Universitat de Girona
Facultat de Medicina

DOES CHRONIC ANTICOAGULATION IMPROVE PROGNOSIS AMONG PATIENTS WITH COVID-19?

A POPULATION-BASED RETROSPECTIVE COHORT

FINAL DEGREE PROJECT
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1. ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
AEMPS	Agència Espanyola de Medicaments i Productes Sanitaris
AF	Atrial Fibrillation
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya
ARDS	Acute Respiratory Distress Syndrome
ATC-DDD	Anatomical Therapeutic Chemical/Defined Daily Dose
CAC	COVID-19-associated Coagulopathy
CEIm	Comitè Ètica Investigació clínica amb medicaments
CMBD	Conjunt mínim bàsic de dades
COVID-19	Coronavirus 19 Disease
CRP	C-Reactive Protein
DIC	Disseminated Intravascular Coagulation
DOAC	Direct Oral Anticoagulation
ECMO	Extracorporeal Membrane Oxygenation
GMA	Grups Morbilitat Ajustats
ICD	International Classification Diseases
ICU	Intensive Care Unit
ISTH	International Society on Thrombosis and Haemostasis
LMWH	Low Molecular Weight Heparin
NAAT	Nucleic Acid Amplification Test
NETs	Neutrophil Extracellular Traps
OAC	Oral Chronic Anticoagulation
OR	Odds ratios
PADRIS	Programa Analítica Dades per la Recerca i Innvació en Salut
PE	Pulmonary Embolism
PHEIC	Public Health Emergency of International Concern
PSM	Propensity Score Matching
PT	Prothrombin Time
RAAS	Renin-Angiotensin-Aldosterone System

RBD	Receptor Binding Domain
RCA	Registre central d'assegurats del CatSalut
RDT	Rapid Diagnostic Test
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus-2
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SISCAT	Sistema Sanitari Integral d'Utilització Pública de Catalunya
SPSS	Statistical Package for the Social Sciences
TMPRSS2	Transmembrane Protease Serine type 2
UdG	Universitat de Girona
UFH	Unfractionated Heparin
VKA	Vitamin K Antagonists
VTE	Venous Thromboembolism
WHO	World Health Organization

2. ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has emerged as a global pandemic, with a considerable morbidity and mortality rate. Despite the fact that almost 80% of the Catalan population is fully vaccinated, the pandemic persist and the health system is overwhelmed. Therapeutic measures to reduce morbidity and mortality are therefore necessary.

Although the main disease expression is in the respiratory tract, there is high evidence that the pathophysiological component of severe COVID-19 may be triggered by a procoagulant state. The coagulation system not only has an important role in macrothrombotic complications, it also contributes to the development of acute respiratory distress syndrome (ARDS). Despite multiple clinical trials performed, there is still no clear consensus on the optimal anticoagulation dose for the treatment of hospitalised patients. Thus, until new evidence emerges, the study of retrospective data on patients infected by SARS-CoV-2 receiving baseline chronic anticoagulation therapy and how this influences their prognosis, could provide new evidence on the importance of such treatment.

Objective: The purpose of this study is to assess whether receiving chronic oral anticoagulation prior to COVID-19 infection is associated with an improved prognosis (reducing hospital admission, need for ventilatory support and mortality).

Design: This study is a population-based retrospective cohort using linked health administration databases in Catalonia, Spain from 1 October 2020 to 31 December 2020.

Participants and Methods: In this population-based study, we will review all patients aged 65 years or older with a laboratory-confirmed SARS-CoV-2 diagnose between 1 October 2020 to 31 December 2020 in Catalonia. Our sample will be divided into those who were receiving chronic anticoagulation for atrial fibrillation (exposed cohort) with those who were not (non-exposed cohort). After Propensity Score Matching (PSM) we will compare the outcomes (hospital admission, need for ventilatory support and mortality) between both cohorts.

Keywords: COVID-19; SARS-CoV-2 infection; chronic anticoagulation; anticoagulants; VKA; DOAC

3. INTRODUCTION

3.1. COVID-19

3.1.1. CONCEPT

Coronavirus 19 disease (COVID-19) is an infectious disease caused by SARS-CoV-2 virus, a newly emergent RNA virus that was firstly recognized in Wuhan, in December 2019 (1).

Initially the virus was called 2019-novel coronavirus (2019-nCoV). Now it is called Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) (2) and it is responsible for the illness named COVID-19.

3.1.2. GLOBAL PANDEMIC

COVID-19 first emerged in December 2019, when a group of patients with pneumonia of unknown cause were recognized in Wuhan, China. On January 7, 2020, Chinese authorities identified a new virus of the Coronaviridae family as the causative agent of the outbreak, which was subsequently named SARS-CoV-2.

Since the first case was identified, there has been a rapid increase in cases worldwide. Due to travellers, it quickly spread to other continents causing the pandemic since March 2020.

On January 30, 2020, The World Health Organization (WHO) declared the outbreak as a Public Health Emergency of International Concern (PHEIC), WHO's highest level of alarm.

On March 11, 2020, due to the alarming levels of spread and severity, WHO made the assessment that COVID-19 could be characterized as a **pandemic** (2,3).

According to WHO, as of 17 January 2022, there have been 326.279.424 confirmed cases of COVID-19, including 5.536.609 deaths. A total of 9.395.058.118 vaccine doses have been administered.

Specifically in Spain, there have been 7.930.529 confirmed cases of COVID-19, including 90.620 deaths. A total of 80.022.219 vaccine doses have been administered (4).

It is possible that this number is underestimated because at the beginning of the pandemic the recommendations were to stay at home and diagnostic test were not available which suggests that there were many under-diagnosed cases.

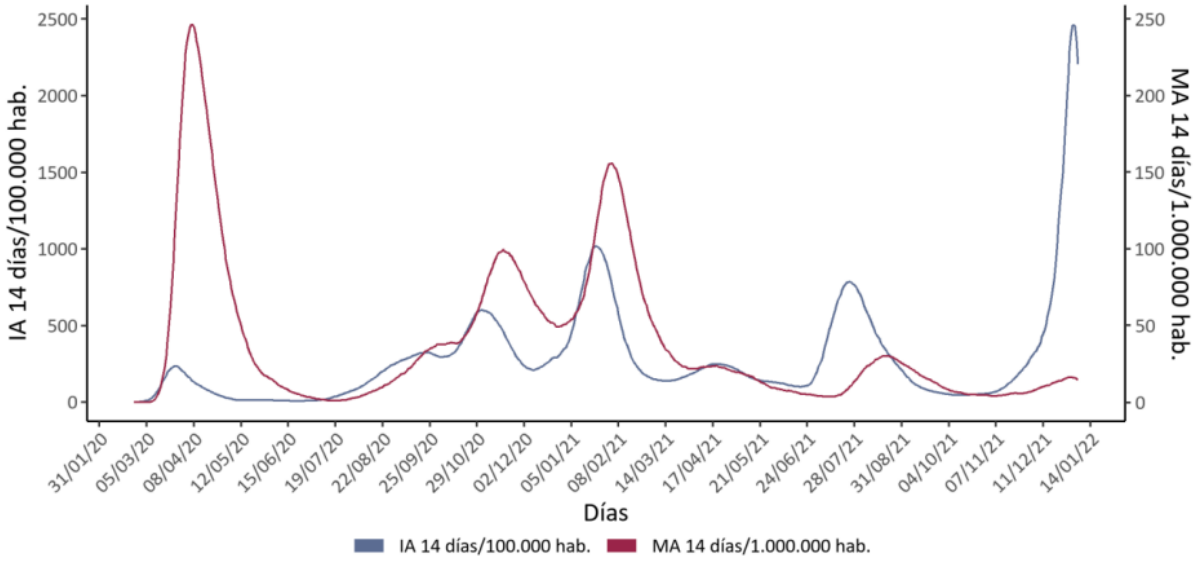

Figure 1. *Evolution of the cumulative 14-days incidence rate (IA) and mortality rate (MA) in Spain (5)*

In Catalonia, a total of 1,506,778 cases have been confirmed, with 24,793 deaths. More than 6 million people are fully vaccinated (6).

Although almost 80% of the Catalan population is fully vaccinated, the appearance of mutant variants has once again dramatically increased the incidence and collapsed the health system (7,8).

Thus, we see how coronavirus disease has a great impact on morbidity and mortality, so it would be of major relevance to know the factors that could prevent the complications of the disease, as well as reduce its mortality.

3.1.3. PHYSIOPATHOLOGY

Coronaviruses are a group of rounded viruses whose membrane has characteristic spicules that represent a distinctive element in their morphology, giving them a crown-like appearance, which explains their name.

Traditionally they had been associated with the common cold and were considered a benign entity, until November 2002, when a new coronavirus (SARS-CoV) emerged, which caused outbreaks of viral pneumonia with a lethality close to 10%.

Consequently, SARS-CoV-2 is so named because its clinical manifestations and prognosis are very similar to the SARS-CoV of 2003. They also share 80% of their genome and use similar recognition mechanisms (9).

SARS-CoV-2 genome encodes four structural proteins: spike (S), envelope (E), membrane (M) and nucleocapsid (N). SARS-CoV-2 entry into host cells is mediated by protein S, which contains what is called the receptor binding domain (RBD). The RBD recognizes and binds specifically to the receptor, which in this case would be **angiotensin-converting enzyme 2 (ACE2)**. After the binding of protein S to the ACE2 receptor, a transmembrane protease serine type 2 (TMPRSS2) facilitates the entry of the virus into the host cell, initiating viral replication. Thus, we see how cellular expression of ACE2 has an essential role in virus infection and replication. The high expression of ACE2 in the upper respiratory tract and in type I and II alveolar epithelial cells of the lung could explain the high prevalence of respiratory symptoms (10,11).

Transmission occurs primarily through respiratory droplets, although aerosols, faecal-oral transmission and direct contact with contaminated surfaces have also been implicated.

There is also evidence that transmission can occur in nonsymptomatic/presymptomatic subjects due to the ability of SARS-CoV-2 to colonize and replicate in the upper respiratory tract in early stages of the disease. For this reason, social separation measures, masks and isolation are very important (10).

The mechanisms that might play a key role in the pathophysiology of multi-organ damage in SARS-CoV-2 infection are:

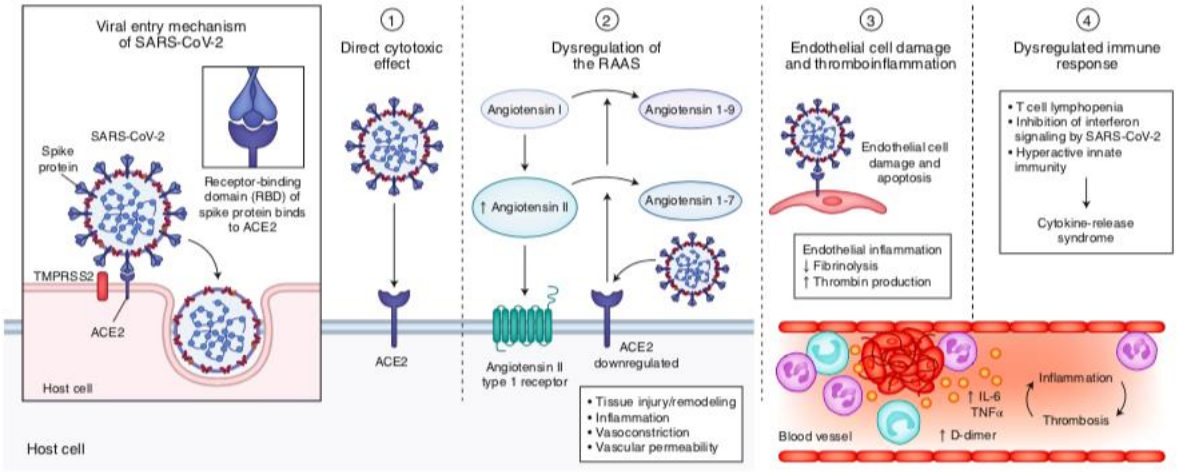

Figure 2. *Pathophysiology of COVID-19 (12)*

1. Direct viral toxicity

As we have seen, SARS-CoV-2 presents a high tropism for those organs with high expression of ACE2. Histopathological studies have demonstrated organotropism mainly for the respiratory tract, but also, to a lower extent, for the renal, gastrointestinal, neurological and cardiovascular systems, among others (13). These findings could explain, in part, the reason for the multiorgan damage (12).

