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Antithrombotic agent's effects in thrombotic events caused by Covid-19: A systematic review

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ABSTRACT
There is an association between COVID-19 and an increased risk of thrombotic events. However, the incidence of such events changes due to the severity of the disease. The aim of this paper was to evaluate the effects of antithrombotic agents on thrombotic events caused by COVID-19. This is a systematic review, with descriptive qualitative evaluation, carried out between 05/28/2021 and 06/21/2021. Scientific articles were searched, from 2019 to 2020, in SciVerse Scopus, Web of Science, PubMed and SCIELO databases. As a result, it was possible to observe that the most commonly used drugs for prophylaxis, and therapeutic of thrombotic events, in patients with COVID-19 were low molecular weight heparin, unfractionated heparin, fondaparinux, oral anticoagulants, antiplatelet agents, argatroban, aspirin, rosuvastatin, vitamin K antagonists, alteplase and other unspecified oral anticoagulants, used in monotherapy or associated. The proposed therapeutic schemes are a variation of the dosage of the drugs used. The use of therapeutic dose (tAC) and prophylactic dose (pAC); tAC, pAC and intermediate dose (iAC); pAC and subtherapeutic dose (subtAC); pAC, subtAC, therapeutic dose of antiplatelet (tAP) and prophylactic dose of antiplatelet (pAP) were found. The drugs used, with the exception of aspirin, showed some type of beneficial response in the recovery of the patient with COVID-19. The best treatment used was therapeutic dosing with enoxaparin, argatroban, fondaparinux and oral anticoagulants. According to the articles evaluated in this review, promising results of the use of antithrombotic agents in C0VID-19 are observed, but more studies are needed.

Keywords: SARS-CoV-2, COVID-19, antithrombotic therapy, antiplatelet therapy.

1 INTRODUCTION

The SARS-COV-2 virus, which is responsible for causing severe acute respiratory syndrome, is composed of a single stranded positive RNA molecule (RNA+) containing approximately 30,000 nucleotides and is the etiologic agent of coronavirus 2019 (COVID-19) disease (Ceraolo & Giorgi, 2020). SARS-COV-2 belongs to the family Coronaviridae, which bears much similarity to the virus

that caused the 2003 SARS outbreak, named, SARS-COV (Benvenuto, 2020). Since its emergence in the city of Wuhan in China in December 2019, COVID-19 has spread rapidly throughout the world, and was considered a pandemic by the World Health Organization (WHO) in March 2020 (PAHO, 2020).

Its severity is very variable, with some infected patients being asymptomatic, or having mild symptoms related to the upper respiratory tract; in other cases, the disease may progress to a viral pneumonia with acute respiratory distress syndrome, multiple organ dysfunction and evolve to death (Zhou et al., 2020). According to Morales et al. (2020), the most common symptoms presented in COVID-19 are cough, fever, and dyspnea. At the onset of the disease, depending on the individual, one may observe myalgia, asthenia, productive cough, headache, dizziness hemoptysis, and gastrointestinal symptoms that can occur even if there are no respiratory manifestations (Huang et al., 2020).

Symptoms arising from complications of COVID-19 are respiratory failure, cardiac, hepatic and renal damage, as well as arrhythmias, coagulopathies, shock and secondary infections (Gouveia & Campos, 2020). They may also present with bilateral pneumonia, systemic inflammation, endothelial dysfunction, and coagulation activation (Longhitano et al., 2020). Some studies have shown an incidence of venous thromboembolic events in patients with COVID-19 (Pancani et al., 2021). Pereira et al. (2021), in a literature review, noted platelet changes, which presented with thrombocytopenia and thrombocytosis. Regarding the alteration in platelet morphology, changes were observed in the blood smear, where the presence of giant platelets were found, being mostly hyperchromatic and vacuolized, with the presence of megakaryocytes, and also large platelet clusters (Pereira et al., 2021).

Activation of coagulation is considered a very important distinctive clinical feature in patients affected by the more severe forms of the disease (Spiezia et al., 2020). Higher rates of venous thromboembolic events have been found to be present in patients with COVID-19 (Helms et al., 2020; Klok et al., 2020 & Middeldorp et al., 2020). The reported incidence of thrombotic events varies depending on disease severity and thromboprophylaxis strategies (Pancani et al., 2021). In addition, disseminated intravascular coagulation (DIC) is correlated with increased mortality rates in COVID-19 (Batschauer & Jovita, 2020).

Patients with COVID-19 often have coagulation disorders, especially those who develop the severe form of the disease. Through a multicenter retrospective study done in the first two months of the epidemic, 46.4% of patients with confirmed infection had D-dimer values (0.5 mg/L), with higher results observed in more severe cases (Middeldorp et al., 2020). Also, according to the elevation of D-dimer levels, another study demonstrated its increase along with prolonged prothrombin time (PT) and decreased fibrinogen and platelets. It was reported in patients who did not survive, some ischemic

changes such as ecchymosis of fingers, toes and worsening of cardiovascular and renal function (Li, Lu & Zhang, 2020).

Other markers were also measured, such as activated partial thromboplastin time (APTT), fibrinogen, antithrombin III (AT III) and fibrin degradation products (FDPs). Significantly higher levels of FDPs, as well as longer APTT, were recorded in the non-survivors' group when compared with the survivors' group. In addition, both fibrinogen and AT III had significantly lower levels. Such findings are suggestive for activation of coagulation and deregulated generation of thrombin and fibrinolysis. DIC was reported in most deaths of patients with COVID-19. Individuals, who develop virus infection, may experience sepsis associated with organ dysfunction. (Tang, Li, Wang & Sun, 2020).

As for anticoagulant therapy, the use of Low Molecular Weight Heparin (LMWH) is considered in all cases of COVID-19, even in non-critical cases, although there are contraindications due to the possibility of bleeding associated with low platelets. Anti-inflammatory properties of heparin have been described as beneficial in SARS-CoV-2 infections, in which pro-inflammatory cytokines are extremely elevated, leading to improvement with better prognosis and decreased mortality (Batschauer & Jovita, 2020; Tang, N & Thachil, 2020).

