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Non-vitamin K antagonist oral anticoagulants for COVID-19 thrombosis

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ABSTRACT

Thrombotic complications appear to be a major predictor of death in COVID-19 patients, and multiple studies have shown that anticoagulants can help to improve the outcome. The Food and Drug Administration's acceptance of non-vitamin K antagonist oral anticoagulants (NOACs) has sparked much excitement about their potential as a replacement for existing oral anticoagulants. NOACs target a single clotting factor, often activated factor X or thrombin, and involve the coagulation factor Xa inhibitors including apixaban, edoxaban, and rivaroxaban, and the thrombin inhibitor dabigatran. COVID-19 is an infectious disease that causes thrombotic events by inducing a pro-inflammatory and prothrombotic condition. This article provides a comprehensive overview of the mechanism behind enhanced thrombogenicity accompanying COVID-19, the clinical range of NOACs, and the role of NOACs in treatment of COVID-19 based on recent investigations and clinical trials.

KEYWORDS: Anticoagulants; COVID-19; NOACs; SARS-CoV-2; Thrombosis

1. Introduction

Coronavirus disease 2019 (COVID-19) is a devastating pandemic triggered by coronavirus 2 (SARS-CoV-2) that drives severe respiratory illness. Thrombotic incidents are an important factor contributing to COVID-19 mortality[1]. According to current clinical data, pneumoembolism and deep vein thrombosis (DVT) account for the majority of the thrombotic events in COVID-19 patients[2]. The increasing incidence of pneumoembolism and DVT has drawn attention to regular thrombotic prevention for COVID-19 care, particularly in critically ill patients and/or those with increased D-dimer values[3,4]. A new classification named "sepsis-induced coagulopathy" (SIC) has been proposed by the International Society of Thrombosis and Haemostasis (ISTH) to label an early stage of septicemia diffuse intravascular coagulation. Patients who satisfy the diagnostic criteria for SIC have benefited from anticoagulant therapy[5,6]. Based on a number of highly relevant reports and trials, this article presents an overview of the mechanism behind enhanced thrombogenicity of COVID-19, the range of non-vitamin K antagonist oral anticoagulants (NOACs) in clinical practice, and their role in COVID-19 treatment.

2. Methods

2.1. Search strategy

Literature searches were conducted using the following keywords: COVID-19, NOAC, anticoagulant, and thrombosis in the databases including Medline, PubMed, and Cochrane Library, as well as manual searches on Google Scholar and the bibliographies of recognized publications.

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2.2. Inclusion and exclusion criteria

Included articles in this review were all observational and interventional studies that investigated the role of NOACs in treatment of COVID-19 thrombosis and were published in the English language. Excluded articles were case reports, letters to editors, commentaries, and reports.

2.3. Study selection and data collection

The studies were chosen based on their titles and abstracts. Then, the suitability of their whole text was examined. Articles that investigated the NOACs in treatment of COVID-19 thrombosis were included in the analysis.

Data and information such as the author's name, the year of publication, the study design and duration, the sample size, and the key findings from each study were extracted according to the PRISMA Scoping Review Checklist.

3. Results

For this review, new articles on the NOACs not older than approximately seven years were preferred. A total of 2 363 articles were found. Among those articles, 1 260 duplicates were deleted. 790 irrelevant articles were removed after the initial reading of the title and abstract. Among those which full-texts were assessed, 151 old articles and 108 articles that are not observational or interventional studies were excluded. Eventually, 54 were included for review (Figure 1).

3.1. Brief introduction on NOACs

NOACs have been proven to be an effective strategy to prevent and cure thrombosis after more than 60 years of use of vitamin K antagonist[7,8]. The development of NOACs is a scientific breakthrough with bright prospects. The vitamin K antagonist has several drawbacks, including a narrow therapeutic index, an increased risk of bleeding, an individualized dose regimen,