2. Dysregulation of the immune response

SARS-CoV-2 can lead to dysfunction and dysregulation of innate and adaptive immunity. This dysfunction is marked by: 1) an increased neutrophil/lymphocyte ratio 2) Decreased CD4 lymphocytes and natural killer cells 3) Massive activation of monocytes/macrophages, which can trigger massive release of proinflammatory cytokines (IL-6 among others), leading to acute respiratory distress syndrome (ARDS)(12) (14).

Elevated IL-6 levels have been associated with a worse prognosis and increased morbidity. For this reason, one of the therapeutic options used in severe cases is tocilizumab (recombinant humanized monoclonal antibody that inhibits IL-6) (15).

This cytokine storm has a major role in activating coagulation and has been linked to elevated D-dimer, ferritin and fibrinogen levels, which are associated with poor prognosis (14).

3. Dysregulation of the renin-angiotensin-aldosterone system

Dysregulation of the Renin-Angiotensin-Aldosterone System (RAAS) may also contribute to the pathophysiology of multiorgan damage.

The RAAS is constituted by a set of peptides, whose function is to maintain the homeostatic balance of the body, as well as to regulate blood pressure, ionic concentrations...

ACE2, apart from being the receptor of protein S, is a potent counter-regulator of the RAAS pathway. It cleaves angiotensin I to angiotensin 1-9 and angiotensin II to angiotensin 1-7, which has vasodilator, anti-inflammatory and antifibrotic activity (13) (16).

The binding of protein S to ACE2 causes its downregulation in the cell membrane, which promotes the accumulation of angiotensin II, leading to the activation of the RAAS (16).

Angiotensin II accumulation exerts an important role in **prothrombotic effects**, as well as platelet activation or vasoconstriction.

4. Endothelial cell damage and thromboinflammation

One of the most important pathophysiological mechanisms consists on thromboinflammation. Endothelial cells of arteries and veins express the ACE2 receptor; this facilitates viral entry and **endothelial dysfunction**.

This endothelial injury can lead to excessive thrombin production, inhibiting fibrinolysis and activating complement pathways. All this causes thromboinflammation and leads to microthrombus deposition and microvascular dysfunction.

The hyperactivation of monocytes/macrophages and their consequent release of cytokines, as well as the formation of neutrophil extracellular traps (NETs) induce a proinflammatory state, which also enhances the formation of microthrombus.

Also, the direct cytotoxic effect of the virus can also produce a pro- and anticoagulant imbalance (13).

This endothelial dysfunction, as well as the release of cytokines can lead to a decrease of antithrombin and protein C expression, as well as an increase in the levels of plasminogen activator inhibitor, fibrinogen, factors V, VII, VIII and X and von Willebrand factor, favouring a **hypercoagulable state** (17,18).

It is also important to note that the clinical manifestations of the disease (fatigue, dyspnea...), as well as its complications (ARDS, myocarditis...) can lead to a limited mobility, promoting **venous stasis** (17).

Thus, we see how in COVID-19 the 3 components of **Virchow's triad** (triad that includes the main risk factors for thrombus formation) are represented (**Figure 3**).

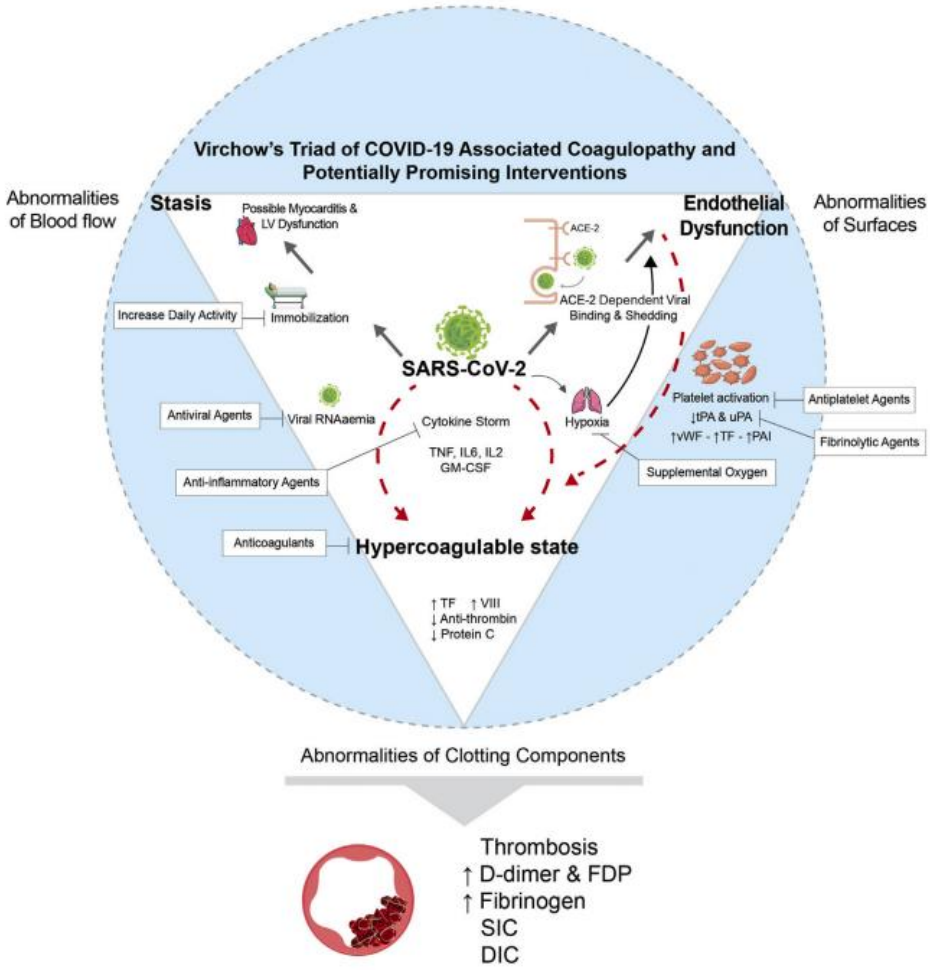

Figure 3. *Virchow's Triad and COVID-19 Associated coagulopathy (17)*

Therefore, we see how thrombotic complications are of great importance in the pathophysiology, where their incidence is proportional to the severity of the disease.

According to different studies, we see how the prevalence of macrothrombotic complications (Venous Thromboembolism – VTE – or Pulmonary Embolism – PE-) in patients admitted to the Intensive Care Unit (ICU) is significantly higher than in other infectious diseases (19 –21).

Its importance not only lies in the complications of large vessels, it is also important at the microvascular level, especially in the lung. This suggests that it is considered to be a major cause of **respiratory failure** in COVID-19 (12).

Postmortem studies have shown the presence of generalized microthrombosis and microangiopathy in pulmonary tissues (22), as well as a high incidence of thrombotic complications in critically ill patients (19,23).

Other findings that show coagulopathy are laboratory abnormalities.

In early stages it is common to see elevations of D-dimer and fibrinogen, which are secondary to excessive inflammation. High D-dimer levels have been associated with poor prognosis (12).

However, in advanced stages of the disease, apart from D-dimer elevation, we observed a decrease in fibrinogen (in contrast to the initial stages), a prolonged prothrombin time (PT) and a decrease in platelet count. These analytical alterations may be secondary to systemic activation of coagulation, known as **COVID-19-associated coagulopathy (CAC).**

Whether CAC is considered a subtype of disseminated intravascular coagulation (DIC) is a matter of debate. Some researchers consider it as a separate entity, as they consider DIC to be a consuming coagulopathy, where bleeding is a frequent clinical event. However, in CAC, thrombotic events are frequent but bleeding is not (24).

Other findings that suggest that they are distinct entities is that, according to *International Society on Thrombosis and Haemostasis* (ISTH) (25) the diagnostic criteria for overt DIC are:

1. Elevated levels of a fibrin-related marker (D-dimer)
2. Prolonged PT
3. Decreased platelet count
4. Decreased fibrinogen level

Of these criteria, only elevated D-dimer is present in the early stages, where fibrinogen is elevated and the other parameters are not altered, providing evidence against being a consumptive coagulopathy (24).

Thus, different mechanisms have been described that increase thrombotic risk. For this reason, one of the therapeutic lines used is anticoagulation.

There has been controversy about the ideal dose for anticoagulant treatment (prophylactic dose vs. therapeutic dose).

Some previous studies have already suggested that the standard prophylactic dose was insufficient in hospitalized patients.

According to the HEP-COVID study (26) (randomized clinical trial of October 2021), **therapeutic doses** of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) reduced mortality and ventilatory support in admitted non-critically ill patients, without increasing bleeding complications, compared to prophylactic doses. However, in patients admitted to the Intensive care unit (ICU), no improvement was demonstrated.

This study confirms what has already been reported by other previous clinical trials. These studies have changed some therapeutic guidelines on anticoagulation in patients hospitalized for COVID-19.

3.1.4. RISK FACTORS OF SEVERE COVID-19

Risk factors for developing severe COVID-19 have been described. Patients with these comorbidities have to take many precautions to avoid becoming infected as they have a worse prognosis.

The main comorbidities that have been associated with a worse prognosis (higher rate of hospitalization, ICU admission and mortality) in COVID-19 are hypertension, obesity, chronic lung disease, diabetes mellitus and cardiovascular disease.

To a lesser extent we also found chronic renal failure and patients with active neoplastic processes (27).

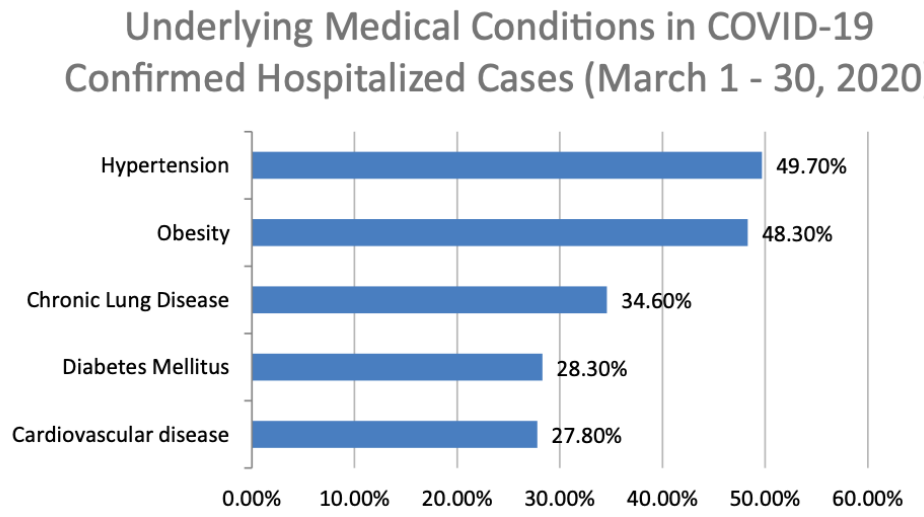

Figure 4. *Data showing hospitalization rates and characteristics of those patients, during the period of March 1-30, 2020 (27)*

Age and gender have also been shown to be independent risk factors for the disease.

It has been shown that advanced age is associated with increased inflammatory activity, disease severity and consequently an adverse prognosis (28).

On the other hand, according to a meta-analysis, male sex has been described as a risk factor for admission to the ICU and mortality (29).

