we will contract, will help us with administrative, coordination, quality and validity issues.

Furthermore, we consider it feasible to carry out a clinical trial of these characteristics in hospitals from Catalonia because they already have both echocardiographic equipment and cardiologist specialised in cardiac imaging techniques in each centre. As a matter of fact, *Hospital Universitari Doctor Josep Trueta* team of echocardiographers already give numerous echocardiography courses in Girona throughout the year to all audiences, so offering echocardiography training to the study researchers before recruitment seems feasible. Although we are aware of the difficulty of coordinating a multicentre study, the fact that the cardiology department of *Hospital Universitari Doctor Josep Trueta* is currently leading 11 studies in collaboration with other hospitals and health centres, gives them the necessary experience and leadership to make this project feasible. Moreover, the good relationship

that exists between the *Hospital Universitari Doctor Josep Trueta* and the *Societat Catalana de Cardiologia* is outstanding, as they share numerous professionals from the Girona healthcare field and the *HUDJT* has hosted several talks and conferences, so we can ensure a collaborative and supportive framework between the two entities.

This clinical trial is also feasible because it has many diagnostic tests, drug administratión and monitoring within routine clinical practice, so most of the procedures in the study are already covered by the National *Health System*.

10.1. PROJECT IMPACT

LVT is a relatively prevalent complication of AMI - with an estimated annual incidence of 200 people in Catalonia - which also presents considerable life-threatening complications. Nowadays, surprisingly enough given its remarkable morbidity and mortality, there are still many gaps in research regarding the best anticoagulation regimen.

Although standard treatment of LVT is carried out with the administration of VKAs, such as Acenocoumarol in Spain, their use in this indication currently has low levels of evidence and low levels of recommendation worldwide. In addition, the introduction of DOACs in recent years has proven to be a more convenient alternative for the patient (no dose variation, high on-off activity, no monitoring or dietary interactions), equally effective and safer in some clinical settings in which they are approved, especially Apixaban.

Therefore, retrospective studies have been conducted over the last decade to study their potential indication in the context of LVT, but only a few small clinical trials have been conducted in recent years. Importantly, European and American guidelines, as well as numerous authors, call for further research in this regard so that DOACs can have a defined role in the therapeutic arsenal of LVT, especially in consideration of the increasing number of prescriptions of DOACs in off-label indications.

Thus, this protocol proposes the conduct of a multicentre randomised double-blind double-dummy clinical trial with sufficient statistical power to demonstrate the non-inferiority efficacy of Apixaban compared to Acenocoumarol in the resolution of LVT. This study, in addition to comparing both safety profiles, may assist in identifying those characteristics which may play a role in thrombus persistence. However, although this clinical trial is not specifically designed to answer other questions about LVT treatment (optimal target and INR range in Acenocoumarol treatment, duration of triple therapy or indicated therapeutic approach in patients with LV aneurysm), its results may shed some light and guide future lines of research in these regards.

We believe that the results of this research will help to provide quality evidence and, if the hypothesis is confirmed, will possibly be taken into account in future modifications of European and American guidelines. With the inclusion of DOACs such as Apixaban within the indications for LVT, there would be a notable improvement in quality of life and possible safety of patients during treatment, as well as an increase in the confidence of physicians when prescribing it.

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12. ANNEXES

12.1 ANNEX 1: CLASSES OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

CLASSES OF RECOMMENDATIONS	DEFINITION	SUGGESTED WORDING TO USE
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	**Data derived from multiple randomised clinical trials or meta-analyses.**
Level of evidence B	**Data derived from a single randomised clinical trial or large non-randomised studies.**
Level of evidence C	**Consensus of opinion of the experts and/or small studies, retrospective studies, registries.**

Table 8. ***Classes of recommendations and levels of evidence.*** Adapted from (1).

12.2 ANNEX 2: INFORMATION FORM

SPANISH VERSION

HOJA DE INFORMACIÓN AL PACIENTE

Nombre del estudio: Eficacia y seguridad del Apixaban como tratamiento para la trombosis ventricular izquierda después del infarto miocárdico con elevación del segmento ST: un ensayo clínico multicéntrico, randomizado a doble ciego y doble simulación.