Because COVID-19 is a recent and serious infectious disease, many studies are needed in order to bring reliable data, to make more appropriate therapeutic conducts, since there is still no specific treatment. It seems that Venous Thromboembolism (VTE) is a very frequent complication associated with more severe cases of COVID-19. The use of LMWH in prophylactic and therapeutic doses after hospital discharge has shown clinical improvement and low risk of bleeding complications. That said, there is a high risk of patients developing VTE in COVID-19, and the heparin administration, with its various dosing options, should be performed aggressively in patients who are not at high risk of bleeding, especially in patients with multiple risk factors such as obesity, diabetes, and cancer (Rossi, 2020). The administration of therapeutic doses is not proven by evidence in patients who have not been diagnosed with thromboembolism or who do not require extracorporeal membrane oxygenation. The risk-benefit ratio still needs to be better analyzed in prospective studies before deciding on a more aggressive anticoagulation approach (Joly, Siguret & Veyradier, 2020). Within this context, several studies have already confirmed how beneficial anticoagulant use is in reducing the risk of these complications and contributing positively to patient survival (Aghajani et al., 2021).

Recently, statins are being used as an alternative in the treatment of COVID-19. Although their traditional use is employed in the treatment of serum cholesterol lowering, their anti-inflammatory and antithrombotic properties in the treatment of COVID-19 have drawn attention. Statins appear to have the potential to decrease both the impact of myocardial injury and thrombotic events correlated with the more severe forms of COVID-19 (Bikdeli, Madhavan & Gupta et al., 2020). According to a single

cohort longitudinal study, dyslipidemia may act as a protective factor for pulmonary embolism (PE). Patients without cardiovascular risks recorded in their medical records had a nine times higher risk for PE when compared to patients with dyslipidemia. The hypothesis behind this, would be that patients previously treated with statins, showed a potential benefit, due to the immunomodulatory action or preventing cardiovascular damage (Gomez et al., 2021).

COVID-19 is associated with intense inflammation and a pro-thrombotic state that leads to a poor prognosis, resulting in an increase in FDPs as well as D-dimer, with possible thromboembolic events in the venous and arterial circulation. These findings relate to the great association between thrombotic and inflammatory events, since coagulation factors and platelets act directly in modulating the host immune response, leading to pro-inflammatory events that are independent of hemostatic effects. Therefore, the systematization of evidence on the use of anticoagulants and antiplatelet agents in thromboembolic events in patients with COVID-19 is justified and relevant. Thus, the objective of this work was to perform a systematic review on the effects of anticoagulants and antiplatelet agents in thrombotic events caused by COVID-19.

2 METHODOLOGIES

This work consisted of a systematic review regarding the topic "effect of anticoagulants and antiplatelet agents on COVID-19 thrombotic events", performed between 05/28/2021 and 06/21/2021, by searching for original and experimental scientific articles, published in English, from 2019 to 2020, in the SciVerse Scopus, Web of Science, PubMed and Scientific Electronic Library Online databases. The following were used as descriptors: "COVID-19" or "SARS-CoV-2" or "coronavirus" or "severe acute respiratory syndrome coronavirus 2" or "2019 new coronavirus" or "2019 novel coronavirus" or "2019-nCoV" AND "anti-coagulants" or "anti-coagulant" or "antithrombotic" or "antithrombotics" or "antithrombotic therapy" or "antithrombotic treatment" or "antithrombotics therapy" or "antithrombotics treatment "or "anti-coagulant treatment" or "anti-coagulant therapy" or "anti-coagulants treatment" or "anti-coagulants therapy" or "antiplatelet" or "antiplatelets" or "antiplatelet treatment" or "antiplatelets treatment" or "antiplatelet therapy" or "antiplatelets therapy". The inclusion of the article in this review was performed according to the previously established eligibility criteria: original and experimental scientific articles, published in the English language, period from 2019 to 2020, considering a combination of relevant aspects to answer the main objective of the review, described below.

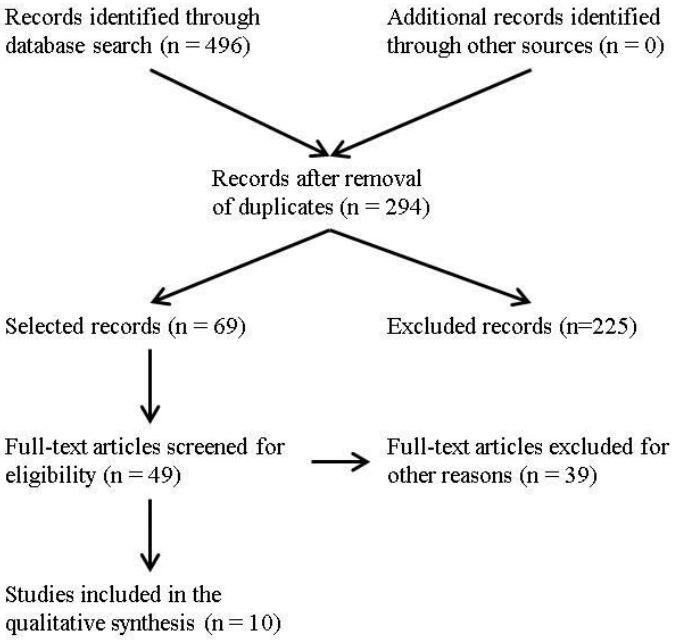
Systematic reviews, narrative reviews, integrative reviews, meta-analysis, book chapters, event abstracts, case reports, editorials, and opinion articles were excluded. Sequentially, the articles obtained were selected for the reading of the title and abstract, and should have contained terms and subject matter related to the effect of anticoagulants and antiplatelet agents on COVID-19 thrombotic

events. Subsequently, the articles that met the inclusion and exclusion criteria were read in full with data extraction. This systematic review had a descriptive qualitative evaluation. To avoid bias, the selections of articles and data extraction were carried out independently by three reviewers, with a subsequent consensus meeting to resolve discrepancies. The systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA (Page, et al. 2021).

3 RESULTS AND DISCUSSION

At the time of this systematic review, with the search and selection of articles made through scientific databases, 496 articles were found referring to the proposed theme (Figure 1).

Figure 1. Search process and article selection, via databases.



After all the criteria were applied, only 10 scientific articles were catalogued, because they faithfully followed the objective of the work. The remaining articles were excluded for not meeting the study objective and for fitting the exclusion criteria. The articles reviewed and that met the inclusion criteria are listed in Table 1, 2, 3 and 4.