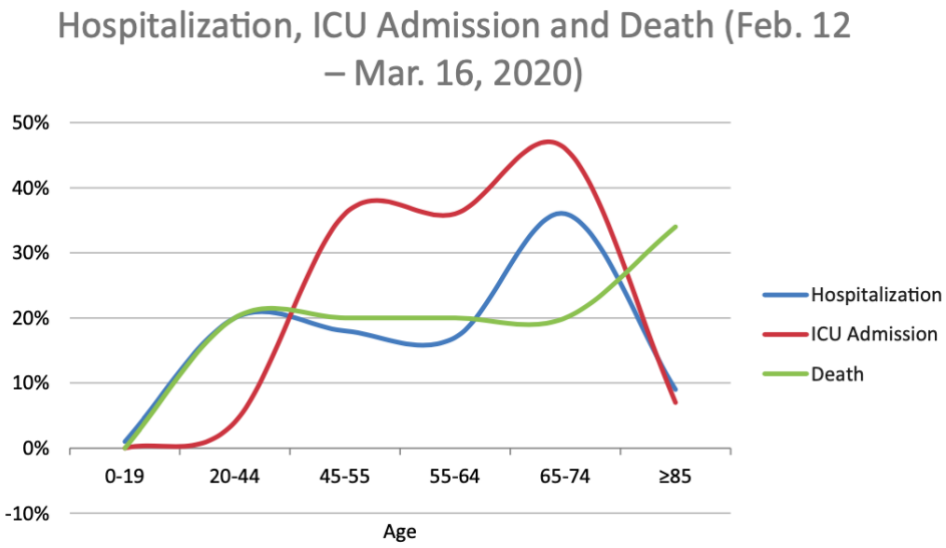

Figure 5. *Data showing severe outcomes depending on the age among patients COVID-19+ in the USA from February 12, 2020 through March 16, 2020 (27)*

3.1.5. TREATMENT OF COVID-19

Results from some clinical trials are now available. However, the evidence available for the management of these patients remains limited. Further research is needed.

We classify the treatment of COVID-19 into four main pillars:

- **Symptomatic treatment** In patients with SARS-CoV-2 infection, symptomatic treatment associated with hygiene and hydration measures and measures to promote venous circulation are necessary. The first-line treatment is paracetamol, due to its safety profile (30).

  Oxygen +/- ventilatory support if needed.

- **COVID-19 specific main treatments** *Treatment of moderate-severe pneumonia* (**Figure 6**)

  - **Remdesivir:** According to *Servei Català de Salut,* this treatment can be assessed in patients with less than 7 days of evolution if they require supplemental oxygen and meet at least 2 of the 3 criteria: 1) Respiratory rate ≥ 24 breaths per minute (bpm) 2) Oxygen saturation ≤ 94% 3) PaO2/Fio2 <300 (30).

    Loading dose of 200mg intravenous (IV) followed by 100mg IV/day during 5 days.

    However, WHO does not recommend its use due to it has not demonstrated a decrease in mortality rate. New antivirals, such as molnupiravir, are now emerging (31).

  - **Dexamethasone:** According to *Servei Català de Salut***,** it is recommended in severe patients with an evolution of more than 7 days requiring supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Recommended dose is 6 mg oral or IV per day during 10 days (30).

  - **Tocilizumab:** According to *Servei Català de Salut*, it is recommended in severe patients with an evolution of more than 7 days requiring supplemental oxygen AND with inflammatory parameters (defined by an increase in C-Reactive Protein (CRP) concentrations ≥ 75 mg/L). Single dose which varies according to weight (30).

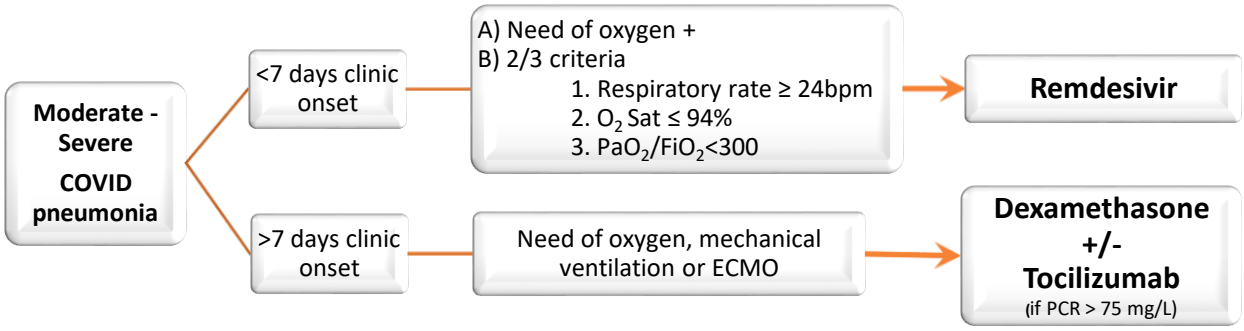

Figure 6. *COVID-19 specific treatment algorithm for moderate-severe pneumonia*

- **Antibiotic treatment:** Only consider it if associated bacterial infection is suspected. Do not administer them systematically (30,31).
- **Thromboprophylaxis:** According to *Servei Català de Salut,* at the present time, it is recommended to use LMWH at prophylactic doses in all hospitalised patients or at intermediate doses if high D-dimer values (>3000) are present (30).

  However, as previously mentioned, the latest scientific evidence has shown that the use of therapeutic doses of LMWH or UFH is associated with an improved prognosis (lower mortality rate and thromboembolic complications) in hospitalised patients who are not in the ICU.

  It has been demonstrated in recent clinical trials, most importantly a multi-platform clinical trial (ATTACC, ACTIV-4a, and REMAP-CAP) and in the HEP-COVID study, cited previously.

  Therefore, data supports the use of therapeutic doses among non-critical hospitalized patients.

  Nevertheless, these studies highlight areas where further investigation is needed (32).

3.2. ATRIAL FIBRILLATION

3.2.1. CONCEPT AND EPIDEMIOLOGY

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults. It consists of the total disorganisation of atrial electrical activity and its absence of contraction, which translates as the absence of a p-wave on the electrocardiogram (33).

Currently, its estimated prevalence in adults is 2-4% and is expected to increase by 2-3 more times due to the increased longevity of the population and the intensification of the search for undiagnosed AF (33–35). In Spain, the latest data indicates that the prevalence of atrial fibrillation could be > 4% in those over 40 years of age, and 9% in those over 65 (35) (**Figure 7**).

The lifetime risk of developing AF had been estimated at 1 in 4 individuals, but in a recent review it has been estimated at 1 in 3 European individuals (33).

Therefore, older age is one of the most important determinants of incidence and prevalence. The older the age, the more common the appearance of AF. Other factors that influence its appearance are hypertension, ischaemic cardiopathy, obesity, diabetes, chronic kidney disease, among others (33–35) (**Figure 8**).

It has also been shown that the age-adjusted incidence rate, prevalence and lifetime risk of AF are lower in females than in males, with male sex being a risk factor (33–35).

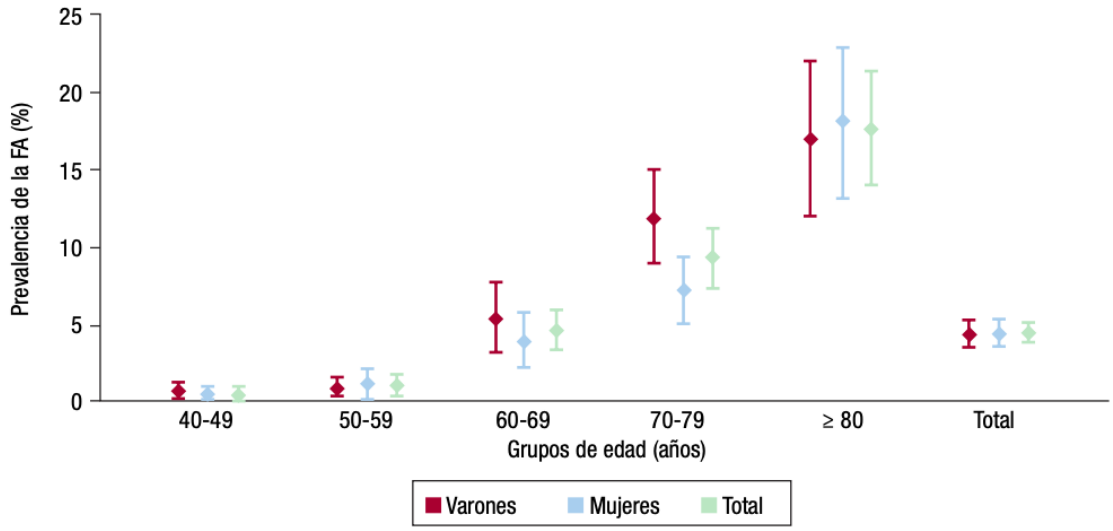

Figure 7. *AF prevalence, expressed as a percentage, in Spain adjusted by sex and age groups, according to OFRECE study (35)*

Figure 8. *Risk factors and underlying comorbidities in AF (36)*

3.2.2. ANTICOAGULANT THERAPY; PREVENTION OF SYSTEMIC EMBOLISM

When a person develops AF, the fact of having it implies a reduction in life expectancy due to the strong correlation between AF and cardioembolic stroke. Overall, AF increases 5 times the risk of stroke (33).

When the atrium fibrillates, its contribution to ventricular filling is lost and this pooling of blood in the left atrium, especially in the atrial appendage, facilitates thrombus formation due to blood stasis. If one of these thrombus breaks off, it is very likely to cause a cardioembolic stroke.

Approximately 20-30% of all cerebral infarctions are due to AF (37).

For this reason, anticoagulant therapy is of vital importance in these patients.

In fact, atrial fibrillation is the most common indication for oral chronic oral anticoagulation (OAC) (38).

According to The *European Society of Cardiology (ESC),* CHA_2DS_2-VASc scale is used to determine whether or not chronic oral anticoagulation (OAC) is indicated. This scale assigns a number of points depending on the patient's characteristics. The higher the score, with a maximum of 9, the higher the risk of embolism (33).

Table 1. *Risk factors for systemic embolism in CHA_2DS_2-VASc scale*

RISK FACTORS		POINTS
C	Congestive heart failure	+1
H	Hypertension	+1
A	≥75 years	+2
D	Diabetes Mellitus	+1
S	Stroke	+2
V	Vascular disease	+1
A	64-74 years	+1
Sc	Sex (female)	+1

Table 2. *OAC indication depending on CHA_2DS_2-VASc scale*

CHA_2DS_2-VASc SCORE	OAC indication
0 points (men) **/1 point** (women)	**Not indicated** (*Evidence A)*
1 point (men) **/ 2 points** (women)	**Recommended** (*Evidence B)*
≥2 points (men) **/ ≥3 points** (women)	**Indicated** *(Evidence A)*

Therefore, these would be the indications for chronic oral anticoagulation, in the absence of absolute contraindications (33).

There are basically two main anticoagulants used for the prevention of embolic events in AF:

1. **Vitamin K Antagonists (VKA):** Its main indication is patients with valvular AF (AF with mitral stenosis or mechanical heart valve). Requires monitoring with International Normalized Ratio (INR) (33).

2. **Direct oral anticoagulants (DOAC); apixaban, dabigatran, edoxaban and rivaroxaban:** In patients with non-valvular AF, their use is recommended over VKAs (33).