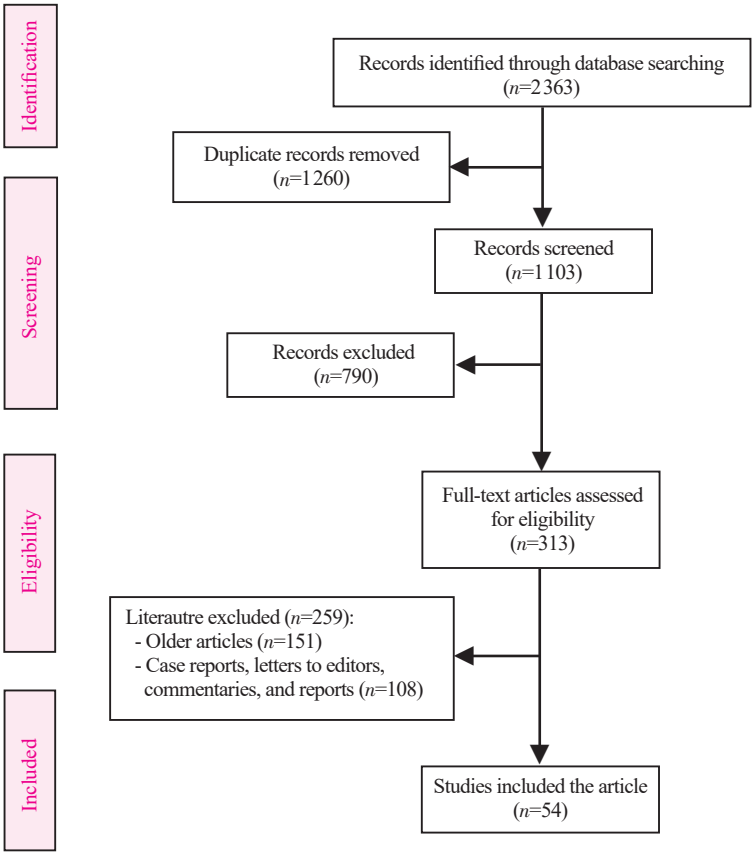

Figure 1. The study flowchart.

and others[9]. NOACs have a substantial difference in resolving these problems. These medications have been recently approved by the European Union and other countries for the prevention of venous thromboembolism (VTE) following elective knee or hip replacement surgeries[10]. Furthermore, these medicines do seem to offer a benefit over warfarin when it comes to lowering stroke risks associated with atrial fibrillation (AF)[11]. These new anticoagulants, also famed as target-specific or novel oral anticoagulants, precisely and selectively block the central basics of the coagulation cascade. Unlike traditional anticoagulants, which work by blocking the production of vitamin K-dependent factors, NOACs function by directly blocking a coagulation factor, such as thrombin or activated factor Xa. Dabigatran, as one example of NOACs, subdues thrombin by stopping thrombin from breaking down fibrinogen and preventing the formation of fibrin. Apixaban, rivaroxaban, and edoxaban are examples of NOACs that inhibit factor Xa, a trypsin-like serine protease engaging in blood clotting, by integrating the extrinsic and intrinsic coagulation tract into the common coagulation pathway. The drugs block factor Xa from converting prothrombin into thrombin by binding directly to it[12]. NOACs have target-specific anticoagulant action (Figure 2). Since these drugs are direct inhibitors, they have the following advantages: a fast onset of action, a consistent pharmacologic profile, an oral method of delivery, no requirement for routine laboratory testing for anticoagulant activity, and minimal food or medication interactions[13,14]. The trials have shown that these novel anticoagulant drugs are non-inferior to vitamin K antagonists (VKA) in preventing thromboembolic events and relieving bleeding[15]. NOACs have the potential to boost anticoagulant absorption for long-term thromboembolic event prevention in individuals at high risk of recurrence. Although NOACs are a significant step forward, there are still obstacles to overcome, such as the anxiety of bleeding in the absence of relevant antidotes, higher drug acquisition costs, the concern that unmonitored anticoagulant therapy will compromise treatment adherence, and the belief that monitoring is necessary[14]. NOACs may aid in dose optimization, especially in sensitive patient populations like the elderly or those with impaired renal function.

3.2. Spectrum of NOACs use in clinical practice

NOACs are increasingly being used in clinical practice, according to a growing body of research. As a result of their attractive benefit-to-risk profiles, NOACs are being studied in new areas, such as heart disease, peripheral artery disease, kidney disease, embolic stroke triggered by uncertainties, and bioprosthetic heart valves. Furthermore, researches are being conducted on thromboprophylaxis in medically unwell individuals, AF patients receiving percutaneous coronary intervention and prolonged VTE therapy, and patients with cancer-mediated thrombosis.