In the 10 articles selected for this review, a predominance of patients aged over 55 years diagnosed with COVID-19 was observed (Table 1). The main comorbidities found in these patients were hypertension, diabetes, obesity, hyperlipidemia, chronic obstructive pulmonary disease (COPD), and asthma. According to the Centers for Disease Control and Prevention (CDC, 2021), elderly people are more likely to develop severe complications and/or die from COVID-19. Souza et al. (2021) conducted a study regarding deaths from COVID-19 in Brazil and the most recorded comorbidities were heart disease (40.1%), diabetes (28.4%), obesity (10.3%), neurological diseases (5.0%), kidney

diseases (4.7%), and pneumopathies (4.5%). According to Singh et al. (2020), patients who have diabetes, hypertension, cardiovascular and cerebrovascular diseases, COPD, and cancer were associated with an increased risk of having more severe symptoms of COVID-19, with people with cerebrovascular diseases, COPD, and cancer having a higher risk of mortality. Also, in the present review, it was found that the majority of hospitalizations were male with 7,141 patients, while female patients were 6,722. The length of hospitalization ranged from 13 to 74 days, with a mean of 44.3 days.

Table 1 – Demographic data of the studies

Author	Sample size (n)	Sample age	Sample gender	Hospitalization (days)	Comorbidities
Cardillo et al. 2021.	N = 100 patients	< 40 years: 9 (9%) 40 - 60 years: 51 (51%) ≥ 60 years: 53 (53%)	♀: 37 (37%) ♂: 63 (63%)	02/18/2020 to 04/30/2020 (73 days)	Unreported
Ionescu et al. 2021.	N=3,717 patients	average age: 64.5 years	♀: 1,792 (51.5%) ♂: 1,688 (48.5%)	03/13/2020 to 05/05/2020 (54 days)	hypertension, hyperlipidemia, coronary artery disease, peripheral arterial disease, heart failure, stroke/transient ischemic attack, atrial fibrillation, chronic kidney disease grade 3 or higher, hemodialysis dependence, history of malignancy, history of venous thromboembolism, immunocompromised state, connective tissue disease, chronic lung disease
Friedrich et al. 2020.	N=31 patients	average age: 60 ± 15 years	♀: 10 (32%) ♂: 21 (68%)	04/06/2020 to 05/13/2020 (38 days)	cardiovascular, pulmonary, diabetes, renal, obesity, coagulation disorders, neoplasm
Sahai et al. 2021.	N= 1,936 patients	Unreported	No aspirin ♀: 847 (51.3%) ♂: 804 (48.7%) Aspirin ♀: 113 (39.6%) ♂: 172 (60.4)	03/13/2020 to 05/13/2020 (62 days)	hemodynamic instability; COPD; asthma; diabetes; hypertension; coronary artery disease; heart failure; cancer; history of immunosuppressive treatment transplantation; multiple sclerosis; connective tissue disease; inflammatory bowel disease; immunosuppressive disease
Frohlich et al. 2021.	N= 6,637 patients	< 60 years (31.8%) 60-69 years (16.9%) 70-79 years (20.9%) 80-89 years (25.2%) ≥90 years (5.3%)	♀: 3,132 (47.2%) ♂: 3,505 (52.8%)	02/01/2020 to 04/15/2020 (75 days)	hypertension, renal failure, diabetes, atrial fibrillation, heart failure, pulmonary circulatory disorders
Giannis et al. 2021.	N = 146 patients (118 VTE)	18–59 years: 43.2% 60-75 years: 26.7% >75 years: 30.1%	♀: 52 (35.6%) ♂: 94 (64.4%)	03/01/2020 to 04/27/2020 (58 days)	hypertension, diabetes, hyperlipidemia, chronic lung disease (asthma and COPD), coronary artery disease, heart failure, chronic kidney disease/end-stage renal disease, chronic liver disease, cancer, peripheral arterial disease/peripheral vascular disease; cerebrovascular disease; prior history of VTE

Li et al. 2021.	N= 1,125 patients	Average age: 58.3 years	♀: 564 (50.1%) ♂: 561 (49.9%)	21 (± 13) days	hypertension, diabetes; coronary artery disease
Pesavento et al. 2020.	N= 324 patients	average age: 71 years	Prophylactic Dose (N = 240): ♀: 110 (45.8%) ♂: 130 (54.2%) Sub therapeutic Dose (N = 84): ♀: 33 (39.3%) ♂: 51 (60.7%)	02/26/2020 to 04/06/2020 (41 days)	obesity, cancer, venous insufficiency, personal or family history of VTE, known thrombophilia, or continuous treatment with hormonal or antipsychotic drugs
Escalard et al. 2020.	N = 10 patients	COVID-19: average age: 59.5 years non COVID-19: average age: 72 years	♀: 2(20%) ♂: 8(80%)	03/01/2020 to 04/15/2020 (46 days)	hypertension, diabetes; hypercholesterolemia
Longhitano et al. 2020.	N= 74 patients	average age: 68.6 years	ICU ♀: 3 (16.6%) ♂: 15 (83.3%) Non-ICU ♀: 27 (48.2%) ♂: 29 (51.8%)	05/18/2020 to 05/30/2020 (13 days)	atrial fibrillation, chronic renal failure, obesity, diabetes, cardiovascular disease, COPD, asthma, cancer.

The main thrombotic outcome reported was VTE, reported by 6 (66.6%) of the 10 studies, these being: Cardillo et al. (2021); Ionescu et al. (2021); Sahai et al. (2021); Giannis et al. (2021); Pesavento et al. (2020); Longhitano et al. (2020). The next most reported outcome was Deep Vein Thrombosis (DVT), cited by 5 (55.5%): Friedrich et al. (2020); Frohlich et al. (2021); Giannis et al. (2021); Li et al. (2021) and Longhitano et al. (2020). PE was cited by 5 (55.5%): Friedrich et al. (2020); Frohlich et al. (2021); Giannis et al. (2021); Li et al. (2021) and Longhitano et al. (2020). Other events, such as stroke, acute myocardial infarction (AMI), myocarditis, pulmonary edema, gastrointestinal tract bleeding, intracranial hemorrhage, and transient ischemic attack, have also been reported (Table 2, 3, 4). All events are observed in patients who were using some antiplatelet and/or antithrombotic drug during hospital stay, either in the prophylaxis or therapy.

Table 2: Data regarding the study type and objective in COVID-19.