Centro asistencial:

Investigador principal:

Bienvenido/a:

Nos dirigimos a usted para proponerle participar en un estudio de investigación llevado a cabo por los servicios de cardiología y unidades de imagen cardíaca de varios hospitales en Cataluña. Este estudio ha sido aprobado por el *Comité de Ética e Investigación Clínica* del *Hospital Universitario Doctor Josep Trueta* y por la *Agencia Española del Medicamento y Productos Sanitarios*, de acuerdo a la legislación vigente, Ley 14/2007 de 3 de julio, de Investigación biomédica.

Nuestra intención con este documento es que usted conozca y entienda el motivo por el que se realiza este estudio, para que así pueda evaluar correctamente su participación en él o no. Para ello, le rogamos lea esta hoja informativa con atención y consulte cualquier duda que le surja y nosotros se la aclararemos, poniendo a su disposición toda la información necesaria. Además, puede consultar con las personas que considere oportunas.

Tómese el tiempo que necesite, no es necesario que nos comunique su decisión el mismo día.

PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es completamente voluntaria, puede decidir no participar en él y puede cambiar su decisión y retirar su consentimiento en cualquier momento, sin que aquello suponga ningún cambio en su relación con el facultativo que le atienda, ni perjuicio en el tratamiento prescrito.

DESCRIPCIÓN DEL ESTUDIO Y OBJETIVOS

La trombosis ventricular izquierda es una complicación del infarto cardíaco debido a una disfunción de la capacidad del ventrículo izquierdo para bombear la sangre correctamente, en un ambiente que favorece la inflamación y la coagulación. Su identificación y tratamiento precoces son esenciales para su adecuado manejo, ya que este trombo alojado en el ventrículo izquierdo del corazón puede viajar a cualquier parte del cuerpo e incluso llegar al cerebro, donde puede obstruir alguna arteria que le lleve sangre y producirle un ictus o derrame cerebral.

Actualmente, lo que aconsejan las guías médicas es tratar a estos pacientes con terapia anticoagulante oral con Warfarina (cuyo nombre comercial es Aldocumar®) o, más conocido en España, con Acenocumarol (Sintrom®) durante 6 meses. Es por muchos sabido que estos fármacos son algo molestos para los pacientes, ya que presentan interacciones con muchos alimentos y otros fármacos, además de requerir de análisis de sangre periódicos para controlar el INR. Además, el grado de recomendación y nivel de evidencia en esta indicación es relativamente baja por lo que, si bien es la mejor opción conocida hasta la fecha para tratar la trombosis ventricular izquierda, queda mucha investigación pendiente para determinar el mejor régimen de anticoagulación.

Sin embargo, durante los últimos años han salido al mercado unos *nuevos anticoagulantes orales*, que han sustituido el uso de Sintrom® en algunas enfermedades, ya que han demostrado ser igual de efectivos para tratar dichas patologías, además de ser más seguros en algunos casos y mucho más cómodos de usar para el paciente, ya que no presentan interacciones alimentarias ni requieren de monitorización del INR.

De entre todos estos *nuevos anticoagulantes orales*, nosotros destacamos el Apixaban (Eliquis®), ya que es el más estudiado para tratar el trombo intraventricular, el más seguro en otras de sus indicaciones y el que ha ofrecido mayor satisfacción global a sus pacientes.

Por ello, el objetivo de nuestro ensayo clínico es comparar el tratamiento de la trombosis ventricular izquierda con Acenocumarol (Sintrom®) respecto al Apixaban (Eliquis®) para poder valorar su eficacia en la resolución del trombo, así como su seguridad. Como resultado de este estudio, dispondremos de mayor evidencia y fuerza de recomendación para incluir este fármaco en la práctica clínica habitual o no.

METODOLOGÍA E INTERVENCIÓN

En este estudio participarán un total de 264 pacientes. Como es habitual en este tipo de estudio, cada uno de ellos será distribuido aleatoriamente a uno de los dos grupos de intervención, estando conformados ambos por el mismo número de pacientes (grupo A y B):

- Los pacientes del grupo A serán tratados con Acenocumarol (Sintrom®) durante 6 meses, siendo este el tratamiento estándar, y funcionando en nuestro estudio a modo de *grupo control*.
- Los pacientes del grupo A serán tratados con Apixaban (Eliquis®) durante 6 meses.