A randomized research compared the effect of rivaroxaban with VKA on AF patients with elective cardioversion. The study found that there was a similar incidence of stroke or other cardiovascular

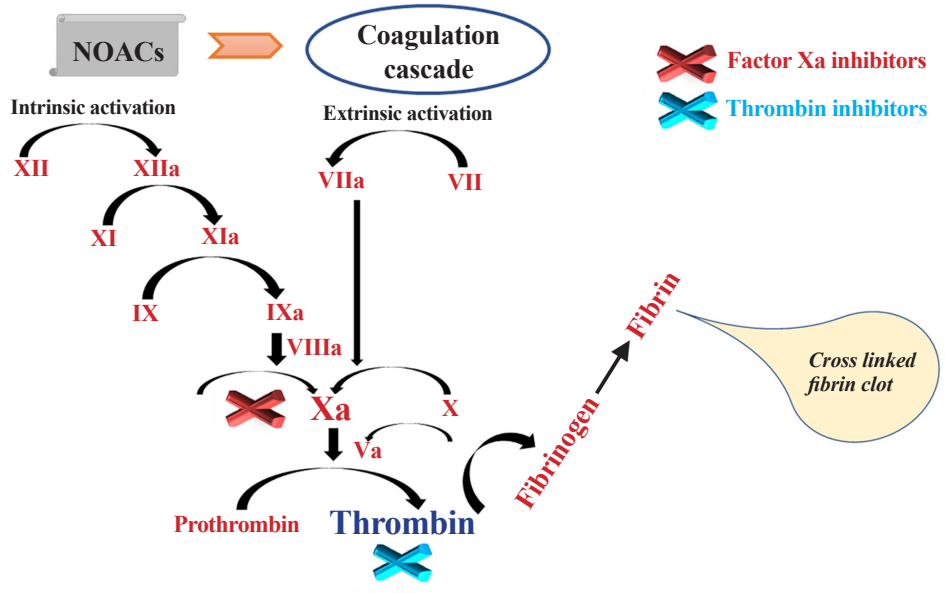

Figure 2. Summary of the target-specific oral anticoagulant action of non-vitamin K antagonist oral anticoagulants.

events as well as bleeding, while there was a significant reduction in cardioversion time in the rivaroxaban group[16]. Apixaban reduced bleeding and hospitalizations more significantly than VKA in treating AF patients with percutaneous coronary intervention or acute coronary syndrome who were treated with an inhibitor P2Y12 in a AUGUSTUS study[17]. A SELECT-D open-label pilot study showed a threefold relative increase in clinically relevant non-major bleeding after treatment with rivaroxaban compared to dalteparin[18]. A COMPASS trial evaluated the effect of rivaroxaban on patients with chronic paroxysmal atrial fibrillation or coronary artery disease as a secondary prevention strategy. Combination use of rivaroxaban and aspirin reduced myocardial infarction, cardiovascular mortality, stroke, fatal hemorrhage, or symptomatic bleeding into a critical organ compared to aspirin alone[19]. According to the Food and Drug Administration and the European Commission, aspirin 100 mg plus rivaroxaban 2.5 mg twice daily can reduce the risk of atherothrombotic events in patients with peripheral artery disease and coronary artery disease[20]. A Hokusai VTE cancer report found that oral edoxaban was not inferior to subcutaneous dalteparin in preventing recurrent VTE of cancer patients with acute symptoms or incidental VTE. Edoxaban reduced risk of recurrence of DVT and recurrence rate of VTE more significantly than dalteparin[21]. A ADAM-VTE research compared apixaban with dalteparin in treating patients with malignant tumor and VTE. The findings implied that using oral apixaban to treat VTE in cancer patients could reduce significant bleeding and VTE recurrence rates[22]. A AVERT studied the safety and effectiveness of apixaban for thromboprophylaxis in patients with malignant tumor. Compared to placebo, apixaban at a dosage of 2.5 mg twice daily substantially decreased VTE risk in cancer patients who commenced chemotherapy and had a transitional risk of VTE[23]. Table 1 shows details of key clinical trials of NOACs.