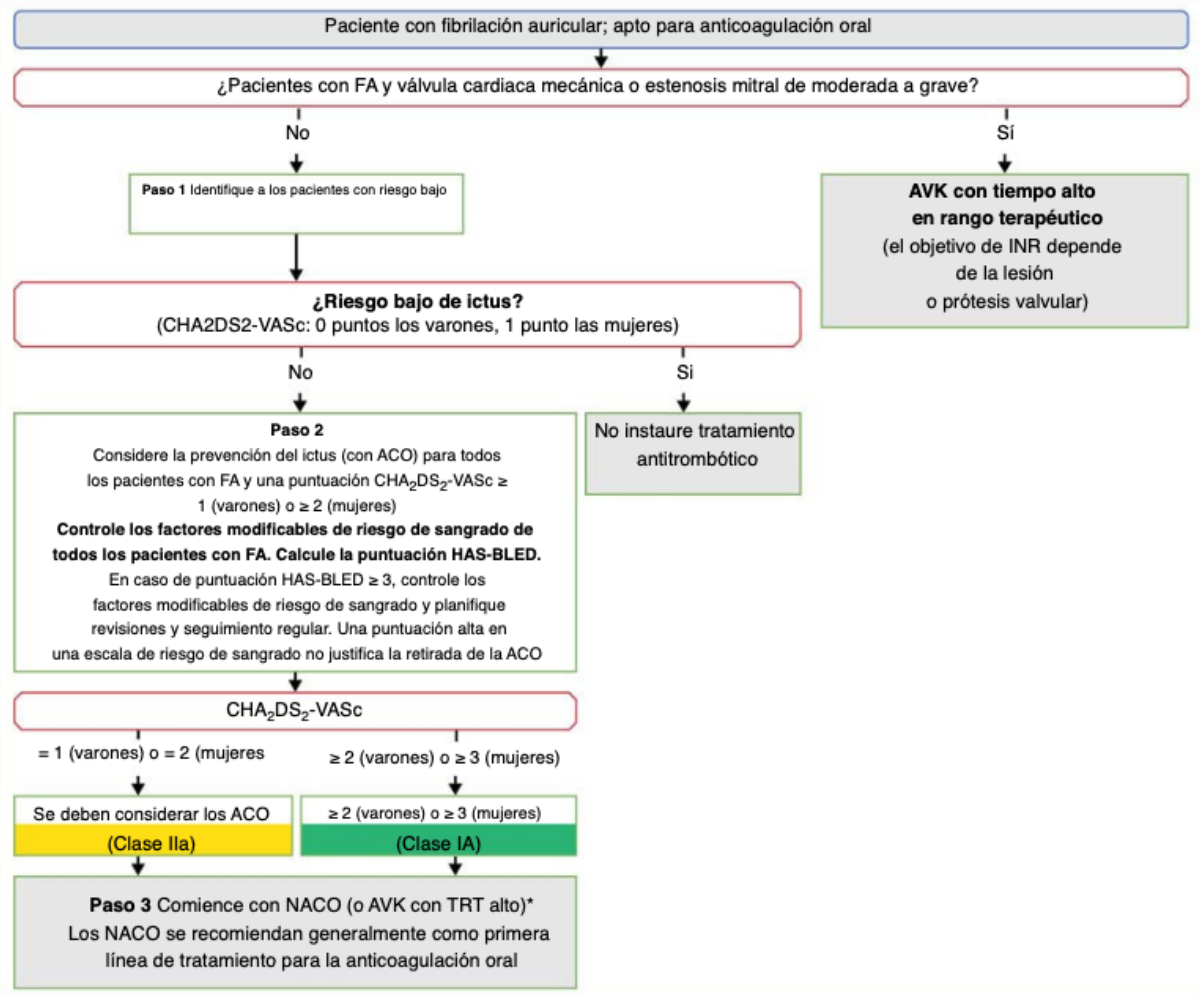

Figure 9. *Therapeutic algorithm for stroke prevention in AF patients, according to ESC (33)*

4. JUSTIFICATION

In the context of the SARS-CoV-2 current pandemic, measures to prevent related morbidity and mortality are highly valued.

Although the main disease expression is in the respiratory tract, there is high evidence that other organs and systems are involved, especially the coagulation system, which not only has an important role in macrothrombotic complications, it also contributes to the development of ARDS (12).

Thus, because thrombotic implications in COVID-19 lead to a worse prognosis, it is plausible that anticoagulation could be a protective factor. Therefore, multiple clinical trials are underway to find the optimal anticoagulant dose for patients admitted to hospital (26).

Until clearer indications on anticoagulation guidelines emerge, the analysis of retrospective data on infected SARS-CoV-2 patients receiving baseline anticoagulation therapy and how this influences their prognosis, could provide further evidence of the importance of such treatment, not only in therapy but also, in prevention.

At the time of writing and despite multiple studies having been conducted, there is no clear evidence on whether the use of anticoagulants prior to infection could improve prognosis. The most recent published studies (39–45) (**Table 3**), have shown controversial results and have **methodological limitations** such as

1. They compare heterogeneous cohorts
2. Their sample is limited to hospitalised patients, which implies that
    a. Results cannot be generalised to non-hospitalised patients (with no severity criteria)
    b. It cannot be determined whether OAC can prevent the development of severe disease (and therefore does not require hospital admission)
    c. They do not take into account the influence of interventions after patients were hospitalised (especially the use of prophylactic anticoagulantion), which could bias their results.

The present study will **add value** by studying the impact of previous anticoagulation on:

1. A homogenised cohort. We will study patients taking anticoagulants due to atrial fibrillation (because it is their most frequent indication).
2. Subjects diagnosed with SARS-CoV-2 and not patients already hospitalised, which will allow us to take hospital admission as a primary outcome and therefore being able to assess the possible protective effect of anticoagulants prior to hospitalisation.
3. A population-based study, which will facilitate having a very large sample and therefore obtaining statistically significant results.

Table 3. *Summary of the most recent published articles assessing the influence of anticoagulation prior to COVID-19*

Author; Date of publication	Study Design	OAC regimen	Sample	Primary outcome	Results
Tremblay et al; July 2020 (39)	Retrospective cohorts adjusted by Propensity Score Matching (PSM)	Prior DOAC or VKA before hospital admission	Hospitalized patients - OAC $_n$= 139 - Control $_n$= 417	All-cause mortality	No statistically significant difference in survival
Fröhlich et al; January 2021 (40)	Retrospective cohort adjusted by PSM	Prior DOAC or VKA at least 180 days before hospital admission	Hospitalized patients - OAC $_n$= 731 - Control $_n$= 5059	All-cause mortality, or need for invasive / non-invasive ventilation or ECMO	Use of prior OAC was associated with an improvement of clinical outcomes
Russo et al; April 2021 (41)	Multi-center retrospective cohorts adjusted by 1:2 PSM	Prior DOAC or VKA before hospital admission	Hospitalized patients - OAC $_n$= 87 - Control $_n$= 174	ARDS risk and all-cause mortality	No difference on ARDS risk or survival
Chocron et al; April 2021 (42)	Multi-center retrospective cohorts adjusted by PSM	Prior DOAC or VKA before hospital admission	Hospitalized patients - OAC $_n$= 382 - Control $_n$= 1146	Time from diagnosis to death or ICU admission	Prior OAC was associated to a decreased mortality and ICU admission
Buenen et al; June 2021 (43)	Single- center prospective cohorts adjusted by PSM	Prior DOAC or VKA before hospital admission	Hospitalized patients - OAC $_n$= 110 - Control $_n$= 387	All-cause mortality within 30 days	Prior OAC was associated with a better survival
Covino et al; July 2021 (44)	Single-center Prospective cohorts adjusted by 1:1 PSM	Prior DOAC or VKA at least 1 month before hospital admission	Hospitalized patients >65 years - OAC $_n$= 92 - Control $_n$= 92	All-cause in-hospital mortality	No survival difference
Hozayen et al; September 2021 (45)	Multi-center (hospitals and clinics) prospective cohorts study adjusted by PSM	Prior DOAC, VKA or heparin before positive COVID + diagnostic	Patients with COVID + test - AC $_n$= 160 - Control $_n$= 5437	Risk for hospitalization and mortality	Prior OAC was associated to reduced risk in hospital admission

5. HYPOTHESIS

5.1. MAIN HYPOTHESIS

Receiving baseline oral anticoagulation prior to COVID-19 infection would reduce the risk of hospital admission.

5.2. SECONDARY HYPOTHESIS

Receiving baseline oral anticoagulation prior to COVID-19 would improve other COVID-19-related outcomes such as mortality or non-invasive mechanical ventilation, mechanical ventilation, orotracheal intubation or tracheostomy.

6. OBJECTIVES

6.1. MAIN OBJECTIVE

1) To assess whether receiving chronic oral anticoagulation prior to COVID-19 is associated with a decreased risk of hospital admission.

6.2. SECONDARY OBJECTIVES

2) To assess whether receiving prior chronic oral anticoagulation reduces mortality due to COVID-19.

3) To assess whether receiving chronic oral anticoagulation prior to COVID-19 reduces the need for non-invasive mechanical ventilation, mechanical ventilation, orotracheal intubation or tracheostomy.

7. MATERIALS AND METHODS

7.1. STUDY DESIGN

This study is a population-based retrospective cohort using linked health administration databases in Catalonia, Spain from 1 October 2020 to 31 December 2020.

7.2. STUDY POPULATION

In our study we will include all individuals ≥ 65 years old insured by the Catalan public health System with a first positive SARS-CoV-2 diagnostic test (either with a positive Nucleic Acid Amplification Test (NAAT) or positive SARS-CoV-2 Antigen-Rapid Diagnostic Test (RDT)) between 1 October 2020 and 31 December 2020. The day of diagnosis will be defined as the **index day**.

This SARS-CoV-2 diagnosed cohort will be divided into an exposed cohort and a non-exposed cohort.

The exposed cohort will be all subjects taking oral anticoagulation therapy (VKA or DOAC) due to non-valvular AF, at the index day and, at least, 3 months prior. The non-exposed cohort will be all subjects who do not take any type of anticoagulants.

All those subjects taking anticoagulants due to other reasons apart from non-valvular AF will be excluded from the study. Subjects who are currently taking DOAC but started taking it less than 3 months or those subjects who were taking DOAC 3 months ago but are not currently taking it, will also be excluded.

For each exposed subject, two non-exposed subjects matched for age, sex and comorbidities will be chosen.

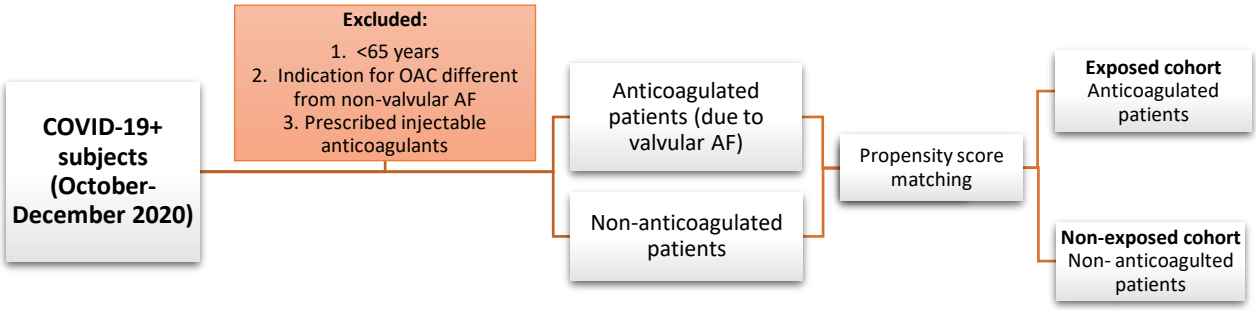

Figure 10. *Diagram of study cohort*

Our study population is based on subjects aged ≥65 years because the vast majority of people taking chronic oral anticoagulants are aged 65 years and older (35).
Including people of all ages would have meant that few young subjects would have been able to falsify statistical results (as measures of central tendency, such as the mean).

In order to homogenise our exposed cohort, we have focused on atrial fibrillation as the indication for anticoagulation, because it is the most prevalent indication in our setting (35). Valvular atrial fibrillation has been excluded because of added risk factors (mitral stenosis and mechanical valve), which would make matching more difficult.

The study time chosen was between 1 October 2020 and 31 December 2020, as this is the time of the second and the beginning of the third waves, which will allow us to obtain a larger sample.
The first wave was discarded because, due to the stay-at-home recommendations and the lack of diagnostic tests, there were many under-diagnosed cases.
From the third wave onwards, vaccination campaigns started, which could be a potentially confounding variable.

7.2.1. INCLUSION CRITERIA

Exposed cohort

1. Subjects with a positive SARS-CoV-2 diagnostic test (NAAT or Antigen-RDT) between 1 October 2020 and 31 December 2020
2. Aged 65 years or older
3. Taking oral anticoagulation therapy (VKA or DOAC) due to non-valvular AF at the time of SARS-CoV-2 diagnosis (index date) and, at least, the previous 3 months

Non-exposed cohort

1. Subjects with a positive SARS-CoV-2 diagnostic test (NAAT or Antigen-RDT) between 1 October 2020 and 31 December 2020
2. Aged 65 years or older

7.2.2. EXCLUSION CRITERIA

Exposed cohort

1. Subjects who have injectable anticoagulants prescribed on the index day.
2. Subjects diagnosed with AF associated with mitral stenosis or mechanical heart valve (which would define valvular AF) on the index day

Non-exposed cohort

1. Taking any type of anticoagulants on the index day or during the previous 3 months

7.3. SAMPLE

7.3.1. SAMPLE SELECTION

This population-based retrospective cohort will be done using linked health administration databases in Catalonia. We will use anonymized data provided by the Agency for Health Quality and Assessment of Catalonia (AQuAS) within the framework of the Data Analytics Program for Health Research and Innovation (PADRIS) (46).