Author	Study type	Study objective
Cardillo et al. 2021.	Retrospective cohort	To evaluate the antithrombotic and anti-inflammatory effects of fondaparinux and enoxaparin in patients with COVID-19 according to selected laboratory markers in the FONDENOXAVID study.
Ionescu et al. 2021	Retrospective multicenter cohort analysis	To evaluate the impact of using different doses (therapeutic and prophylactic) of anticoagulant on survival in patients with COVID-19.
Friedrich et al. 2020	Single-center retrospective study	To investigate coagulation markers and the incidence of thromboembolic events in COVID-19 patients receiving anticoagulants.
Sahai et al. 2021	Cohort, retrospective studies conducted by consulting medical records	To determine whether the antiplatelet effect of aspirin can reduce the risk of myocardial infarction, stroke, and venous thromboembolism in patients with COVID-19.
Frohlich et al. 2021	Retrospective cohort	To investigate the impact of long-term concomitant use of ACE inhibitors and oral anticoagulant, on clinical outcomes in hospitalized patients with COVID-19.
Giannis et al. 2021	Retrospective cohort	To identify the incidence of VTE and mortality in patients with initial presentation of COVID-19.
Li et al. 2021	Retrospective cohort	To investigate the prevalence of systemic thromboembolism, venous thromboembolism, bleeding and mortality in relation to underlying risk factors and also to evaluate the impact of anticoagulation use in hospitalized patients with COVID-19.
Pesavento et al. 2020	Retrospective cohort	To assess the incidence of relevant bleeding complications in association with the antithrombotic strategy.
Escalard et al. 2020	Experience report	To describe the initial experience treating patients with COVID-19 presenting with acute ischemic stroke due to large vessel occlusion during the first 6 weeks of the COVID-19 outbreak.
Longhitano et al. 2020	Prospective and observational study	To evaluate the thrombotic risk in COVID-19 patients presenting with pneumonia and acute respiratory failure and compare populations treated with three different antithrombotic prophylaxis protocols.

The most commonly used drugs were unfractionated heparin (UFH), LMWH (enoxaparin, fondaparinux), antiplatelet agents (aspirin), direct thrombin inhibitors (argatroban), oral anticoagulants such as Vitamin K Antagonist (VKA), as well as other direct oral anticoagulants (DOACs) not specified in the study, fibrinolytics (alteplase) and Statins (Table 3).

Table 3: Data regarding the therapy employed in COVID-19.

Author	Thrombotic event (*1)	COVID-19 Medication (*2)	Anticoagulant/antithrombotic medication (*3)
Cardillo et al. 2021	VTE	AB; IB; ES; IM NSAIDs; ACF	Enox - 40 mg or 60 mg 1x day (n=62); ♂: 40 (65%) ♀: 22 (35%) Fond – 2.5 mg 1x day (n=38); ♂: 23 (61%) ♀: 15 (39%)
Ionescu et al. 2021	TIA; VTE	COR; HQ; AZ; HQ+ AZ	tAC (28,7%) - (a) UFH; (b) Enox s.c. - 1 mg / kg, 2x day or 1,5 mg / kg, 1 x day; (c) i.v. ARG infusion; (d) Fond s.c. 5-10 mg 1x day; (e) OAC prescribed before and continued during hospitalization pAC (60,9%) - a) UFH 5,000 units 1x or 2x day; Enox injection s.c. daily in doses of 30-40 mg 1x day; or Fond s.c. 2.5 mg 1x day Not receiving anticoagulant (non-AC) (10.4%)
Friedrich et al. 2020	PE, DVT	NI	Therapy without dosage - ICU patient on heparin (16%); LMWH: therapeutic and prophylactic (6%); ARG used in patients with heparin-induced thrombocytopenia (6%); No anticoagulation (13%)

Sahai et al. 2021	CVA, AMI, VTE	NI	Aspirin 81mg and patients treated with NSAIDs
Frohlich et al. 2021	AMI, MIO, PE, TVP, PEd, CVA, Patients requiring Hemofiltration	ACEI, ARB, MRA, CCB, BB, statins and diuretics (different from MRA), insulin and non-insulin antidiabetics, IMS.	VKA, DOAC, ANP Dosage: NI
Giannis et al. 2021	VTE, PE, DVT	HQ in 41.1%, COR in 22.6%, Statins in 21.2%, AZ in 19.2%	Dosage= NI antiplatelet agents in 20.6%, anticoagulants in 20.6% (with 14.4% at tAC and 6.2% at pAC)
Li et al. 2021	DVT, PE, CVA, BGIT, IHC	antiviral (70%); ARB (62.5%); RIBV (17.3%); LOP/RIT (5.8%); CLOP (3.8%); GAN (2.6%); REM (0.1%); GLICO (18%)	OAC (7.7%); ACONAK (7.3%); VFA (0.4%); ACP (18.6%); LMWH (9.9%); heparin (9.2%); OAC+ACP (4.2%); Asp (6.8%) CLO (4.4%); Others (0.1%) Asp+CLO (1,9%); heparin+ LMWH (0,4%)
Pesavento et al. 2020	VTE	Prophylactic dose (n = 240) - LOP/RIT (17.5%); HQ (75%); TZM (2.5%); REM (0.4%); AB (70.8%); ES (32.1%); IBP (64.2%) Sub Therapeutic dose (n = 84) - LOP/RIT (25.0%); HQ (84.5%); TZM (16.7%); REM (2.4%); AB (67.9%) ES (32.1%); IBP (81.0%)	pAC (n= 240) - UFH 5000 U (0.4%); LMWH 40 mg OD (80.8%); Fond 2.5mg (18.8%) subtAC (n=84) - LMWH 40 mg OD (92.9%); Fond 7.5 mg (7.1%) pAP (n=240) – none (77.5%); SAPT (20.8%); DAPT (1.7%) subtAP (n=84) – none (78.6%); SAPT (20.2%); DAPT (1.2%)
Escalard et al. 2020	CVA	NI	Five patients (50%) were treated with intravenous alteplase, in a mean time of 175 minutes. All 10 patients were treated with mechanical thrombectomy, all procedures were started within 6 hours of stroke onset. Drug treatments with antiplatelet and neutrophil extracellular traps targeting were used, but not described.
Longhitano et al. 2020	VTE, PE	NI	pAC (34.5%) - Enox: 80U/kg /day (29.7%); heparin 5000UI (5.4%); Fond 2.5 mg /day (1.4%) Highest dose prophylaxis (intermediate and therapeutic) (63.5%) Intermediate dose (32.4%) – Enox <200 and >80 U/kg /day (29.7%); heparin >15000 and < 25000 U/kg /day (1.4%); Fond 5mg/24h (1.4%) tAC (31.1%) - Enox 100 U/kg (9.5%); heparin 12500 U (21.6%)