3.3. Thrombosis mechanism in COVID−19

COVID-19 is an emerging threat due to the proclivity of SARS-CoV-2 to cause venous and arterial microvascular thrombosis, thus aggravating organ detriment. Coronaviruses have been shown to enter cells through adjoining angiotensin-converting enzyme 2 (ACE2) found mostly on the alveolar endothelium and epithelium[37]. The fundamental driver of the increasingly recognized thrombosis problem is assumed to be endothelial cell activation[38]. The association between COVID-19 and vascular coagulopathy suggests that many pathways are dysregulated throughout the clinical course of the illnesses, contributing to the related thrombosis. Platelet activation and the coagulation cascade are two aspects of the thrombotic response. Activated platelets boost their aggregation ability by raising the quantity of membrane P selectin, which promotes contacts and accumulation with monocytes, neutrophils, and T cells *via* the mitogen-activated protein kinase path and thromboxane synthesis[39]. A past study found that SARS-CoV-2 RNA in thrombocytes, as well as a higher platelet-associated cytokine, resulted in hyperactive platelet activity and thrombosis in COVID patients[40]. Platelet adherence and aggregation are mediated by the glycoprotein von Willebrand factor, which is generated by active endothelial cells, platelets, and exposed subendothelium. COVID-19 patients have a high level of the von Willebrand factor, which could indicate a proclivity for platelet plugging and thrombosis[41]. It has been proposed that SARS-CoV-2 contagion of host cells can affect the ACE/ACE2 ratio, resulting in ACE2 down-regulation. Consequently, dysregulation of the renin-angiotensin-aldosterone system in a COVID-19 patient's vasculature may result in an exaggerated coagulopathy. The stimulation of the SARS-CoV-2 spike protein to the ACE2 receptor by the host serine protease, transmembrane protease serine 2, enhances viral endocytosis and replication[42,43]. The immune system responds strongly to endothelium injury and viral release, possibly leading to greater endothelial dysfunction. Thrombin activates protein C on the endothelium surface by forming a thrombin-thrombomodulin complex, which is increased by the protein C receptor. As a result, an endothelial injury may affect the protein C pathway[44,45]. In moderate-to-severe COVID-19 patients, hypoxia develops, which can cause endothelial dysfunction and hypercoagulability[46]. Furthermore, alveolar hypoxia and tissue hypoxia are capable of activating the endothelial cyclooxygenase pathway, leading to the constricting of thromboxane's A2 and B2 receptors, which in turn causes constriction of the smooth muscle cells in the vascular system[47].

In hospitalized COVID-19 patients, various nonspecific markers of inflammations like ferritin, C-reactive protein, and erythrocyte sedimentation rate as well as some procoagulant factors like von Willebrand factor and Factor VIII, are markedly elevated. Several proinflammatory cytokines are also on the rise, such as interleukin-2 receptor and tumor necrosis factor-alpha[44,48]. Inflammation promotes thrombosis by causing endothelial trauma and maintaining a hypercoagulable condition through decreased fibrinolysis and the tissue factor pathway activation. In response to inflammation, neutrophils produce neutrophil extracellular traps by a specialized mechanism known as NETosis, which involves the release of condensed neutrophil and chromatin clusters. Emerging evidence bespeaks that NETosis has been linked to increased thrombosis risk in COVID-19 patients[49]. Complement is another possible thrombosis promoter, with the membrane attack complex C5b-9 rising in SARS-CoV-2 infected individuals, as well as other endothelial activation indicators including plasminogen activator, plasminogen activator inhibitor-1, and von Willebrand factor[50]. COVID-19 is associated with immunothrombosis. Innate immune

Table 1. Key clinical trials with NOACs.