First, we will identify all subjects diagnosed with SARS-CoV-2 in our study period via an specific epidemiological mandatory registry for SARS-CoV-2 infection, where outpatient, inpatient and laboratory diagnosed cases of SARS-CoV-2 are reported.

Subsequently, based on the inclusion and exclusion criteria, we will obtain our exposed cohort and our non-exposed cohort.

Finally, based on sociodemographic characteristics (age and gender) and comorbidities, for each individual in the exposed cohort, we will match 2 individuals from the non-exposed cohort, using propensity score matching (PSM).

Whenever possible, we will try to match each subject of the exposed cohort, making that sample selection almost identical to the study population.

To select the match in the unexposed cohort group, **stratified probability sampling** will be used, as subjects will be matched on the basis of their demographic characteristics and comorbidities.

7.3.2. SAMPLE SIZE

We estimated our sample size, using GRANMO application (47), for our main dependent variable (hospital admission).

According to *Servei Català de la Salut (48),* On 1 October 2020, 33.2% of people diagnosed with SARS-CoV-2 aged 65 years or older in Catalonia were admitted to hospital. On 31 December 2020, this rate was 29.5%.
This rate has not significantly changed over the course of our study period.

Thus, we estimate that the **hospitalisation rate in our unexposed cohort** would be **31%.**

According to *Hozayen et al.* (see table 3 above) (45)*,* outpatients with COVID-19 who were on chronic anticoagulation on the index date experienced a 43% reduced risk of hospitalization. Because this rate has only been obtained from one study and seems to us to be very high, we assume that a relative reduction of 20%, would already represent a significant reduction in the risk of hospitalisation.

Therefore, we have estimated that the risk of **hospitalisation in the exposed cohort** would be **24.8%** (a 20% reduction of 31%).

Assuming an alpha risk of 0.05 and a beta risk of 0.1 and a ratio between the two groups 2:1, for each subject in the exposed cohort, two subjects from the unexposed cohort will be matched.
Taking into account these parameters, GRANMO (47) states that to find statistically significant differences, it would be necessary to include **823 subjects** in the exposed cohort and **1.646** in the unexposed cohort. Based on the fact that this is a population-based retrospective cohort study, the dropout rate will be 0.

According to *Servei Català de la Salut (6)* and its COVID-19 database, between 1 October 2020 and 31 December 2020, there were 58.520 new cases of SARS-CoV-2 in people aged ≥60 years.

Table 4. *Subjects diagnosed with SARS-CoV-2 between 1 October 2020 and 31 December 2020 in Catalonia*

Age Range (years)	Number of cases
60-69	23.877
70-79	16.027
80-89	12.438
≥90	6.178
TOTAL	**58.520**

However, our study population does not include subjects aged 60-64 years.

According to the "Institut d'Estadística de Catalunya (Idescat) (48)", Catalonia is home to 850.137 people aged 60-69, 459.948 of whom are aged 60-64 (54%) and 390.189 are aged 65-69 (46%).

Taking this into account, we can estimate that 46% of cases between 60-69 years of age (10,983) would correspond to the 65-69 age group.

Thus, we estimate that in our study period, **45.626 subjects** were diagnosed with SARS-CoV-2.

According to *OFRECE study (35)*, the prevalence of AF in subjects aged ≥65 years is approximately 9%.

Thus, calculating 9% of 45,626 and taking into account that the fact of having AF does not influence the risk of becoming infected, we estimate that we will obtain an **exposed cohort of 4.106 subjects** and a **non-exposed cohort of 41.520 subjects.**

Although with 823 subjects we could already obtain statistically significant differences, the study will be conducted with the entire exposed cohort (4.106 subjects) to further increase the power of the study.

Group sample sizes of 4106 in group 1 and 8212 in group 2 achieve **100% power** to detect a difference between the group proportions of -0,062. The risk of hospital admission in group 1 (the exposed cohort) is assumed to be 0,31 under the null hypothesis and 0,248 under the alternative hypothesis. The risk of hospital admission in group 2 (the control group) is 0,31. The test statistic used is the two-sided Z-Test with unpooled variance. The significance level of the test is 0,05.

Thus, we see that with our sample size, the probability of accepting a false null hypothesis (type II error) is practically non-existent that gives a statistical power of 100%.
Therefore, the study will be conducted with a sample of approximately 4106 subjects in the exposed cohort and 8212 in the unexposed cohort (1:2 ratio).

7.4. VARIABLES AND METHODS OF MEASUREMENT

7.4.1. INDEPENDENT VARIABLE

The independent variable is the intake of chronic oral anticoagulant therapy, anti-VKA or DOAC, in the context of non-valvular AF at the time of SARS-CoV-2 diagnosis and, at least, within the previous 3 months.

We considered that subjects had chronic exposure to anti-VKA/DOAC if, according to electronic prescription, they had been prescribed anti-VKA/DOAC at least on the index day and also during the previous 3 months or more.

Thus, we will obtain two groups according to this variable; the exposed cohort and the non-exposed cohort.

7.4.2. STUDY VARIABLE

The study variables are outcomes related to the prognosis of SARS-CoV-2 infection.

The main outcome is **hospital admission**. It is defined as the first hospital admission with a primary diagnosis of COVID-19 that occurs between 2 days before and 14 days after the index day. Thus, we will take into account hospital admissions between 29 September 2020 and 14 January 2021 (periods ranging from 2 days before to 14 days after the start and end dates of the study).

To obtain this data, we will use the "*Conjunt mínim bàsic de dades d'hospitalització d'aguts (CMBD-HA)".*

Secondary outcomes would consist of the need for **non-invasive mechanical ventilation**, **mechanical ventilation**, **orotracheal intubation** or **tracheostomy** and **mortality** due to infection.

Considering that there are hospitals that admit patients with non-invasive mechanical ventilation to the ICU and hospitals that do not, we considered that the parameter "ICU admission" could be influenced by in-hospital protocols. This is why we preferred to analyse the different methods of ventilatory support separately.

We define the need for **non-invasive mechanical ventilation , mechanical ventilation, orotracheal intubation or tracheostomy** as the need for this support during hospitalization. This information will be obtained through the CMBD, where the information of the

procedures performed during hospitalization can be obtained via International Classification Diseases 10 Procedure Coding System (ICD-10-PCS).

Mortality is defined as any death occurring within 30 days of a hospital admission with a primary diagnosis of COVID-19. This means that patients hospitalized during the month of December (or during the month of January if the index day is before 1 January 2021) and whose death occurs in the month of January (or February) will also be included. This data will be obtained from the *Registre central d'assegurats del CatSalut (RCA),* which is another record that PADRIS has access to, and not from the mortality register, as the register takes 2 years to be formalised.

All dependent variables are dichotomous qualitative variables, which are expressed as yes or no.

7.4.3. COVARIABLES

According to the literature review (27–29, 33–35), we identified covariates that are both associated with the exposed cohort and the risk of severe COVID-19 outcomes and therefore could be confounding variables which bias the results.
However, by knowing the confounding variables and their association with the exposure of interest, the confounding bias could be controlled for. Therefore, to reduce the confounding bias we will use propensity score matching (PSM).

Covariables include:

1. **Gender:** Phenotype the subject was born with. Expressed on *Male/Female.*
2. **Age**: Subject's age on the index day. Expressed in *years*.
3. **Comorbidities** Comorbidities that the subject presents on 1 January 2020. It will be expressed in *adjusted morbidity groups (GMA).*

GMA (49) is a morbidity score developed using health system data. It allows the generation of an adequate population stratification and shows good explicative results in indicators of health resource use.

This score is structured taking into account two factors: **multimorbidity and complexity**.

Multimorbidity is collected in large groups, called morbidity groups, where users are classified according to the typology of their illnesses (acute, chronic or oncological) and in the case of the presence of chronic illness, identifying whether this is unique or not (multimorbidity).

Thus, the morbidity groups generated are:

1. Healthy population
2. Pregnancy
3. Acute pathology
4. Chronic disease in a system
5. Chronic disease in 2 or 3 systems
6. Chronic disease in 4 or more systems
7. Neoplasms in the period

Each morbidity group (except for the healthy population) is subdivided into 5 subgroups, according to the levels of **complexity,** which are identified at the individual level, taking into account all the morbidity present in the patient. This is obtained from models where variables such as admission risk, mortality risk, visits to primary care or pharmacological pre-registration are collected.

Thus, in the end, **31 GMA** are obtained from the combination of morbidity groups and level of complexity. **(ANNEX 2)**

In order to homogeneously define the degree and severity of the patient's comorbidities, we have used GMA and not another system because :

1) There are many comorbidities that could act as confounders (such as hypertension, obesity, diabetes mellitus, chronic obstructive pulmonary disease….). Identifying all of them would be very laborious and would make matching difficult.

2) This classification is done at the beginning of each year and each individual is already classified in his or her corresponding group, so this will not involve an investment of resources.

3) This is the only way that the variable atrial fibrillation does not act as a confounding factor. If we match for each comorbidity specifically, atrial fibrillation could not be matched and could act as a confounder.

4) It is a validated classification developed by the "Servei Català de la Salut" and "Institut Català de la Salut", widely used in national studies.

Table 5. *Independent, dependent and covariables*

VARIABLE	DEFINED BY	OBTAINED FROM	VARIABLE KIND & *VALUE CATEGORIES*
Anticoagulant therapy	Intake of OAC therapy on the index day and, at least, within the previous 3 months	Electronic prescription	Independent Binary qualitative & *Exposed cohort / Non-exposed cohort*
Hospital admission	1st hospital admission that occurs between 2 days before and 14 days after the index day	CMBD-HA	Main outcome Binary qualitative & *Yes/No*
Non-Invasive mechanical Ventilation	Need for NIV during hospitalization	ICD-10 codes for procedures (CMBD-HA; URG)	Secondary outcome Binary qualitative & *Yes/No*
Mechanical ventilation	Need for Mechanical ventilation during hospitalization	ICD-10 codes for procedures (CMBD-HA; URG)	Secondary outcome Binary qualitative & *Yes/No*
Orotracheal intubation	Need for orotracheal intubation during hospitalization	ICD-10 codes for procedures (CMBD-HA; URG)	Secondary outcome Binary qualitative & *Yes/No*
Tracheostomy	Need for tracheostomy during hospitalization	ICD-10 codes for procedures (CMBD-HA; URG)	Secondary outcome Binary qualitative & *Yes/No*
Mortality	Any death of any cause within 30 days of a hospital admission	RCA	Secondary outcome Binary qualitative & *Yes/No*
Gender	Phenotype the subject was born with	Demographics	Covariable Binary qualitative & *Male/Female*
Age	Years of the subject on the index day	Demographics	Covariable Continuous quantitative & *Years*
Comorbidities	Comorbidities that subject presents on 1 January 2020	Multiples levels of the health system	Covariable Qualitative & *GMA*

7.5. DATA COLLECTION

Data will be extracted from the "Programa d'Analítica de Dades per a la Recerca i la Innovació en Salut (PADRIS)", which is a programme that corresponds to the organisation "l'Agència de Qualitat i Avaluació en Salut (AQuAS)". It is an organization whose objective is to provide related health data to the scientific community in order to promote research through the cross-referencing of health data generated by the "Sistema Sanitari Integral de Utilització Pública de Catalunya (SISCAT)", in accordance with the programme's legal and regulatory framework, ethical principles and principles of transparency towards the public. **(ANNEX 3)**

Data extraction is carried out via AQuAS with a public budget, without financial compensation, in the context of a multidisciplinary team in which managers, technicians and researchers collaborate.
Subsequent to data extraction, data is made available to the research team. These data is previously pseudoanonymised and depersonalised, so that it is impossible to identify the subjects.

In order to be able to apply for the data, our research team will be affiliated to a university research centre, the “Universitat de Girona (UdG)”. We will make a request for access to the programme, where we will specify which data we want and which crossings must be carried out.