Es importante destacar que los pacientes que participen NO sabrán qué fármaco han recibido hasta el final del estudio, así como los ecocardiografistas; aunque los cardiólogos, hematólogos y enfermeras que les atiendan, sí. Este tipo de estudio, llamado doble ciego, nos obliga a realizar una doble simulación, donde los pacientes recibirán el mismo número de fármacos y el mismo número de analíticas sanguíneas en ambos grupos. Esto se hace con la intención de reducir los sesgos del estudio y así obtener unos resultados más *fiables*. Con tal fin, deberán acudir periódicamente al hospital participante con el objetivo de realizarles analíticas sanguíneas y posibles ajustes en las dosis recibidas.

Si usted ha sido asignado/a al grupo A tomará, sin saber su contenido, una dosis diaria de Acenocumarol (Sintrom®), junto con otra dosis de un comprimido placebo, ambas encapsuladas y espaciadas entre sí aproximadamente 12 horas. Además, recibirá inicialmente inyecciones subcutáneas con Enoxaparina (Clexane®) durante 4-5 días para

inducir a la anticoagulación, junto con analíticas sanguíneas periódicas para valorar el INR, generalmente mensuales, aunque puedan hacerse más frecuentemente en algunos casos. Es posible que el facultativo que le controle la anticoagulación le modifique las dosis, aunque al estar encapsuladas no lo percibirá.

Si usted ha sido asignado/a al grupo B tomará, sin saber su contenido, dos dosis diarias de Apixaban (Eliquis®), ambas encapsuladas y espaciadas entre sí aproximadamente 12 horas. Además, recibirá inicialmente inyecciones subcutáneas con placebo (suero fisiológico) durante 4-5 días, junto con analíticas sanguíneas periódicas para no romper el ciego, generalmente mensuales, aunque puedan hacerse más frecuentemente en algunos casos. Es posible que el facultativo que le controle la anticoagulación le modifique las dosis, aunque al estar encapsuladas no lo percibirá.

Al inicio del tratamiento se le tomará una ecocardiografía basal con contraste (se elimina con la respiración), que se le repetirá durante el seguimiento que usted lleve a los 3 y 6 meses, donde también nos comunicará las complicaciones y molestias que haya presentado durante ese tiempo.

DURACIÓN DEL ESTUDIO

La duración de su participación en el estudio será de 6 meses. Esperamos tener los resultados del ensayo clínico, ya analizados y listos para ser publicados, en 2026.

BENEFICIOS Y RIESGOS

Es importante que evalúe las ventajas y desventajas de participar en este estudio antes de que usted decida inscribirse.

Aunque el Apixaban (Eliquis®) no esté indicado actualmente en el tratamiento del trombo intraventricular, se han realizado multitud de estudios retrospectivos durante los últimos años sobre su utilización fuera de ficha, pero escasos estudios prospectivos, como supone este mismo ensayo clínico. Cabe destacar que las conclusiones que podemos extraer de la evidencia disponible actualmente es que podemos considerar al Apixaban (Eliquis®) como una alternativa de eficacia y seguridad *a priori* comparables al Acenocumarol (Sintrom®); sin

embargo, se requieren de grandes ensayos clínicos que aporten mayor evidencia para ser incluidos en las guías de práctica clínica con total seguridad en este contexto clínico.

Por todo ello, no esperamos un riesgo de daño mayor que el inherente a la terapia anticoagulante, como es el frecuente riesgo hemorrágico menor, con complicaciones como la anemia o la hipotensión, las náuseas o malestar general y la elevación de las enzimas hepáticas. En ambos casos pueden aparecer complicaciones más graves como las hemorragias mayores, pero son menos frecuentes.

ALTERNATIVAS AL PROCEDIMIENTO

Si usted decide finalmente no participar en este ensayo clínico, se le administrará el tratamiento estándar para la trombosis ventricular izquierda, que consiste en una dosis diaria de Acenocumarol (Sintrom®) durante 6 meses, simultáneamente a la administración subcutánea de Enoxaparina (Clexane®) durante los primeros 4 o 5 días, y una monitorización periódica del INR mediante analíticas sanguíneas. A su vez, se mantendrá el mismo seguimiento ecocardiográfico de forma basal, y a los 3 y 6 meses.