Authors and year	Ref	Study design and duration	Drug	Paticipant and sample size (*n*)	Outcome
Cappato *et al*. (2014)	[16]	Open-label, 3-8 weeks	Rivaroxaban	1 504 AF patients receiving elective cardioversion	Shorter time to cardioversion compared with VKAs
Lopes *et al*. (2018)	[17,26]	Open-label, 6 months	Apixaban	4 600 patients suffering from AF, acute coronary syndrome, or PCI	Prevention of stroke or systemic embolism
Connolly *et al*. (2018)	[19]	Double-blind, randomized, 3 years	Rivaroxaban	27 395 with stable coronary artery disease	Reduce morbidity and mortality from coronary artery disease
Raskob *et al*. (2018)	[21]	Open-label, 6 months	Edoxaban	1 050 acute symptomatic or accidental VTE in malignant patients	Lower rate of recurrent VTE
Carrier *et al*. (2019)	[23]	Double-blind, 6 months	Apixaban	563 patients undergoing thromboprophylaxis with placebo among ambulatory malignant patients	Lower rate of VTE
Ezekowitz *et al*. (2018)	[24]	Open-label, 3 years	Apixaban	1 500 patients diagnosed with AF receiving cardioversion	Decline stroke, systemic embolic events, mortality, and bleeding events
Goette *et al*. (2016)	[25]	Open-label, 12 months	Edoxaban	2 199 non-valvular AF patients receiving electrical cardioversion	Low clinically meaningful non-major bleeding and thromboembolism event
Gibson *et al*. (2016)	[27]	Open-label, 1, 6, or 12 months	Rivaroxaban	2 124 patients having AF who had had PCI with stent implantation	Lower risk of bleeding
Cannon *et al*. (2016)	[28]	Open-label PROBE design, 30 months	Dabigatran	2 725 percutaneous coronary remodeling in patients with non-valvular AF	Reduced thrombotic event
Vranckx *et al*. (2019)	[29]	Open-label, 12 months	Edoxaban	1 506 AF patients who underwent PCI	In terms of bleeding, edoxaban was non-inferior to VKA, with no significant differences in ischemic events
Hart *et al*. (2018)	[30]	Double-blind, 3 years	Rivaroxaban	7 213 patients with recent ischemic stroke	Stroke or systemic embolic events
Anand *et al*. (2019)	[31]	Double-blind, 5 years	Rivaroxaban	27 395 patients with peripheral arterial disease or chronic coronary artery disease	Prevent vascular disease
Diener *et al*. (2019)	[32]	Double-blind, randomized trial, 12 weeks	Dabigatran	5 390 patients who had an embolic stroke	Non-major bleeding episodes were more common in the dabigatran group
Zannad *et al*. (2015)	[33]	Double-blind, 30 months	Rivaroxaban	5 000 patients who had chronic heart failure	Reduced cardiovasular event
Weitz *et al*. (2017)	[34]	Double-blind, 12 months	Rivaroxaban	3 365 patients with VTE	Recurrent VTE
Liu *et al*. (2015)	[35]	Randomized trial, 4 years	Apixiban	5 365 patients with VTE	Patients with acute VTE had fewer allcause hospitalizations and a shorter length of stay
Spyropoulos *et al*. (2020)	[36]	Double-blind, 45 days	Rivaroxaban	4 913 patients who are medically unwell and have extra risk factors for VTE.	Lower rate of VTE

AF: atrial fibrillation, VKA: vitamin K antagonists, PCI: percutaneous coronary intervention, VTE: venous thromboembolism.

cell stimulation, endothelial dysfunction, and excessive coagulation play a role in immunothrombosis, all of which contribute to prothrombotic states. The overall response of immune system to SARS-CoV-2, including immune cell production of prothrombotic proteins and inflammation, is promising to have a role in COVID-19[51].

3.4. Various anticoagulant options in COVID-19 thrombosis

Expert guidelines for anticoagulant use have been reported, reflecting the identification of the dysregulation of clotting in this entity. In COVID-19, ISTH has issued quick interim recommendations on coagulopathy detection and clinical management. ISTH recommends that in high-risk COVID-19 patients, half-therapeutic-dosage low molecular weight heparin (LMWH) (1 mg/kg daily) could be used for prophylaxis, with a 50% increase in the dose for obesity sufferer[52]. In addition, the American College of Chest Physicians recommends prophylaxis with LMWH or fondaparinux rather than unfractionated heparin or NOACs for all hospitalized COVID patients without contraindications such as current bleeding. Fondaparinux is advised for people who previously had heparin-induced thrombocytopenia. Mechanical thromboprophylaxis (*e.g.*, pneumatic compression device) is also recommended when anticoagulants are unavailable or contraindicated[53,54]. LMWH treatment appears to improve mortality of COVID-19 patients with an increased D-dimer or a high SIC grade, according to publications[55]. Barrett *et al*. discussed the ISTH recommendations, proposing the use of unfractionated heparin (UFH) instead of LMWH for systemic anticoagulation[56]. This is because of the higher risk of renal failure after acute respiratory distress syndrome and the availability of the UFH protamine sulphate antidote. Zhai *et al*. described LMWH as a first-line treatment and UFH as second-line therapy for patients with creatinine clearance of less than 30 mL/min. Both LWMH and UFH may provide further benefits to COVID-19 patients because of their secondary anti-inflammatory characteristics[57].

Only one guideline, the Global COVID-19 Thrombosis Collaborative Group, addresses non-hospitalized COVID-19 patients and advocates extended prophylaxis for people with restricted mobility, a history of VTE, or a current malignancy[58]. The National Institutes of Health and CHEST also recommend routine post-hospital discharge prophylaxis[59]. The National Institutes of Health, the American Society of Haematology, the Anticoagulation Forum, the Global COVID-19 Thrombosis Collaborative Group, and the ISTH recommend individualized therapeutic regimen, such as regimen for intensive care unit patients. The guidelines recommend rivaroxaban or enoxaparin for 14 to 45 d following discharge, depending on the circumstances. For the management of VTE in hospitalized COVID-19 patients, most recommendations advocate parenteral anticoagulation followed by a switch to a NOAC when the patient are transferred to an outpatient environment[58,60].