(*1) (VTE): Venous thromboembolism; (TIA): Transient ischemic attack; (PE): Pulmonary embolism; (DVT): Deep vein thrombosis; (CVA): Cerebrovascular accident; (AMI): Acute myocardial infarction; (VT): Venous thrombosis; (PEd): Pulmonary edema; (MIO): Myocarditis; (BGIT) Bleeding of the Gastrointestinal Tract, (ICH) Intracranial hemorrhage.
(*2) (AB) Antibiotics; (IB) Immunobiologics, (AV) Antivirals; (ES) Steroids; (IM) Immunomodulator; (NSAIDs) Nonsteroidal anti-inflammatory drug; (ACF) Acetominophen; (COR) Corticosteroid; (HQ) Hydroxychloroquine; (AZ) Azithromycin; (HQ+AZ) Hydroxychloroquine + azithromycin; (NI) not informed, (REM) Remdesivir; (FAV) Favipiravir; (LOP/RIT) Lopinavir/Ritonavir; (ATA/RIT) Atazanavir/Ritonavir; (int.d) intermediate dose; (st.d) standard dose; (ACEI) angiotensin-converting enzyme inhibitors; (ARB) angiotensin receptor blocker; (MRA) mineralocorticoid receptor antagonist; (CCB) calcium channel blockers; (BB) beta blockers; (IMS) immunosuppressants; (Asp) Aspirin; (VFA)

warfarin; (TZM) Tocilizumab; (IBP) proton pump inhibitors; (ARB) Arbidol; (RIBV) Ribavirin; (CLOP) Chloroquine phosphate; (FOS) Phosphate; (CLO) Chloroquine; (GAN) Ganciclovir; (GLICO)Glucocorticoids.
(*3) (Enox): Enoxyparin; (Fond): Fondaparinux; (tAC): Therapeutic anticoagulant dose; (ARG) argatroban; (pAC): Prophylactic anticoagulant dose; (s.c.): subcutaneous; (i.v.) intravenous; (OAC) oral anticoagulants: warfarin, apixaban, rivaroxaban, dabigatran; (ICU): Intensive care unit, (LMWH): Low molecular weight heparin; (IRAA) Renin-angiotensin-aldosterone system inhibitors, (TZM) Tocilizumab; (int.d) intermediate dose; (st.d) standard dose, (IRP - ADP P2Y12) platelet receptor inhibitors, (VKA) vitamin k antagonist, (ANP) antiplatelet, (DOAC) direct oral anticoagulants; (UFH) unfractionated heparin; (OD): once daily; (BID): twice daily; (SAPT) single antiplatelet therapy; (DAPT) dual antiplatelet therapy; (ACONAK) oral anticoagulant not vitamin k antagonist; (VFA) warfarin; (ACP) parenteral anticoagulant; (CLO) Chloroquine; (Asp) Aspirin; (subtAC): sub Therapeutic anticoagulant dose; (pAC): Prophylactic anticoagulant dose; (subtAP): sub Therapeutic antiplatelet dose; (pAP): Prophylactic antiplatelet dose

Table 4: Data regarding the outcomes of the therapy employed in COVID-19.

Author	Outcomes of treatment for thromboembolic diseases	Conclusion
Cardillo et al. 2021.	No significant differences were observed between patients on prophylaxis with enoxaparin (Enox) or fondaparinux (Fond), regarding clinical characteristics. In the analysis of D-dimer, fibrinogen, CRP, LDH and IL-6 markers, on the day of admission and three weeks thereafter, the following results were observed: A progressive reduction of D-dimer: occurred in both groups Enox or Fond. However, there was no statistical difference between the two in relation to D-dimer, although treatment with Enox was more effective in this reduction. When assessing fibrinogen, no statistical difference was observed, both drugs Enox and Fond showed no effect on this marker. Regarding CRP it was observed that Enox (HL >0) was not effective in reducing this marker, but Fond (HL<0) was able to reduce it. Both drugs (Enox; Fond) were effective in reducing Lactate dehydrogenase (LDH) Both drugs (Enox; Fond) were effective in reducing Interleukin-6 (IL-6)	In conclusion the anti-inflammatory effects of fondaparinux and enoxaparin after 3 weeks of prophylactic treatment were similar when considered the levels of fibrinogen and D-dimer, LDH and IL-6. Regarding CRP, Fondaparinux was more effective. Furthermore, it is important to emphasize that no statistical differences were observed in relation to clinical characteristics
Ionescu et al. 2021	After 25 days of admission, different survival probabilities were observed when comparing patients receiving tAC with those who received only pAC in both populations (ICU and non-ICU) -ICU (56.3% vs 22.5%) - non-ICU (78.5% vs 65.7%). pAC was associated with a 65% reduction in the risk of death and tAC was associated with an 86% decreased risk of death. Anticoagulants use: 90% of patients - 2/3: prophylactic doses; 1/3: therapeutic doses Hemorrhagic events in 147 patients: 81% of the patients with tAC doses, 5.5% without anticoagulante and 2.3% with pAC doses Severe thrombocytopenia: 3.4% in the tAC group, 2.8% in the no anticoagulant group, and 1.3% in the pAC group	According to this cohort study, there is a strong association between anticoagulant treatment and reduced mortality. The greatest impact was observed in patients who were critically ill. However, a benefit was also noted in patients outside the ICU.
Friedrich et al. 2020	Fibrinogen: Mean value 6.4± SD 1.8g/l, with a peak at the third week of disease and no significant decrease over time. D-dimer: Mean value 5.1±4.4mg/l with a peak of 6.8±5.3mg/l at the fourth week of illness, and a subsequent decrease. In the ICU patients, the d-dimer value was higher. Platelets and Prothrombin time: showed no significant changes over time.	Changes in coagulation were observed in patients with COVID-19, with the presence of hypercoagulability, peaks in coagulation marker dosages are observed in the third and fourth week, even with the use of antithrombotic agents. This increase in coagulation markers may indicate the need to increase the timing of thromboprophylaxis in critically ill patients or those with prothrombotic risk factors.