CONFIDENCIALIDAD

Solicitamos su permiso para utilizar los datos de carácter personal obtenidos únicamente para la realización de este estudio con fines de investigación, de forma totalmente confidencial y sin acceso a estos por parte de terceros, almacenados en una base de datos computarizada y anonimizada para su análisis estadístico de acuerdo a la legalidad vigente (Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales). Los datos recogidos en el estudio serán identificados mediante un código numérico, evitando así cualquier elemento que pueda revelar la identidad del paciente. El acceso a esta información sólo estará disponible para investigadores de este estudio y otras autoridades sanitarias, si así lo solicitan. En caso de aceptar participar en el estudio, puede consultar, corregir o eliminar sus datos en cualquier momento, simplemente ha de solicitarlo a los investigadores. De acuerdo a la legislación vigente sobre protección de datos, Reglamento General de Protección de Datos (Reglamento 2016/679 del Parlamento Europeo y del Consejo de 27 de abril de 2016), le garantizamos que ninguna información personal será revelada, ni su identidad aparecerá en ninguna publicación de los resultados

del estudio.

Le informamos que estamos obligados a conservar sus datos durante al menos 5 años después de la finalización del estudio. Una vez superado ese período, sólo serán conservados por el centro y el investigador principal, con fines sanitarios y de investigación, respectivamente, si se hubiera otorgado el debido consentimiento. Tanto el hospital como el investigador principal son responsables del tratamiento de sus datos y se comprometen a cumplir con la normativa vigente de protección de datos, respecto al marco jurídico en España y en la Unión Europea.

DIFUSIÓN DE RESULTADOS

Una vez finalizado el estudio y analizado los datos obtenidos, pretendemos difundir los resultados a través de publicaciones en revistas científicas y/o congresos nacionales e internacionales. Reiteramos que los resultados se publicarán de forma global y nunca de forma individualizada, por lo que será imposible la identificación de los pacientes.

COMPENSACIÓN ECONÓMICA

La participación en el estudio no conlleva ningún tipo de compensación económica, por lo que ni usted ni ninguno/a de los/as participantes obtendrán beneficio monetario alguno, aunque tampoco costes añadidos. Los investigadores de este estudio tampoco obtienen beneficio económico.

RESPONSABILIDAD Y SEGURO

Los promotores de este estudio tienen contratada una póliza de seguro para su realización, acorde a la legislación vigente. En caso de perjuicio o detrimento de su salud a causa de la participación en el presente ensayo clínico, se le abonará la correspondiente indemnización.

CONTACTO

Le recordamos que nos puede consultar cualquier duda que tenga en este momento. Si le surgen más dudas, ya bien sea durante el estudio o después de la realización del mismo, podrá consultarlas poniéndose en contacto con:_____.

CATALAN VERSION

FULLA D'INFORMACIÓ AL PACIENT

Nom de l'estudi: Eficàcia i seguretat de l'Apixaban com a tractament per a la trombosi ventricular esquerra després de l'infart miocàrdic amb elevació del segment ST: un assaig clínic multicèntric, randomitzat a doble cec i doble simulació.

Centre assistencial:

Investigador principal:

Benvingut/da:

Ens dirigim a vostè per proposar-vos participar en un estudi de recerca dut a terme pels serveis de cardiologia i unitats d'imatge cardíaca de diversos hospitals a Catalunya. Aquest estudi l'han aprovat el *Comitè d'Ètica i Investigació Clínica* de l'*Hospital Universitari Doctor Josep Trueta* i l'*Agencia Española del Medicamento y Productos Sanitarios*, d'acord amb la legislació vigent, Llei 14/2007 de 3 de juliol, de recerca biomèdica.

La nostra intenció amb aquest document és que vostè conegui i entengui el motiu pel qual es realitza aquest estudi, perquè així pugui avaluar correctament la seva participació o no. Per això, us preguem llegiu aquest full informatiu amb atenció i consulteu qualsevol dubte que us sorgeixi i nosaltres us l'aclarirem, posant a la vostra disposició tota la informació necessària. A més, podeu consultar amb les persones que considereu oportunes.

Preneu-vos el temps que necessiteu, no cal que ens comuniqueu la vostra decisió el mateix dia.

PARTICIPACIÓ VOLUNTÀRIA

Ha de saber que la seva participació en aquest estudi és completament voluntària, pot decidir no participar-hi i pot canviar la seva decisió i retirar-ne el consentiment en qualsevol moment, sense que això suposi cap canvi en la seva relació amb el facultatiu que l'atengui, ni perjudici en el tractament prescrit.

DESCRIPCIÓ DE L'ESTUDI I OBJECTIUS

La trombosi ventricular esquerra és una complicació de l'infart cardíac degut a una disfunció de la capacitat del ventricle esquerre per bombejar la sang correctament, en un ambient que afavoreix la inflamació i la coagulació. La seva identificació i tractament precoços són essencials per al seu adequat maneig, ja que aquest trombe allotjat al ventricle esquerre del cor pot viatjar a qualsevol part del cos i fins i tot arribar al cervell, on pot obstruir alguna artèria que li porti sang i produir-li un ictus o vessament cerebral.