PADRIS allows the traceability of Catalan residents in several databases of the health administration. These databases include information on:

- Demographics (age and gender)
- Acute and emergency hospitals and emergency discharge datasets (“*conjunt mínim de dades d’urgències hospitalàries (CMBD-URG)*” and “*conjunt mínim de dades d’hospitalitzats aguts (CMBD-HA)*”), which includes procedures and outcomes of medical admissions in the public hospitals in Catalonia
- Comorbidities and date of diagnosis (“*conjunt mínim de dades d’atenció primària (CMBD-AP)*”)
- Laboratory data, results and diagnoses (includes data of SARS-CoV-2 diagnoses)

- Electronic prescription, which contains the medications received at the outpatient and inpatient level
- Specifical epidemiological mandatory registry for SARS-CoV-2 infection (apart from the diagnoses made by health care institutions, it includes the results of private laboratories, which are obliged to report the results)

All CMBD databases register the information of diagnoses and procedures using the Tenth Revisions of the International Classification of Diseases Codes (ICD-10-MC/PCS) and the electronic prescription uses Anatomical Therapeutic Chemical/Defined Daily Dose (ATC-DDD) index codes established by the WHO.

First, we will select all individuals ≥65 years of age insured in Catalonia who present a diagnosis of SARS-CoV-2 between 1 October 2020 and 31 December 2020. The day of diagnosis is defined as the index day.
We will obtain these patients through the **specific epidemiological mandatory registry for SARS-CoV-2 infection**, which includes both cases diagnosed in primary and hospital care and by public and private system laboratories. In this way, we will be able to get all patients diagnosed in a reliable way.

Subsequently, we will exclude from our initial sample all patients who had been **prescribed in electronic prescription** with drugs of the ATC Classification System groups corresponding to heparin (ATC B01ABxx, C05BA03, S01XA14 or C05BA53) at the index day. As heparin has no indication for treatment in AF, we excluded these patients (fulfilling the exclusion criteria).

Our next step will be to define our exposed cohort (non-valvular AF patients with VKA or DOAC at least 3 months prior to infection) and our non-exposed cohort.

To obtain our exposed cohort, we will cross-reference data from **drugs prescribed in electronic prescription** and **CMBD (AP, URG, HA).**

On the one hand we will select patients who had been **prescribed in electronic prescription** with drugs of the ATC Classification System groups corresponding to VKA or DOAC (ATC B01AA07, B01AE07, B01AF01, B01AF02 or B01AF03) on the index date and, at least, during the previous 3 months.

On the other hand, by **CMBD,** we will select patients diagnosed with AF by ICD-10 code (I48.0, I48.1, I48.2 or I48.91), whose diagnosis is prior to the index day. Using ICD-10 codes, we will exclude patients who meet the criteria for valvular AF (mitral stenosis code, I05.0, I05.2, I34.2 and prosthetic valve code, Z95.2, Z95.3 or Z95.4). Thus, we will finally obtain patients diagnosed with non-valvular AF.

Once we have these two databases, we will cross-reference them and the patients who are present in both groups will mean that their reason for anticoagulation is non-valvular AF. That way, we will get our exposed cohort.

On the one hand, patients receiving VKA or DOAC, who had no previous diagnosis of AF, will be excluded (exclusion criteria). On the other hand, in theory, all patients with a diagnosis of AF should also be in the anticoagulant group (remember that our initial sample consists of patients aged ≥65 years, who already have an indication for anticoagulation).

The remaining patients will be those who will become part of the non-exposed cohort (who will neither have AF nor take any type of anticoagulant).

Subsequently, for each subject of both cohorts, we will obtain his/her socio-demographic variants (age and gender), as well as his/her GMA (which will represent the subject's multimorbidity).

Once I have the two cohorts and the characteristics of each subject, I will obtain the 3 outcome variables (hospital admission, ventilatory support, and mortality).

For **hospital admission**, this will be obtained by CMBD-HA, where the first hospital admission with a primary diagnosis of COVID-19 (ICD-10 codes for clinical diagnosis of SARS-CoV2 infection: B34.2, B97.29, J12.81, J12.89) occurring between 2 days before and 14 days after the index day will be included. Thus, for each positive result, it will be checked whether the person has been admitted to hospital up to 14 days after the index day. To obtain hospital admission, the study time range will be extended from 29 September 2020 to 14 January 2021 (on the condition that the index day is between 1 October 2020 and 31 December 2020).

The need of **non-invasive mechanical ventilation , mechanical ventilation, orotracheal intubation or tracheostomy** will be obtained by ICD-10 codes for procedures (5A1935Z, 5A1955Z, 5A093, 5A094, 5A095, 0BH17EZ, 0B9100Z, 0B110F, 0B110Z, 0B113F, 0B113Z, 0B114F, 0B114Z) that were performed during the hospital stay.

Mortality will be obtained by RCA, where all deaths within 30 days of a hospital admission with a primary diagnosis of COVID-19 will be included. Thus, for each positive, it will be checked whether they have died 30 days after the hospital admission day. To obtain mortality information, the study range will be extended to 14 February 2021 (on the condition that the index day is between 1 October 2020 and 31 December 2020).

So these will be the data and cross-linkages that we will ask to be carried out. This cross-referencing and data collection will be carried out by AQuAS, which will ensure that all ethical and legal principles are complied with, as well as the pseudoanonymisation of the data.

Once the data is obtained, AQuAS will send us the database, where the information specified by each individual will be available.
Subsequently, we will perform the propensity score matching and statistical analysis.

Table 6. *CD-10-MC codes used to define SARS-CoV2 infection and procedures and ATC codes used to identify drug use*

ICD-10 codes for clinical diagnosis of SARS-CoV2 infection: **B342, B9721, B9729, J1281, J1289**

ICD-10 codes for diagnosis of atrial fibrillation:

- Paroxysmal atrial fibrillation: **I48.0**
- Persistent atrial fibrillation: **I48.1**
- Chronic atrial fibrillation: **I48.2**
- Unspecified atrial fibrillation: **I48.91**

ICD-10 codes for diagnosis of mitral stenosis and prosthetic valve:

- Rheumatic mitral stenosis: **I05.0**
- Rheumatic mitral stenosis with insufficiency: **I05.2**
- Non-rheumatic mitral stenosis (valve): **I34.2**
- Cardiac valve implant (functional)
  - Prosthetic: **Z95.2**
  - Specified type NCAL: **Z95.4**
  - Xenogenetic: **Z95.3**

ICD-10 codes for procedures that were performed during hospitalization:

- Mechanical ventilation: **5A1935Z, 5A1955Z**
- Non-invasive mechanical ventilation: **5A093, 5A094, 5A095**
- Orotracheal intubation: **0BH17EZ**
- Tracheostomy: **0B9100Z, 0B110F, 0B110Z, 0B113F, 0B113Z, 0B114F, 0B114Z**

ATC codes used to identify drug use:

- Acenocoumarol: **B01AA07**
- Dabigatran: **B01AE07**
- Rivaroxaban: **B01AF01**
- Apixaban: **B01AF02**
- Edoxaban: **B01AF03**

- Heparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, danaparoid, tinzaparin, bemiparin : **B01ABxx**
- Heparin combinations: **C05BA03, C05BA53, S01XA14**

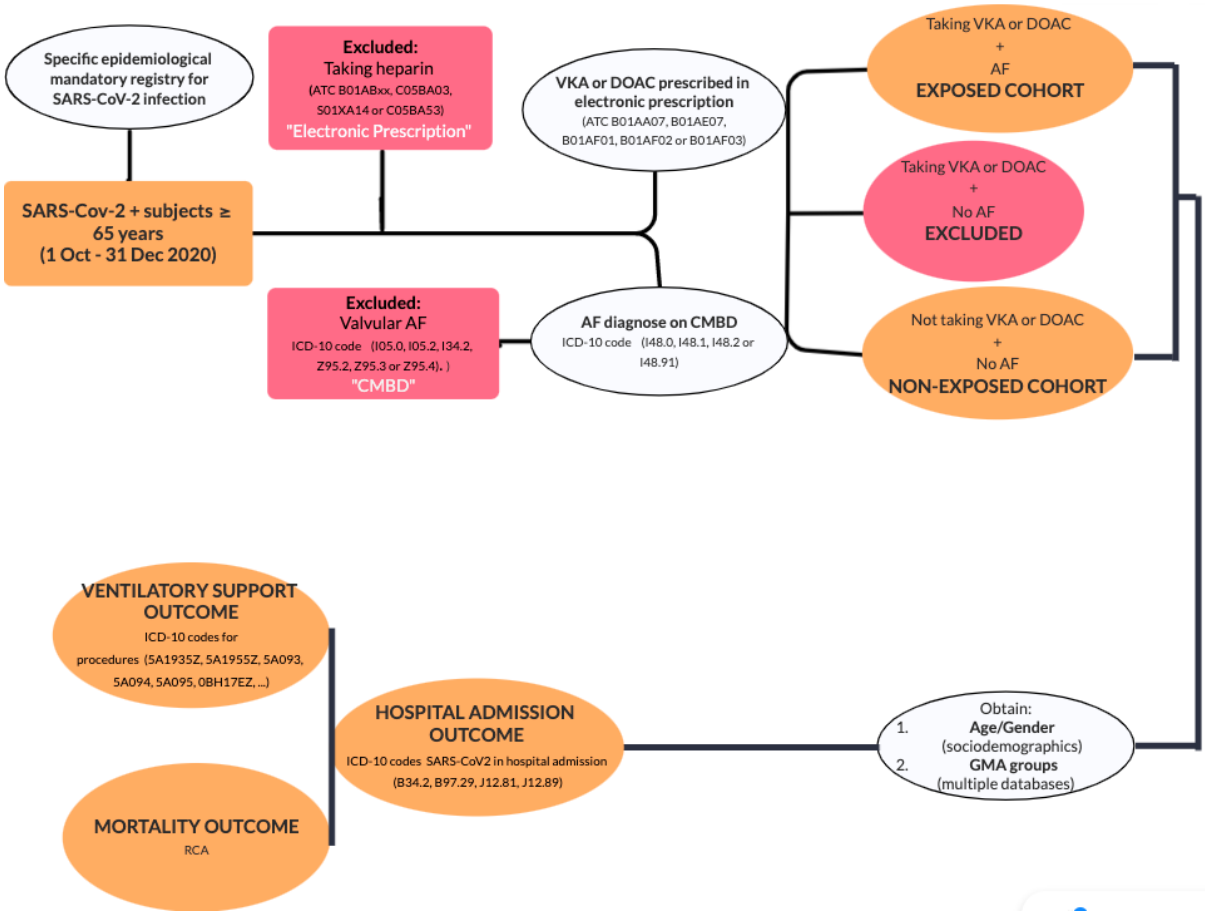

Figure 11. *Outline of data collection*

8. STATISTICAL ANALYSIS

8.1. PROPENSITY SCORE MATCHING

Using PSM can change the target population by shifting the distribution of patients characteristics contributing to the analysis. Thus, PSM are used to reduce bias in the comparison between a population who received a treatment (exposed cohort) and a control population (non-exposed cohort) (50). Therefore, the aim of PSM is to be able to attribute differences in outcomes (hospital admission, ventilatory support or mortality) to the independent variable (taking anticoagulant therapy) and not to potential cofounding variables (such as age, gender or comorbidities).

Based on gender, age and comorbidities (categorized as GMA groups), PSM will be calculated by a regression model using the nearest neighbour matching technique (greedy matching) without replacement (which means that each non-exposed subject is matched to only one exposed subject) at a 1:2 ratio of exposed cohort and non-exposed cohort. A caliper of 0.2 of standard deviation will be established as the maximum tolerated difference between matched patients, to avoid poor matching, as is considered to be the optimal caliper for PSM in observational studies (51). Patients for whom no match exists within the bound are excluded.

To perform this PSM we will use the “Matching” package in R (52), which will allow us to build the control group (to choose our control population, approximately 8212 subjects, from the approximately 41,520 subjects available to us).

To examine the equality of each covariate between the treatment and the control group, the standardized mean difference before and after matching will be calculated using the Tableone package in R (53). We will consider the groups well balanced if the standardized mean difference is <0.10 for each covariate.

8.2. DESCRIPTIVE ANALYSIS

Categorical variables will be summarized using absolute values and relative frequency. Main and secondary categorical outcomes will be summarized using absolute and relative frequencies with respective 95% confidence interval (95% CI).

Continuous variables will be summarized using means and standard deviations for normal distributions and by medians and the 25th and 75th percentiles for non-normal distributions. Kolmogorov-Smirnov test will be used to examine if continuous variables are normally distributed.