	Thromboembolic events were diagnosed in 13% of patients and 16% of patients died during the observation period.	
Sahai et al. 2021	There was no statistical difference in relation to mortality in patients treated with aspirin or not. There was no statistical difference in patients treated with aspirin or not in relation to events such as acute myocardial infarction and venous thromboembolism. However, the use of aspirin was associated with the incidence of stroke. In addition, in patients treated with NSAIDs or not, the incidence of acute myocardial infarction, venous thromboembolism and stroke was not significant and the mortality was not different in patients treated with aspirin in relation to those treated with other NSAIDs.	It is suggested that low-dose aspirin does not protect against thrombotic events or deaths in patients diagnosed with COVID-19. The use of traditional antiplatelet agents, does not protect against thrombotic events or mortality in COVID-19 and may cause harm.
Frohlich et al. 2021	The multivariable model demonstrated that therapy: direct oral anticoagulants (DOAC) associated with vitamin K antagonist (VKA) were the therapy related to thrombotic event reduction. Antiplatelet (ANP) use was not associated with a reduction in thrombotic events.	Antithrombotic therapy with VKA or DOAC, except ANP therapy, showed better results. There is a need for retrospective randomized studies to confirm this result.
Giannis et al. 2021	Venous thromboembolism (VTE) was diagnosed in 1.09% of patients, pulmonary embolism in 0.93%, and deep vein thrombosis in 0.16%. Statin and antiplatelet use was associated with reduced VTE and mortality.	The study showed the incidence of thrombotic events in patients with COVID-19 and a relationship between the use of statins and antiplatelet agents and the reduction of VTE and mortality. Based on these results, there is a need to study the possible benefits of antithrombotic agents in COVID-19 patients in prehospitalization, especially in patients who have cardiovascular or thrombotic risk factors.
Li et al. 2021	Oral and parenteral anticoagulants are associated with reduced thromboembolism over a 21-day interval, as well as reduced risk of death.	Patients diagnosed with COVID-19 have a high risk for thromboembolic and bleeding events, associated with a high mortality rate. Therapy with anticoagulants, especially parenteral ones, considerably decreased the risk of outcomes containing such events.
Pesavento et al. 2020	Major bleeding complications among patients taking (under) therapeutic doses greatly exceeded those of patients treated with preventive doses.	As for thrombotic events, the incidence of major or relevant bleeding complications during hospitalization was considerably higher in patients treated with therapeutic dose medication than in those who received prophylactic doses of antithrombotic medications.
Escalard et al. 2020	40% of the patients had proximal artery reocclusion, even though they were using anticoagulation. 90% of patients had successful recanalization. 60% of the patients died during hospitalization. Most patients (70%) had mild or absent respiratory symptoms at the time of stroke. This suggests that there is no correlation between the severity of respiratory symptoms and the risk of acute ischemic stroke with large vessel occlusion.	Although the study results require further confirmation, pharmacological approach such as the use of antiplatelet or other antithrombotic therapy should be investigated to take into account inflammatory and coagulation disorders associated with COVID-19. Therefore, this study does not agree that COVID-19 was responsible for acute ischemic stroke with large vessel occlusion, since most patients had some risk factor for stroke.
Longhitano et al. 2020	Hemorrhagic events: 6 cases (2 cases on standard antithrombotic prophylaxis and 4 cases on the increased antithrombotic dose). At the increased dose, 3 cases of hemorrhagic shock and 3 cases of significant spontaneous bleeding were observed. Mortality was 3 times higher in patients on the increased dose in the intermediate-dose prophylaxis group than in patients on standard prophylaxis.	There were thrombotic complications in a high number of patients who had acute respiratory failure secondary to COVID-19 infection. And the worst results were with high-dose therapies. Therefore, further studies are important to discuss the best thromboprophylactic strategy in patients with COVID-19.

According to Wannmacher (2007), heparin is divided into UFH and LMWH. Both have indications to similar diseases, but the LMWH is prescribed in a simpler scheme of administration, has a safer dose-response relationship, has a low thrombocytopenia index (TI) and bleeding, and is more used than UFH. LMWH was synthesized in order to obtain an easier substance to administer, and it is the result of depolymerization of UFH (Weitz, 1997). Because of its predictable anticoagulant response when administered subcutaneously, it does not require laboratory monitoring. In addition, its use is permitted once or twice daily and does not require venous access and an infusion pump (Litin, Heit & Mees, 1998).

UFH has little absorption via the oral route, with intravenous (IV) or subcutaneous (SC) infusion being its most commonly used routes of administration (Nutescu, 2016). Its clinical use is in the prevention and treatment of VTE (Ministry of Health, 2021). The anticoagulant mechanism of heparins is through their binding with a serine protease inhibitor, in this case AT III, forming a UFH-AT III complex. This bond changes the conformation of the antithrombin molecule, inhibiting factors IIa (thrombin) and Xa (Nugent, 2000), and other coagulation factors such as XIIa, XIa and IXa, being inhibited both extrinsic and intrinsic and common coagulation enzymes (Albuquerque & Albuquerque, 2001). When exerting anticoagulant activity, heparin promotes clinical changes by increasing PT, APTT and thrombin time (TT) (Funk, 2012).

Other anticoagulants were used in the articles presented in this review, such as the direct-acting anticoagulants; however, these were not specifically mentioned. Direct thrombin inhibitors, for example dabigatran, inhibit both soluble thrombin and fibrin-bound thrombin, do not require a cofactor to bind to thrombin, and have no antiplatelet effect (Kam, Kaur & Thong, 2005; Lee & Ansell, 2011). In the form of parenteral use only, there is argatroban, acting in stroke prevention in atrial fibrillation (AF), acute coronary syndromes, prevention and treatment of DVT (Flato et al., 2011; Drug Bank, 2022; Pimenta et al., 2016). As for Factor Xa inhibitors, these bind directly to the active site of Factor Xa itself, making its activity in coagulation impossible (Eriksson, Quinlan & Weitz, 2009). Factor Xa inhibitors indicated for the treatment of DVT are: rivaroxaban, apixaban and edoxaban (Brandão et al., 2018). Fondaparinux is a synthetic pentasaccharide anticoagulant, which acts by indirectly inhibiting factor Xa through plasma antithrombin (Andrade et al., 2012), and is the most recent synthetic derivative of heparin, synthesized in 2004 (Smythe, Priziola, Dobesh, Wirth, Cuker & Wittkowsky, 2016).

It was reported in one of the studies, the use of VKAs that are anticoagulants acting in modulating the carboxylation of vitamin K-dependent coagulation factors. Factors II, VII, IX and X require carboxylation for their thrombotic effect (pro-coagulant activity). VKA has a narrow therapeutic range, with large variations in results, and may interact with other drugs and certain types of food. As such, their laboratory monitoring is extremely rigorous. Warfarin is the most widely used

VKA and has a longer time interval to reach its maximum anticoagulant effect (Protocolo de Anticoagulação Ambulatorial, 2020).