3.5. Benefits of NOACs

NOACs are great advances in recent medicine because they overcome many disadvantages of traditional anticoagulants. NOACs are selective, synthetic, direct inhibitors of either thrombin or factor Xa. Direct thrombin inhibitors and factor Xa inhibitors act in key areas of the clotting cascade that could limit the formation of plaque. These drugs may be useful in some clinical settings as they inactivate both circulating and thrombus-associated activating coagulation factors and do not induce antiplatelet antibodies[61]. NOACs reduce the risk of severe courses and negative outcomes of SARS-CoV-2 infection, indicating that coagulation play an essential role in COVID-19 pathogenesis. Inhibition of active coagulation factors using NOACs holds promising potential for the therapy of diffuse intravascular coagulation, as some studies have revealed[62]. When compared to VKAs, NOACs had considerably reduced incidence of serious bleeding and provided a net therapeutic benefit, as well as a reduced risk of VTE recurrence even after withdrawal of anticoagulant[63]. Moreover, NOACs have a stronger benefit-risk profile than VKAs, so they are likely to be more useful at discharge[64]. Furthermore, chronical treatment with NOACs could decrease mortality of elderly COVID-19 patients. However, several case reports of thrombotic problems treated by NOACs such as rivaroxaban or apixaban have been published[65]. In addition, a survey of elderly AF patients found that either pre-hospital or in-hospital VKAs or NOACs were positively related to longer survival[66]. Previous use of NOAC therapy is associated with a reduced risk of arterial or venous thrombotic sequelae in COVID-19 outpatients with cardiovascular disease[67]. Retrospective studies have found that edoxaban provides protection against COVID-19-related complications[68]. However, when symptomatic clinically stable COVID-19 outpatients were randomly assigned with aspirin or apixaban, hospitalization rates of patients with cardiovascular illnesses did not decrease when compared to placebo[69]. The liberation of neutrophil extracellular traps, which is a critical driver of COVID-19 immunothrombosis, was significantly reduced by dabigatran[49]. Dabigatran has excellent effectiveness, safety, and a minimal venture of liver toxicity. It is not metabolized by cytochrome P450 and has a peculiar reversal agent, so it might be utilized as a first-choice anticoagulant in AF patients with COVID-19[70]. Antiviral drugs, such as tocilizumab and remdesivir, which have been shown to be effective in treating severe COVID-19, may cause hepatotoxicity; therefore, it is prudent to use drugs that are likely to cause liver injury, not just for drug-drug action but also for hepatotoxicity[71,72]. However, a ENGAGE AF-TIMI 48 analysis discovered that incidence of hemorrhage, but not thromboembolic

consequences, were increased among patients with liver illnesses receiving oral anticoagulation. Despite the fact that there were no significant differences between the two medications, drug-induced hepatic damage was recorded in 2 (0.03%) of patients who received edoxaban, 1 (0.01%) of patients who received low-dose edoxaban, and none of the patients who received warfarin[73]. In fact, NOAC is not regarded as a desirable alternative in any of these seven recently released guidelines on the issue. It is therefore advised to utilize LMWH or UFH in patients treated with dexamethasone, anti-IL6/1 or antiviral, which can subsequently be transferred to a NOAC[74]. However, the usage of NOACs in COVID-19 patients in hospital wards is being investigated. For COVID-19 patients with low-risk thromboembolism, a patient-tailored algorithm that uses D-dimer limits to design a patient-specific anticoagulation standard enoxaparin regimen is recommended[75]. Low-intensity rivaroxaban is being studied in the ACOVACT (Austrian Coronavirus Adaptive Clinical Trial) and XACT (Factor Xa Inhibitor Versus Standard of Care Heparin in Hospitalized Patients with COVID-19) studies. These will evaluate outcomes such as intensive care unit admission, intubation in hospitalized patients, and all-cause mortality.

4. Conclusion

COVID-19 is an infectious disease that causes thrombotic events by inducing a pro-inflammatory and prothrombotic condition. As a result, early detection and close monitoring of COVID-19 thrombotic consequences could save lives. Recently, NOACs have generated a lot of excitement about their anticoagulant potential. NOACs will likely be used more extensively in COVID-19 management for their advantages in direct action, absence of anticoagulation monitoring, and easy dosage regimens with oral delivery.

Conflict of interest statement

The authors report no conflict of interest.

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