Actualment, el que aconsellen les guies mèdiques és tractar aquests pacients amb teràpia anticoagulant oral amb Warfarina (el nom comercial del qual és Aldocumar®) o, més conegut a Espanya, amb Acenocumarol (Sintrom®) durant 6 mesos. És per molts sabut que aquests fàrmacs són una mica molestos per als pacients, ja que presenten interaccions amb molts aliments i altres fàrmacs, a més de requerir anàlisis de sang periòdiques per controlar l'INR. A més, el grau de recomanació i nivell d'evidència en aquesta indicació és relativament baixa, per la qual cosa, si bé és la millor opció coneguda fins ara per tractar la trombosi ventricular esquerra, queda molta investigació pendent per determinar el millor règim d'anticoagulació.

Tot i això, durant els darrers anys han sortit al mercat uns nous anticoagulants orals, que han substituït l'ús de Sintrom® en algunes malalties, ja que han demostrat ser igual d'efectius per tractar aquestes patologies, a més de ser més segurs en alguns casos i molt més còmodes d'utilitzar per al pacient, ja que no presenten interaccions alimentàries ni requereixen de monitorització de l'INR.

D'entre tots aquests nous anticoagulants orals, nosaltres destaquem l'Apixaban (Eliquis®), ja que és el més estudiat per tractar el trombe intraventricular, el més segur en altres

indicacions i el que ha ofert més satisfacció global als seus pacients.

Per això, l'objectiu del nostre assaig clínic és comparar el tractament de la trombosi ventricular esquerra amb Acenocumarol (Sintrom®) respecte a l'Apixaban (Eliquis®) per poder valorar-ne l'eficàcia en la resolució del trombo, així com la seva seguretat. Com a resultat d'aquest estudi, disposarem de més evidència i força de recomanació per incloure aquest fàrmac a la pràctica clínica habitual o no.

METODOLOGIA I INTERVENCIÓ

En aquest estudi hi participaran un total de 264 pacients. Com és habitual en aquest tipus d'estudi, cada un serà distribuït aleatòriament a un dels dos grups d'intervenció, tots dos estan conformats pel mateix nombre de pacients (grup A i B):

- Els pacients del grup A seran tractats amb Acenocumarol (Sintrom®) durant 6 mesos, sent aquest el tractament estàndard, i funcionant al nostre estudi a manera de *grup control*.
- Els pacients del grup A seran tractats amb Apixaban (Eliquis®) durant 6 mesos.

És important destacar que els pacients que hi participin NO sabran quin fàrmac han rebut fins al final de l'estudi, així com els ecocardiografistes; encara que els cardiòlegs, hematòlegs i infermeres que els atenguin, sí. Aquest tipus d'estudi, anomenat doble cec, ens obliga a fer una doble simulació, on els pacients rebran el mateix nombre de fàrmacs i el mateix nombre d'analítiques sanguínies en tots dos grups. Això es fa amb la intenció de reduir els biaixos de l'estudi i així obtenir uns resultats més *fiables*. Amb aquesta finalitat, hauran d'anar periòdicament a l'hospital participant amb l'objectiu de fer-los analítiques sanguínies i possibles ajustaments a les dosis rebudes.

Si vostè ha estat assignat al grup A prendrà, sense saber-ne el contingut, una dosi diària d'Acenocumarol (Sintrom®), juntament amb una altra dosi d'un comprimit placebo, ambdues encapsulades i espaiades entre si aproximadament 12 hores. A més, inicialment rebrà injeccions subcutànies amb Enoxaparina (Clexane®) durant 4-5 dies per induir a l'anticoagulació, juntament amb analítiques sanguínies periòdiques per valorar l'INR, generalment mensuals, encara que es puguin fer més freqüentment en alguns casos. És

possible que el facultatiu que controli l'anticoagulació li modifiqui les dosis, encara que en estar encapsulades no ho percebrà.