We will create contingency tables between our independent variable (taking or not anticoagulation therapy) and the outcomes.

8.3. BIVARIATE INFERENCE

- **Bivariate inference for covariables**

  Despite performing the PSM, to ensure that the covariates (age, gender and GMA group) have been well balanced in both cohorts, we will use the chi-square test for categorical variables and t-Student test in case of quantitative variables (or Mann-Whitney test in case of non-normal distribution) in order to test for significant differences between the baselines characteristics of both cohorts.

- **Bivariate inference for outcomes**

  To compare the proportions of the main and secondary outcomes between the two cohorts, the chi-square test (or Exact Fisher Test when the expected frequencies are less than 5%) will be used.

- **Bivariate analysis to determine variables associated with risk of hospital admission**

  The variables associated with hospital admission will be examined using bivariate logistic regression models. The unadjusted odds ratios (OR) and 95% confidence intervals will be determined.

8.4. MULTIVARIATE ANALYSIS

Despite the fact that with PSM we eliminate the confounding factor, we will perform a multivariate logistic regression model with all the explanatory variables.

The variables associated independently with hospital admission will be examined using multivariate logistic regression model. The adjusted odds ratios (aOR) will be determined with the corresponding 95% confidence interval.

The goodness of fit of the multivariate logistic regression model will be evaluated by the Hosmer-Lemeshow test to assess the calibration, and the area under the ROC curve (AUC) with its 95% confidence interval to estimate the discrimination ability.

Statistical analysis will be carried out by the statistical analyst.

A two-sided level of 0.05 ($p < 0.05$) will be considered statistically significant. The data will be analysed and managed using the Statistical Package for the Social Sciences (IBM SPSS) v.206. (IBM Corporation, Armonk, New York).

9. WORK PLAN AND CHRONOGRAM

9.1. RESEARCH TEAM MEMBERS

- **Study coordinator:** Its main function is to coordinate and supervise all aspects of the study. He/she will formalise the application for the use of PADRIS health data and will sign the health data delivery agreement. He/she will contribute to the review/modification of the protocol if necessary. Thus, he/she will act as the point of contact between our research team and PADRIS. He/she will also actively participate in the elaboration of the final report and its subsequent dissemination.
- **Researcher:** It will consist of one specialist in the field who will be permanently updated. Once data from PADRIS is available, he/she will actively participate in the elaboration of the final report and its subsequent dissemination.
- **Data collectors:** Data collection process will be carried out by AQuAS staff. Therefore, our research team will not need data collectors. The PADRIS data acquisition team consists of a multidisciplinary team with knowledge in computer science, statistics, epidemiology and public health. If they have any questions, they will contact our study coordinator.
- **Statistical specialist:** Will be responsible for carrying out statistical analysis.

9.2. STUDY STAGES

STAGE 0: Protocol elaboration November 2021 – January 2022

- Literature review and elaboration of the study protocol.

STAGE 1: Approval by the Ethics Committee (CEIm) February 2022- April 2022

- We will send the protocol to the Clinical Research Ethical Committee (CEIm) of the Josep Trueta Hospital, which is competent to evaluate studies related to drugs and medical devices, awaiting its approval. If necessary, we will carry out the appropriate modifications in order to obtain their approval. Taking into account that we may have to modify our study protocol, we estimate that it will take about 3 months.

STAGE 2: Formal request for access to the PADRIS database May 2022- July 2022

- The study coordinator will send a **request** to the PADRIS Programme (*padris@gencat.cat*) formalising the interest in using their database.

  The request will contain:

  1. Details of the applicant (study coordinator and affiliated organisation)
  2. Title of the study, as well as its hypothesis and objectives
  3. Description of the request and what data is necessary to be obtained
  4. Priority levels based on the current criteria (of which SARS-CoV-2 is a high priority issue)
  5. Justification of the use of their database and what benefits it can bring to the community
  6. Prior approval by CEIm

  If the formal criteria are met and the viability of the use of the requested data is confirmed, an **agreement for the transfer** of data will be signed. With the signing of the agreement, the relationship will be formalised.

  If the criteria cannot be met, the study will be readjusted to make it feasible.

STAGE 3: Data collection August 2022

- Once the agreement has been formalised, the AQuAS team will proceed to obtain the database following the guidelines that were previously established. During the process, care will be taken to ensure that the data are de-identified and do not present a very high risk of re-identification.

  Considering that this is a retrospective study where events have already happened, taking that database will not take more than 1 month.

STAGE 4: Statistical analysis September 2022 – October 2022

- Once the database is available, it will be sent to the statistical specialist, who will be able to carry out the statistical study. Once it has been carried out, it will be sent to the study coordinator.

STAGE 5: Interpretation and elaboration of a final report November 2022

- A meeting of the whole team will be held, where the results will be discussed and conclusions will be drawn. A final report will be elaborated.

STAGE 6: Publication and dissemination of the results December 2022- February 2023

- The results obtained will be published and disseminated to the scientific community. They will be presented at national and international conferences.

  The final report will also be presented to AQuAS, where the results obtained with the reuse of data will be reported. This will benefit, as much as possible, the community and will help to improve public health policies.

9.3. CHRONOGRAM

Table 7. *Study chronogram*

Year	2021		2022												2023	
Months	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Stage 0 Protocol Elaboration																
Stage 1 Approval by CEIm																
Stage 2 Request for PADRIS database																
Stage 3 Data collection																
Stage 4 Statistical analysis																
Stage 5 Elaboration of a final report																
Stage 6 Dissemination of the results																

10. ETHICAL AND LEGAL CONSIDERATIONS

The study will be conducted in compliance with the ethical principles established by the Helsinki Declaration, which was adopted in 1964 and last updated in 2013 (54), and in compliance with the principles stipulated in the Belmont report, with respect to autonomy, justice, beneficence and non-maleficence (55).

Before submitting the project to PADRIS, the protocol will be presented to the "Comitè Ètic d'Investigació amb Medicaments (CEIm)" of the Hospital Universitari Josep Trueta for approval, regulated by Royal Decree 1090/2015 (56).
The committee will check that our study fulfils the ethical principles and any modifications they propose will be implemented in a modified protocol.

Once the CEIm approves the project, the project will be submitted to PADRIS.
PADRIS, under the AQuAS regime, will be responsible for data collection (following our guidelines), which will depersonalise and anonymise all data. A statistical re-identification analysis will be carried out, where the corresponding risk level will be identified and submitted for the approval of the operating committee. Patients with a high risk of re-identification may be excluded from the study.
PADRIS is equipped with a multidisciplinary monitoring committee to ensure the correct application of ethical principles. It also has the right to consult a CEIm for further assessment if considered appropriate.
Thus, only a full unidentifiable database will be available to our research team.
Due to the retrospective character of the study and pseudo-anonymisation, this study will be exempt from the requirement of informed consent.

In this way, it is not necessary to contact each subject to request their informed consent.
The whole process will be carried out in compliance with Law 41/2002 "*Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica"* (57) and the Organic Law 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights, especially its additional provision 17.2 (58).

The study aims to analyse the protective effect of anticoagulants and to contribute, if possible, to the evaluation of possible effective treatments to prevent severe COVID-19. The observational study will be conducted in accordance with Royal Degree 957/2020 with the "guidelines on post-authorisation observational studies for medicinal products for human use" (59).

This study will be classified as "EPA-OD" (Post-authorisation studies with a design different from prospective follow-up, such as cross-sectional or retrospective studies).

EPA-OD studies do not require authorisation by the AEMPS "Agencia Española de Medicamentos y Productos Sanitarios" or by the competent bodies of the Autonomous Regions where they are to be performed.

All researchers will have to declare no conflict of interest and will agree to publish the study, regardless of the results obtained.

11. STUDY LIMITATIONS

The study has a number of limitations that need to be taken into account in order to minimize them.

- First, we found the inherent limitations of an observational cohort.

  In the analysis of covariates, in order not to omit any pathology that could act as a confounding variable, we based ourselves on the GMA groups, where all pathologies are taken into account.

  However, not all individuals classified in a group will present equal degrees of disease, with small differences among them.

  During matching we did not take into account some current medications; some treatments used for autoimmune diseases might influence the severity of the disease. Nevertheless, there is no factor that makes us believe that any of the 2 cohorts is more likely than the other to take these drugs.
- We do not collect information regarding the daily dose of anticoagulant treatment per patient, where the dose could influence on the results. However, because we assess chronic treatments, we consider that prolonged administration of higher doses than prescribed would not be feasible due to side effects.
- Another possible limitation is that we get the drug information from the electronic prescription, but we cannot ensure its adherence. However, because they are chronic treatments, we ensured adherence by checking that they had been prescribed for at least the previous 3 months.
- As our data is obtained from registers of health administration of Catalonia, which are fed by physicians diagnoses, hospital discharge or medicines prescribed on electronic prescription, we may be faced with limitations inherent to administrative information.
- Another possible limitation is the subjects whose characteristics are not known, because they have not had any contact with public health institutions (the PADRIS database does not take into account the medical records of private health centres).

  In this sense, hospitalisations in private hospitals are not available in this analysis. However, during the pandemic, all private hospitals reported COVID-19 cases to the public health system, so we can be sure to identify almost all cases.

- In our study, we will not take into account the anticoagulation regimen carried out during hospitalisation. This may influence our secondary outcomes, such as the need for ventilatory support and mortality.

  However, it will not influence our primary outcome, hospital admission.
- Finally, the cause of death will not be no captured, so there is a possibility that non-COVID-19 related deaths may occur during the study period.

  However, because we limit mortality to 30 days post-hospitalisation, we are very confident that the vast majority of deaths will be due to the disease itself or to complications related to it.

12. BUDGET

- **Personal expenses**

  We include the salary of one researcher and the statistician.

  - Researcher: It has been estimated that it will take three months to produce the final report and disseminate the results. 2.500 euros per month will be paid to him/her.
  - Statistician: It has been estimated that 80 hours will be needed to carry out the corresponding analysis. 50 euros/hour will be paid, so we have calculated a cost of 4.000 euros.

- **Execution expenses**

  No expenses have been involved in the literature review through articles and journals. Therefore, there is no additional cost.

- **Publication and dissemination**

  We will publish the study in an open access scientific journal (this is one of the conditions imposed by PADRIS for the use of its data). We estimate that this will cost approximately 2000 euros.

  We will disseminate the results of the study at a national and an international congress. The study coordinator will represent the entire team. We estimate that each congress will present a cost of 1000 euros including inscription, travel costs, accommodation and diets. Thus, we estimate a cost of approximately 2000 euros.

Table 8. *Study budget*

BUDGET			
Type of expenses	**Unit cost**	**Hours/Unit**	**Total**
Personal expenses			
-Researcher	2.500 €/month	3 months	7.500 €
-Statistician	50 €/hour	80 hours	4.000 €
Publication and dissemination			
-Scientific journal publication	2.000 €		2.000 €
-Congresses (inscriptions, travels, accommodation, diets)	1.000 €	2 congresses	2.000 €
TOTAL			**15.500 €**

13. IMPACT

Although the vaccination campaign has already started and almost 80% of the people in Catalonia are fully vaccinated, the appearance of new mutant variants leads to the fact that we are still in a pandemic situation, where health systems continue to be overwhelmed (7). Therefore, the search for the most effective treatments and their optimal dosage continues to be a priority.

As mentioned above, there is currently no clear evidence on optimal anticoagulation regimens in patients admitted to hospital for COVID-19.

Although the most recent studies (HEP-COVID study) seemed to demonstrate a benefit of therapeutic doses over prophylactic doses, more evidence is needed to modify the therapeutic guidelines (which currently recommend the use of prophylactic doses).

Thus, until more rigorous clinical trials emerge, the collection and analysis of retrospective data on patients on chronic anticoagulation therapy could provide evidence of anticoagulation on COVID-19 morbidity and mortality.

We believe that this study could have a great impact, because although we evaluated the protective impact of anticoagulants, we strongly believe that this could be extrapolated in therapeutics and could help to clarify therapeutic guidelines.

Thus, if our hypothesis is confirmed, these data could provide the impetus for further clinical trials and could be extrapolated to therapeutics if appropriate, suggesting a clear benefit in the use of these drugs.