Aspirin or acetylsalicylic acid (ASA) is a drug, which in the form of rapid release, has antipyretic, anti-inflammatory action, treating pain, fever, flu, cold, inflammation, migraine, among others. In the extended-release form, it reduces the incidence of mortality due to cardiovascular events (blood clots, strokes, and AMI), acting as a platelet antiaggregant (Drug Bank, 2022). Another antiplatelet agent, clopidogrel, was reported in one study. Clopidogrel is an irreversible oral antagonist of the P2Y12 receptor, which is the main target of oral inhibitors, preventing thrombus formation. It is a prodrug, whose antagonist function occurs after its hepatic metabolization, which provides its binding to P2Y12 receptors. About 85% of this substance undergoes hydrolysis and only the rest will be metabolized (Falcão et al., 2013).

In this review, 2 studies using statin drugs were reported. One of the studies had no clinical outcome (Frohlich et al., 2021). The other study showed promising results regarding the use of statins (Giannis et al., 2021). The station is a hypocholesterolemic, with the function of inhibiting 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase), which acts in lowering lipid levels, reducing the risk of cardiovascular disease, such as AMI and stroke (Drug Bank, 2022). With HMG-CoA reductase inhibition, it does not convert to mevalonate, preventing cholesterol synthesis (Moghadasian, 1999). Although used in the treatment of cholesterol, statins have also been used in the prevention of thrombotic events in patients with COVID-19, due to their action on systemic inflammation, stabilizing atheroma plaques and preventing the virus from destabilizing them, causing an acute coronary syndrome (Madjid et al., 2020).

Regarding the therapeutic regimens proposed in the studies used in the present review (Table 3), a variation in the dosage of the drugs used was observed. Some articles adopted the therapeutic (tAC) and prophylactic (pAC) dose of anticoagulants (Ionescu et al. 2021), one article adopted the tAC, pAC and intermediate (iAC) dose of anticoagulants (Longhitano et al. 2020), one article used pAC dose and sub therapeutic (sub tAC) dose of anticoagulant, associated with prophylactic (pAP) and sub therapeutic (sub) tAP doses of antiplatelet (Pesavento et al. 2020). It was also possible to observe articles that did not state the type of dose used Friedrich et al. (2020); Frohlich et al. (2021); Giannis et al. (2021); Li et al. (2021); Escalard et al. (2020). One article compared dosages of enoxaparin and fondaparinux (Cardillo et al., 2021) and lastly, aspirin therapy in association with antiplatelet and with other types of NSAIDs was compared.

Ionescu et al. (2021) did a comparison of different doses of antithrombotic drugs in which there was a considerable difference when comparing the effect of the two therapeutic options: UFH, enoxaparin and argatroban in tAC dose and in pAC dose. The results showed benefit in both tAC and pAC compared to patients who did not receive antithrombotic treatment. Between treatments, a greater

beneficial effect was shown in patients who received tAC compared to pAC. Around 90% of patients used some type of anticoagulant, with ⅔ using prophylactic doses and ⅓ using therapeutic doses. Severe thrombocytopenia occurred in 34 (3.4%) in the tAC group, 10 (2.8%) in the no anticoagulant group, and 27 (1.3%) in the pAC group ($p < 0.01$). The study consisted of outpatients and ICU patients undergoing mechanical ventilation. Regarding the survival probability in ICU inpatients, a rate of 56.3% was observed for tAC compared to 22.5% of the pAC dose. For outpatients, the survival rate was 78.5% for tAC compared to 65.7% for pAC. When mortality was evaluated, the tAC dose therapy showed an 86% decrease in the risk of death compared to pAC which showed a 65% decrease in the risk of death.

In another study, Attacc Investigators et al. (2021) sought to evaluate whether a strategy with anticoagulation using UFH and LMWH in tAC would promote improvements in non-critical patients with COVID-19. The results showed an increased likelihood of survival, with hospital discharge and reduced use of cardiovascular or respiratory support through use of tAC dose. On the other hand, Remap-Cap Investigators et al. (2021) showed that critically ill patients with COVID-19 using tAC dosing of UFH or LMWH did not have an increased likelihood of survival, or even a greater number of days without cardiovascular or respiratory support, when compared to patients on pAC dose treatment (survival rate of 62.7% on tAC and 64.5% on pAC).

Pesavento et al. (2020) analyzed the use of anticoagulant with antiplatelet agent in pAC, sub tAC, pAP and sub tAP doses, and observed a higher incidence of hemorrhage in patients who used sub tAC. Thus, the use of heparin at higher doses was not able to reduce the risk of fatal and non-fatal complications in the face of hemorrhagic risk. According to Flumignan et al. (2020), high dosages of anticoagulants do not show relevant results in the difference of mortality rates and still increase the risk of bleeding, when compared to anticoagulants at lower doses, in patients hospitalized with COVID-19.

Regarding prophylaxis of thrombotic events, Rossi et al. (2020) stated that there is no indication regarding prophylaxis in DVT. However, this prophylaxis when LMWH is used can be useful, especially in patients with a high risk for DVT, when there is no increased risk of bleeding. According to the WHO, the guideline is to use daily prophylactic doses of LMWH or UFH in the subcutaneous form twice daily (WHO, 2020).

Longhitano et al. (2020) evaluated the thrombotic risk in patients with COVID-19 and compared three anticoagulant treatment options, such as enoxaparin, heparin, and fondaparinux, at pAC doses and at higher doses including tAC and iAC. The analysis showed that iAC or tAC doses did not decrease the prevalence of thrombotic events. In addition, 6 cases of severe bleeding complications were reported, with 2 cases occurring when using the pAC dose and 4 cases distributed

over tAC and iAC. The authors found a 3-fold higher mortality (OR 3.38) among users who received such doses.

COVID-19 can cause various damages such as alveolar lung damage, acute respiratory failure with a high prevalence of developing cardiovascular disease and virus-related cardiac lesions (Huang et al., 2020). The fact that it can generate an extremely intense inflammatory process, with production of inflammatory cytokines such as IL-6, contributes to the increased risk of thrombotic events (Ulhaq & Soraya, 2020). Cardillo et al. (2021) found that both fondaparinux and enoxaparin similarly reduced D-dimer levels, although enoxaparin proved to be more effective in this reduction, when analyzed 100 patients under these therapies. However, fondaparinux was more effective in reducing C-reactive protein (CRP), and both drugs were able to reduce lactate dehydrogenase (LDH) and IL-6, but were not able to reduce fibrinogen levels.