Si vostè ha estat assignat/da al grup B prendrà, sense saber-ne el contingut, dues dosis diàries d'Apixaban (Eliquis®), ambdues encapsulades i espaiades entre si aproximadament 12 hores. A més, rebrà inicialment injeccions subcutànies amb placebo (sèrum fisiològic) durant 4-5 dies, juntament amb analítiques sanguínies periòdiques per no trencar el cec, generalment mensuals, encara que es puguin fer més freqüentment en alguns casos. És possible que el facultatiu que controli l'anticoagulació li modifiqui les dosis, encara que en estar encapsulades no ho percebrà.

A l'inici del tractament se li prendrà una ecocardiografia basal amb contrast ecocardiogràfic (s'elimina amb la respiració), que se li repetirà durant el seguiment que porteu als 3 i 6 mesos, on també ens comunicarà les complicacions i molèsties que hagi presentat durant aquest temps.

DURADA DE L'ESTUDI

La durada de la seva participació a l'estudi serà de 6 mesos. Esperem tenir els resultats de l'assaig clínic, ja analitzats i llestos per ser publicats, el 2026.

BENEFICIS I RISCOS

És important que avalueu els avantatges i desavantatges de participar en aquest estudi abans que decidiu inscriure's.

Encara que l'Apixaban (Eliquis®) no estigui indicat actualment en el tractament del trombe intraventricular, s'han realitzat multitud d'estudis retrospectius durant els darrers anys sobre la seva utilització fora de fitxa, però escassos estudis prospectius, com suposa aquest mateix assaig clínic. Cal destacar que les conclusions que podem extreure de l'evidència disponible actualment és que podem considerar l'Apixaban (Eliquis®) com una alternativa d'eficàcia i seguretat *a priori* comparables a l'Acenocumarol (Sintrom®); no obstant això, es requereixen grans assaigs clínics que aportin més evidència per ser inclosos a les guies de pràctica clínica amb total seguretat en aquest context clínic.

Per tot això, no esperem un risc de dany més gran que l'inherent a la teràpia anticoagulant, com és el freqüent risc hemorràgic menor, amb complicacions com l'anèmia o la hipotensió, les nàusees o el malestar general i l'elevació dels enzims hepàtics. En tots dos casos poden aparèixer complicacions més greus com les hemorràgies més grans, però són menys freqüents.

ALTERNATIVES AL PROCEDIMENT

Si decidiu finalment no participar en aquest assaig clínic, se us administrarà el tractament estàndard per a la trombosi ventricular esquerra, que consisteix en una dosi diària d'Acenocumarol (Sintrom®) durant 6 mesos, simultàniament a l'administració subcutània d'Enoxaparina (Clexane®) durant els primers 4 o 5 dies, i un monitoratge periòdic de l'INR mitjançant analítiques sanguínies. Alhora, es mantindrà el mateix seguiment ecocardiogràfic de forma basal, i als 3 i 6 mesos.

CONFIDENCIALITAT

Sol·licitem el vostre permís per utilitzar les dades de caràcter personal obtingudes únicament per a la realització d'aquest estudi amb finalitats de recerca, de forma totalment confidencial i sense accés a aquests per part de tercers, emmagatzemats en una base de dades computaritzada i anonimitzada per a la seva anàlisi estadística d'acord amb la legalitat vigent (Llei Orgànica 3/2018, del 5 de desembre, de Protecció de Dades Personals i Garantia dels drets digitals). Les dades recollides a l'estudi seran identificades mitjançant un codi numèric, evitant així qualsevol element que pugui revelar la identitat del pacient. L'accés a aquesta informació només estarà disponible per a investigadors d'aquest estudi i altres autoritats sanitàries, si ho sol·liciten. En cas d'acceptar participar a l'estudi, podeu consultar, corregir o eliminar les vostres dades en qualsevol moment, simplement heu de sol·licitar-ho als investigadors. D'acord amb la legislació vigent sobre protecció de dades, Reglament General de Protecció de Dades (Reglament 2016/679 del Parlament Europeu i del Consell de 27 d'abril de 2016), us garantim que cap informació personal serà revelada, ni la vostra identitat apareixerà a cap publicació dels resultats de l'estudi.

Us informem que estem obligats a conservar les vostres dades durant almenys 5 anys

després de la finalització de l'estudi. Una vegada superat aquest període, només seran conservats pel centre i l'investigador principal, amb fins sanitaris i de recerca, respectivament, si s'ha atorgat el consentiment degut. Tant l'hospital com l'investigador principal són responsables del tractament de les vostres dades i es comprometen a complir amb la normativa vigent de protecció de dades, respecte al marc jurídic a Espanya ia la Unió Europea.