14. FEASIBILITY

We believe that our study is feasible because:

- On the one hand, due to the retrospectivity of the study and that data acquisition will be carried out by the AQuAS team (which is publicly funded), the budget of the study will be very affordable.
- Regarding the sample size needed to obtain statistically significant differences, given that we are conducting a population-based study, it will not represent a problem to obtain it.
- With respect to obtaining our database via PADRIS, we believe it is feasible because all the requested data are available in their database.

  PADRIS will open a call for studies in early 2022. In case PADRIS received multiple study proposals and they had to apply prioritization criteria, we strongly believe that we would score highly on these criteria. We have reviewed the prioritisation criteria and we have contacted the PADRIS coordinator *(joanalbert.escofet@gencat.cat*) to establish a first informal contact in order to know what the prioritisation criteria are. We strongly believe that our study meets many of these criteria.

  Some of these criteria that our study meets are:

  - Demands a range of data available in their database, with no excessive workload.
  - Can provide a benefit to the community
  - Is based on an issue of major importance

  These three factors represent three very important criteria for prioritization. We therefore strongly believe that such a database would be feasible.
- Our research team will be sufficiently qualified for its role.

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16. ANNEX

ANNEX I: DIAGNOSIS OF COVID-19

According to WHO there are three different scenarios regarding Case Definition of SARS-CoV-2 infection:

- **SUSPECTED CASE**
  - **A)** A person who meets clinical AND epidemiological criteria*
    - Clinical criteria includes acute onset of fever AND cough; OR acute onset of three or more: fever, cough, fatigue, myalgia, headache, coryza, dyspnea, nausea, diarrhoea, altered mental status
    - Epidemiological criteria includes residing, travel or working in a high risk area of transmission of virus anytime within the 14 days prior to symptom onset
  - **B)** A patient with severe acute respiratory illness (history of fever above 38 degrees, cough; that requires hospitalization)
  - **C)** Asymptomatic person not meeting epidemiologic criteria with a positive SARS-CoV-2 Antigen-Rapid Diagnostic Test (RDT) [1]
- **PROBABLE CASE**
  - **A)** A patients who meets clinical criteria and is a contact of a confirmed case
  - **B)** A Suspicious case with chest imaging test showing findings suggestive of COVID-19 disease
  - **C)** A person with new onset anosmia or ageusia without other plausible cause
  - **D)** Death due to respiratory distress, with no other plausible cause, in a subject who was a contact of a probable or confirmed case
- **CONFIRMED CASE**
  - **A)** A person with a positive Nucleic Acid Amplification Test (NAAT)
  - **B)** A person with a positive SARS-CoV-2 Antigen-RDT meeting probable case definition or A/B suspected case definition
  - **C)** An asymptomatic person with a positive SARS-CoV-2 Antigen-RDT who is a contact of a confirmed or probable case

1 NAAT is required for confirmation

ANNEX II: ADJUSTED MORBIDITY GROUPS

Adjusted morbidity groups (GMA) is a morbidity classification that is capable of stratifying the population using data from our health system.

As specified above, a total of 31 GMA are obtained from the combination of morbidity groups and levels of complexity.

For the aggregation, it is necessary to have the morbidity of the users available (coded diagnoses) and the date of their diagnosis. To obtain these data, information from primary care, hospitalization, emergency, outpatient, mental health, etc. is used.
The coded diagnoses are obtained using ICD-9 MC, ICD-10.

Because more than 10,000 codes can be found to code diseases, the codes are grouped in Diagnostic Code Groupings (DCA), with the intention of reducing the codes. Based on the DCA, mortality, care needs and pharmacological prescriptions we can classify the subjects in their morbidity group and complexity.

Based on the above information, the following tasks are carried out:

1. **Morbidity Group (GM) assignment.** The assignment of the GM is carried out by priority levels according to the following sequence, i.e. if in one step the insured person fulfils the condition, the following steps are not considered:
    a. If the insured is identified as suffering from **active neoplasm** then this morbidity group is assigned.
    b. If the insured person is identified as having a pathology related to **pregnancy and/or childbirth,** then she is assigned to this morbidity group.
    c. If the insured has **4 or more systems affected by chronic disease** then he/she is assigned to this morbidity group.
    d. If the insured has **2 or 3 systems affected by chronic disease** then he/she is assigned to this morbidity group.
    e. If the insured has **1 system affected by chronic disease** then this morbidity group is assigned.

f. If the insured person has an identified **acute illness** then this morbidity group is assigned.

g. In the last case, he/she is assigned to the morbidity group of the **healthy population.**

2. **Assignment of the level of complexity (C):** The assignment of the level of complexity of the insured person is carried out separately by morbidity groups and taking into account the total complexity of the insured person.

Finally, the subjects are classified (49).

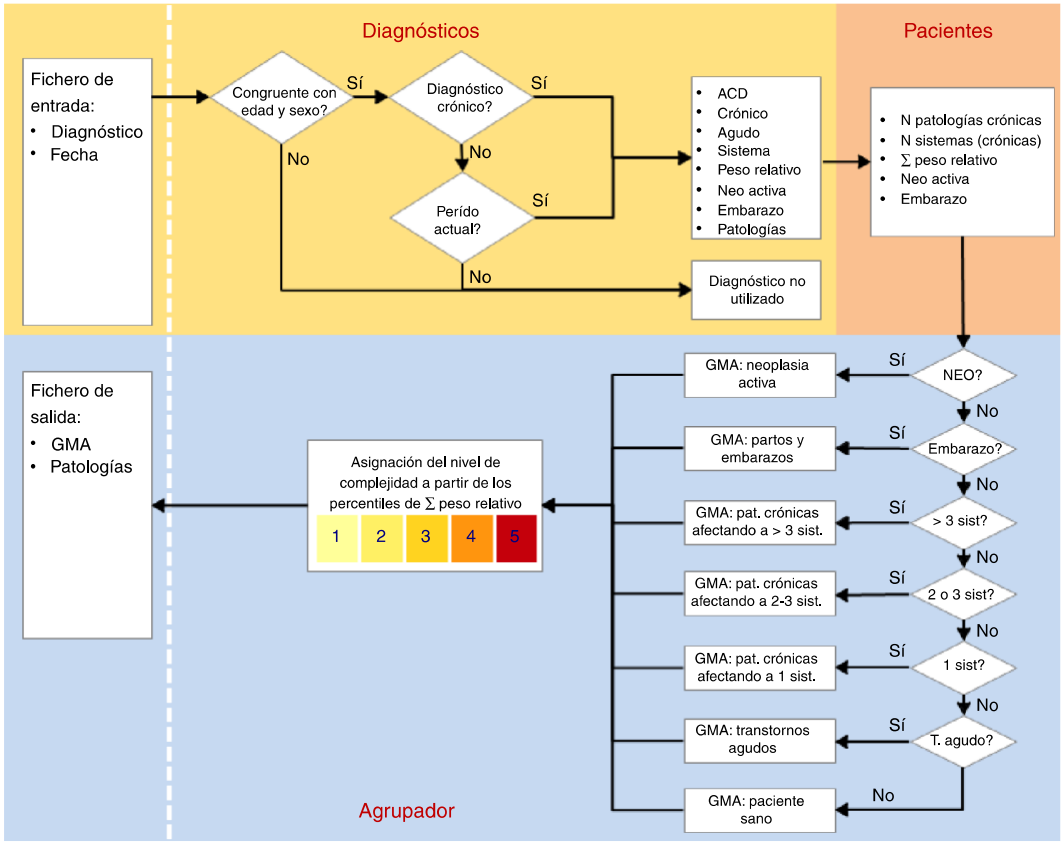

Figure 12. *Clustering algorithm (49)*

ANNEX III: PADRIS

PADRIS is a programme that corresponds to the organisation "l'Agència de Qualitat i Avaluació en Salut (AQuAS)". It is an organization whose objective is to provide related health data to the scientific community in order to promote research through the cross-referencing of health data generated by the "Sistema Sanitari Integral de Utilització Pública de Catalunya (SISCAT)", in accordance with the programme's legal and regulatory framework, ethical principles and principles of transparency towards the public (46).

In order to access its database, certain conditions and criteria must be met.

Firstly, PADRIS is aimed at:

1. Research centres accredited by the *Institució Centres de Recerca de Catalunya (CERCA)*
2. SISCAT centres
3. Public universities
4. Health public administration

In our case, we will be linked to the University of Girona (UdG).

Subsequently, an application for access to the Programme will be made, which must meet certain eligibility criteria:

1. First of all, it must be a quality study with a significant degree of relevance.
2. Each project submitted must explicitly clarify what information needs it presents, what its objectives are and what benefits it will bring to the public. It also has to commit itself to inform AQuAS about the results obtained.
3. All applications must be validated by a CEIm

Once the application is processed and accepted, an agreement has to be signed between the research centre and the AQuAS responsible person.
This agreement regulates the conditions of delivery of health data and establishes the purpose of the transfer, the security and confidentiality measures required, the duration of the contract, among others.

The programme will be managed through the coordinated work of 2 Councils and 2 Committees.

- The **AQuAS Board of Directors** is responsible for the strategic direction and supervision of the programme.
- The **Advisory Board**, made up of experts in biomedical research and statistics, advises on the scientific-ethical level.
- The **Monitoring Committee** is in charge of the scientific-ethical monitoring tasks, risk management and the correct implementation of the programme.
- The **Operating Committee** will be responsible for the proper execution of the project.

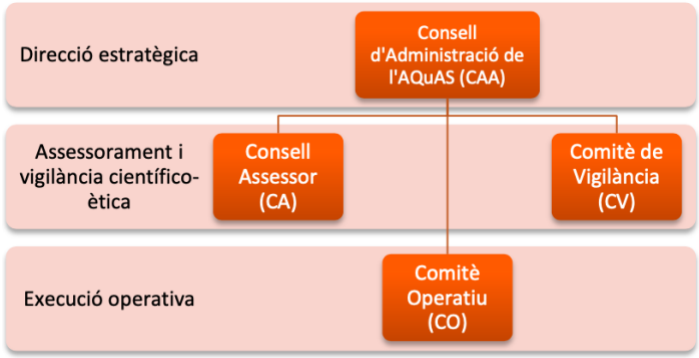

Figure 13. *PADRIS Governance Organisation organigram (46)*

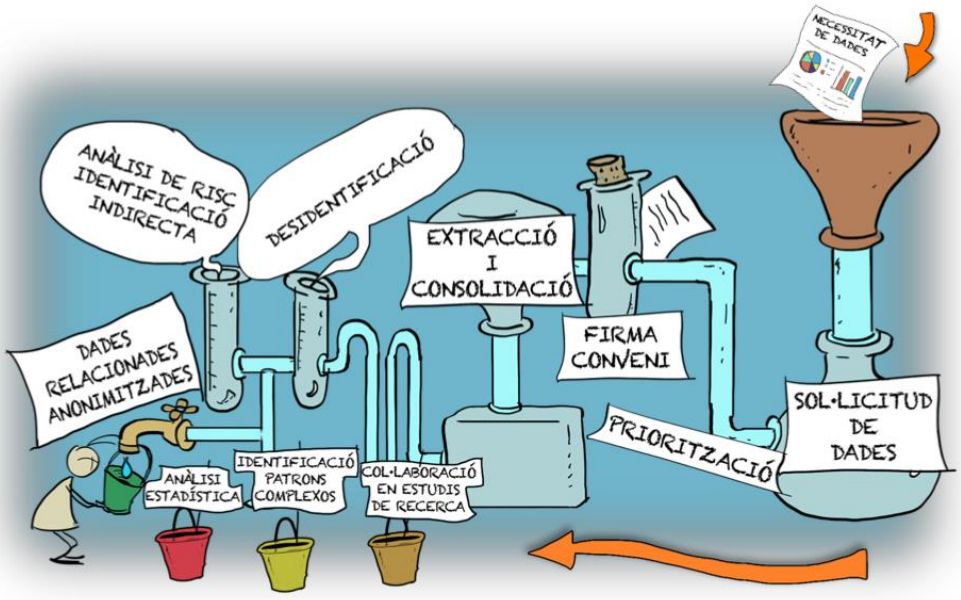

Figure 14. *Data collecting process (46)*