Coagulopathy is evaluated according to some parameters, such as fibrinogen, D-dimer, factor VIII and PT prolongation indexes, as well as APTT. Such factors, when altered, have associations with unfavorable clinical outcome and prevalence of deaths (Tang, Bai, Chen, Gong, Li & Sun, 2020). Evidence has indicated an association of enoxaparin with a reduction in in-hospital mortality as well as in the number of ICU admissions. In addition, they have more significant effects in the elderly, more severely ill patients, and those with high levels of IL-6 and D-dimer. In one of the studies reviewed by the Brazilian Ministry of Health, it was shown that, in an analysis adjusted for population characteristics and severity of COVID-19, enoxaparin has an association with reduced risk of developing severe acute respiratory distress syndrome (ARDS) and mortality (Ministério da Saúde, 2021). Thus, the benefit of heparin use in patients with COVID-19 is highlighted.

Frohlich et al. (2021) analyzed the use of DOACs associated with antiplatelet agents and VKA and reported that this association was able to reduce thrombotic events. However, they point out that the use of DOACs in COVID-19 does not protect against thromboembolic and hemorrhagic complications and that, therefore, substitution to parenteral anticoagulation is necessary. Another study compared prophylactic doses of anticoagulants, UFH, LMWH and argatroban, and demonstrated the occurrence of peaks in the dosage of coagulation markers. This may indicate the need to increase the timing of thromboprophylaxis in critically ill patients or those with additional prothrombotic risk factors, in order to improve the efficacy of the therapy (Friedrich et al., 2020).

Regarding platelet aggregation, Sahai et al. (2021), through a cohort of patients who used aspirin, or other NSAIDs, or both treatments, demonstrated that NSAIDs did not show changes in mortality. According to the study, aspirin failed to realize its protective effect probably due to the dose amount, an inefficient platelet inhibition mechanism, or some altered platelet phenotype. Aspirin, by its inhibition of cyclooxygenase-1, prevents the formation of thromboxane A2 and is considered an excellent platelet antiaggregant drug. The fact that patients, even using aspirin, present cardiovascular

events was the starting point to think about the concept of aspirin resistance in these patients (Oliveira, Silva, Silva & Lima, 2010). The resistance to aspirin was described by Gum et al. (2003).

In the study by Manne et al. (2020), where platelet gene expression and physiological responses of patients with COVID-19 were examined, very expressive changes in platelet gene expression were reported, and an intense reaction in this expression was noted in SARS-CoV-2 infection. Furthermore, in the RNA-seq of the platelet isolate, they identified the expression of 3090 genes among non-ICU patients, and 2,256 genes expressed in ICU patients, compared to healthy donors. They also observed that platelets exhibited more aggregation, adhesion, and dissemination, as a result of increased and released thromboxane A2. These results assume new evidence that the platelet gene is altered, with increased functional responses in COVID-19, suggesting a contribution to the thrombotic events.

Li et al. (2021) evaluated the action of anticoagulants in decreasing thromboembolic risk and found that, in addition to decreasing thromboembolic risk, they decreased the risk of mortality; although patients with AF have a higher risk of systemic thromboembolism, even with the use of anticoagulants. AF is a disorder of atrial electrical activity, with consequent loss of atrial systole and is the most common arrhythmia in clinical practice, involving 3% of the adult population, being more common in advanced age groups (Cintra & Figueiredo, 2021). In this sense, it is indicated to verify if patients with COVID-19 present AF.

Escalard et al. (2020) described an initial experience of treating patients with COVID-19 presenting acute ischemic stroke due to large vessel occlusion. A total of 10 patients were treated with mechanical thrombectomy and there was successful recanalization in 9 (90%) patients. In 5 (50%) patients, treatment with the fibrinolytic agent alteplase was performed. Although 4 patients were treated with anticoagulants, the onset of an acute ischemic stroke with large vessel occlusion could not be prevented, with a total of 6 deaths. Most patients (70%) had mild or absent respiratory symptoms at the time of stroke. This suggests no relationship between severity of respiratory symptoms and risk of acute ischemic stroke with large vessel occlusion.

Giannis et al. (2021), analyzed the incidence of thromboembolic events in patients using anticoagulants and statins associated with antiplatelet agents and showed a reduction in these events. The positive effects of statins in reducing VTE and mortality are already known, however, this is not yet established in the case of COVID-19. Glynn et al. (2009), conducted an intervention study evaluating rosuvastatin against PE or VTE events, and patients receiving rosuvastatin were able to have a significant reduction in the occurrence of symptomatic VTE. According to Madjid et al. (2020), statins act on systemic inflammation by stabilizing atheroma plaques and preventing SARS-CoV-2 from destabilizing them and causing an acute coronary syndrome.

It is known that SARS-CoV-2 entering the host cell through the angiotensin-converting enzyme 2 (ACE2), causes negative regulation of this enzyme and induces pro-inflammatory responses by

activating the Toll-like receptor (TLR)- MYD88-NF-κB pathway (Khavidaki and Khalili, 2020). As statins possess hypolipemic and immunomodulatory properties, it was seen that in experimental models they inhibit MYD88-NF-κB and promote positive ACE2 regulation, generating benefit in patients with COVID-19. However, inhibition in TLR and NF-κB receptor signaling by statins may contribute to an exacerbation of compensatory immune signals, leading to a worse disease prognosis, even though there is an improvement, for example, in lung injury due to their anti-inflammatory action (Khavidaki & Khalili, 2020).

In view of the results analyzed through this systematic review, it was found that treatment with anticoagulants showed greater benefits when used in tAC dosage of the drugs enoxaparin, UFH, argatroban, fondaparinux and oral anticoagulants. Drug combinations also proved beneficial, for example, enoxaparin associated with fondaparinux, as well as DOACs in conjunction with VKA. Importantly, antiplatelet use did not promote a reduction in thrombotic events. However, the use of antiplatelet and statins was associated with reduced VTE and mortality. It was noticed in this review, that when anticoagulants are administered in sub tAC doses the results were not promising, for example in the use of UFH, LMWH and fondaparinux, however with divergences among the studies. Treatments with the fibrinolytic, alteplase also did not show satisfactory results.

4 CONCLUSIONS

In conclusion, there is strong evidence that anticoagulants are beneficial in COVID-19, although there are particularities and contraindications in certain patients who have a predisposition to greater bleeding and, in this case, require another therapeutic option. Thus, more robust studies are still needed to be aware of the real effect of antithrombotic agents on COVID-19, to define the best therapy to be adopted in these patients.

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