DIFUSIÓ DE RESULTATS

Un cop finalitzat l'estudi i analitzat les dades obtingudes, pretenem difondre els resultats a través de publicacions a revistes científiques i/o congressos nacionals i internacionals. Reiterem que els resultats es publicaran de forma global i mai de forma individualitzada, per la qual cosa serà impossible la identificació dels pacients.

COMPENSACIÓ ECONÒMICA

La participació en l'estudi no comporta cap tipus de compensació econòmica, per la qual cosa ni vostè ni cap dels participants obtindran cap benefici monetari, encara que tampoc no hi ha costos afegits. Els investigadors d'aquest estudi tampoc no obtenen benefici econòmic.

RESPONSABILITAT I SEGUR

Els promotors d'aquest estudi tenen contractada una pòlissa d'assegurança per a la seva realització, dacord amb la legislació vigent. En cas de perjudici o detriment de la seva salut a causa de la participació en aquest assaig clínic, se li abonarà la corresponent indemnització.

CONTACTE

Us recordem que ens podeu consultar qualsevol dubte que tingueu en aquest moment. Si us sorgeixen més dubtes, ja sigui durant l'estudi o després de la realització del mateix, podreu consultar-los posant-vos en contacte amb:_____.

12.3 ANNEX 3: INFORMED CONSENT FORM

SPANISH VERSION

CONSENTIMIENTO INFORMADO

Yo,_____, con documento de identificación personal (DNI/NIE)_____, declaro que:

- He recibido una copia de la hoja de información para el paciente.
- He leído y entendido toda la información que aparece en la hoja de información para el paciente.
- He podido exponer cualquier duda que me haya surgido, y se me ha resuelto satisfactoriamente.
- Estoy de acuerdo con la cantidad de información que se me ha proporcionado.
- Comprendo que mi participación es voluntaria y no remunerada.
- Entiendo los potenciales riesgos y beneficios derivados de participar en este estudio.
- Comprendo que mis datos y pruebas serán confidenciales.

Además, comprendo que aún habiendo firmado el consentimiento informado, puedo revocarlo en cualquier momento y que esto no supondrá un perjuicio en mi tratamiento ni en mi asistencia sanitaria.

En consecuencia,

- Doy libremente mi conformidad a participar en el estudio "*Eficacia y seguridad del Apixaban como tratamiento para la trombosis ventricular izquierda después del infarto miocárdico con elevación del segmento ST: un ensayo clínico multicéntrico, randomizado a doble ciego y doble simulación"*.
- Acepto que los investigadores del proyecto puedan ponerse en contacto conmigo en un futuro si se considera oportuno.
- Acepto la obtención de datos de la historia clínica.

☐ SÍ ☐ NO

Firma del paciente **Firma del investigador**

Lugar y fecha: _____, _____ de _____ del año _____.

CATALAN VERSION

CONSENTIMENT INFORMAT

Jo,_____, amb document d'identificació personal (DNI/NIE)_____,declaro que:

- He rebut una còpia del full d'informació per al pacient.
- He llegit i entès tota la informació que apareix al full d'informació per al pacient.
- He pogut exposar qualsevol dubte que m'hagi sorgit i se m'ha resolt satisfactòriament.
- Estic d'acord amb la quantitat d'informació que he proporcionat.
- Comprenc que la meva participació és voluntària i no remunerada.
- Entenc els potencials riscos i beneficis derivats de participar en aquest estudi.
- Comprenc que les meves dades i proves seran confidencials.

A més, comprenc que tot i haver signat el consentiment informat, el puc revocar en qualsevol moment i que això no suposarà un perjudici en el meu tractament ni en la meva assistència sanitària.

En conseqüència,

- Dono lliurement la meva conformitat a participar a l'estudi "*Eficàcia i seguretat de l'Apixaban com a tractament per a la trombosi ventricular esquerra després de l'infart miocàrdic amb elevació del segment ST: un assaig clínic multicèntric, randomitzat a doble cec i doble simulació"*.
- Accepto que els investigadors del projecte es puguin posar en contacte amb mi en un futur si es considera oportú.
- Accepto obtenir dades de la història clínica.

☐ SÍ ☐ NO

Signatura del pacient **Signatura de l'investigador**

Lloc i data: _____, _____ de/d' _____ de l'any _____.

12.4 ANNEX 4: INFORMED CONSENT REVOCATION FORM

SPANISH VERSION

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo,_____, con documento de identificación personal (DNI/NIE)_____, revoco el consentimiento previamente firmado para la participación en el ensayo clínico: "*Eficacia y seguridad del Apixaban como tratamiento para la trombosis ventricular izquierda después del infarto miocárdico con elevación del segmento ST: un ensayo clínico multicéntrico, randomizado a doble ciego y doble simulación"*.

Firma del paciente **Firma del investigador**

Lugar y fecha: _____, _____ de _____ del año _____.

CATALAN VERSION

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo,_____, amb document d'identificació personal (DNI/NIE)_____, revoco el consentiment prèviament signat per a la participació a l'assaig clínic: "*Eficàcia i seguretat de l'Apixaban com a tractament per a la trombosi ventricular esquerra després de l'infart miocàrdic amb elevació del segment ST: un assaig clínic multicèntric, randomitzat a doble cec i doble simulació"*.

Signatura del pacient **Signatura de l'investigador**

Lloc i data: _____, _____ de/d' _____ de l'any _____.

12.5 ANNEX 5: COMPOSITION AND CONTRAINDICATIONS TO STUDY DRUGS

		EXCIPIENTS
ACENOCOUMAROL		*Lactose monohydrate* *Colloidal anhydrous silica* *Corn starch* *Talc* *Magnesium stearate* *Hypromellose*
APIXABAN	Tablet core	*Lactose* *Microcrystalline cellulose (E460)* *Croscarmellose sodium* *Sodium lauryl sulphate* *Magnesium stearate (E470b)*
	Film coating	*Lactose monohydrate* *Hypromellose (E464)* *Titanium dioxide (E171)* *Triacetin* *Iron oxide yellow (E172)*
HEPARIN		*Sodium chloride* *Methyl parahydroxybenzoate (E218)* *Propyl parahydroxybenzoate (E216)* *Apirogenic double distilled water*
ENOXAPARIN SODIUM		*Water for injectable preparations*
ECHOCARDIOGRAPHIC CONTRAST	Powder	*Macrogol 4000* *Distearoylphosphatidylcholine* *Sodium dipalmitoyl phosphatidylglycerol* *Palmitic acid*
	Solvent	*Sodium chloride solution 0.9% w/v for injection*
PLACEBO	Tablet	*Microcrystalline cellulose (E460)* *Sugar alcohol*

Table 9. ***Excipients of study drugs.*** Adapted from (44,48,62-64).

	OTHER CONTRAINDICATED CLINICAL SITUATIONS
ACENOCOUMAROL	*Recent or planned surgical interventions on the CNS, ophthalmological operations and traumatic operations exposing large areas of tissue.* *Peptic ulcer or bleeding in the gastrointestinal tract, urogenital tract or respiratory system as well as cerebrovascular haemorrhages, acute pericarditis and pericardial effusions and infective endocarditis.* *Severe hypertension.* *Severe liver failure.* *Severe renal failure, provided that the bleeding risk outweighs the thrombotic risk.* *Hereditary and acquired coagulopathies and thrombocytopenias with platelet counts lower than 50x109/L.* *Increased fibrinolytic activity (e.g. after lung, prostate, uterine operations, etc.).*
APIXABAN	*Injury or pathology if it is considered to pose a significant risk of major bleeding. This may include an existing or recent gastrointestinal ulcer; presence of malignant neoplasms with a high risk of bleeding; recent brain or spinal damage; recent brain, spinal or ophthalmic surgery; recent intracranial haemorrhage; suspected or known esophageal varices, arteriovenous malformations, vascular aneurysms; or large intraspinal vascular anomalies intraspinal or intracerebral vascular anomalies.* *Concomitant treatment with any other anticoagulant agent such as unfractionated heparins, low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.), except in specific circumstances of change of anticoagulant treatment, when unfractionated heparins are administered at doses necessary to keep a central venous catheter open to keep a central venous or arterial catheter open, or when unfractionated heparin is administered during catheter ablation in patients with atrial fibrillation.*
HEPARIN	*In patients receiving heparin for treatment and not for prophylaxis, the use of regional anaesthesia is contraindicated for scheduled surgery.*
ENOXAPARIN SODIUM	*Spinal or epidural anaesthesia or locoregional anaesthesia, when enoxaparin sodium is used for treatment within the previous 24 hours.*

Table 10. ***Contraindicated clinical situations for anticoagulation treatment.***
Adapted from (44,48,62,63).