Pharmacological Agents Targeting Coagulopathy in COVID-19: A Review

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Abstract

Infection with severe acute respiratory syndrome coronavirus (SARS-CoV-2) and the resultant syndrome COVID-19 has wrecked the entire world. The disease mostly manifests as mild viral pneumonia but in a small proportion of patients it can produce an intense inflammatory and prothrombotic state leading to multi-organ failure and even death. Varying incidences of venous thromboembolism (VTE) have been found in COVID-19 patients. This review describes the role of various pharmacological agents used prophylactically as well as therapeutically for thromboembolism in such patients. The anticoagulants which are administered as antithrombotic therapy can be used parenterally (heparin and direct thrombin inhibitors) or orally (direct oral thrombin inhibitors). The mechanism of action, pharmacology, usage, and adverse effects of such agents has been discussed especially in the context of ongoing COVID-19 pandemic. As a result of various completed and ongoing clinical trials, scientific community has collected promising evidence and formulated guidelines regarding the role of anticoagulants in COVID-19 patients.

Keywords

COVID-19 · Thromboprophylaxis · Anticoagulants · Heparin · DOAC · Prophylactic dose · Therapeutic dose

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18.1 Introduction

COVID-19 has crippled the healthcare system of many countries in the world. It has a detrimental effect on various systems of the body including respiratory system, cardiovascular system, and immune system. One of the major complications of COVID-19 is the development of a pro-thrombotic state. Endothelial injury and proinflammatory cytokines activate the coagulation cascade and thus it results in thromboembolic events. The risk of venous thromboembolism is even higher if the patient is immobilized because of severe disease. This has evoked an interest in the role of anticoagulants in the prevention and treatment of coagulopathy-related complications in COVID-19. Anticoagulant therapy has a role to play as it helps to reduce fibrin deposition and formation of microthrombi and prothrombotic state in such patients.

Recommendations and guidelines issued by various societies dealing with the management of coagulopathy in COVID-19 patients recommend the use of antithrombotic thromboprophylaxis in hospitalized patients (Hajra et al. 2020; Marchandot et al. 2020). Before discussing the recommendations of these guidelines in detail, the pharmacological agents which target various steps of the coagulation cascade (Fig. 18.1) will be elaborated.

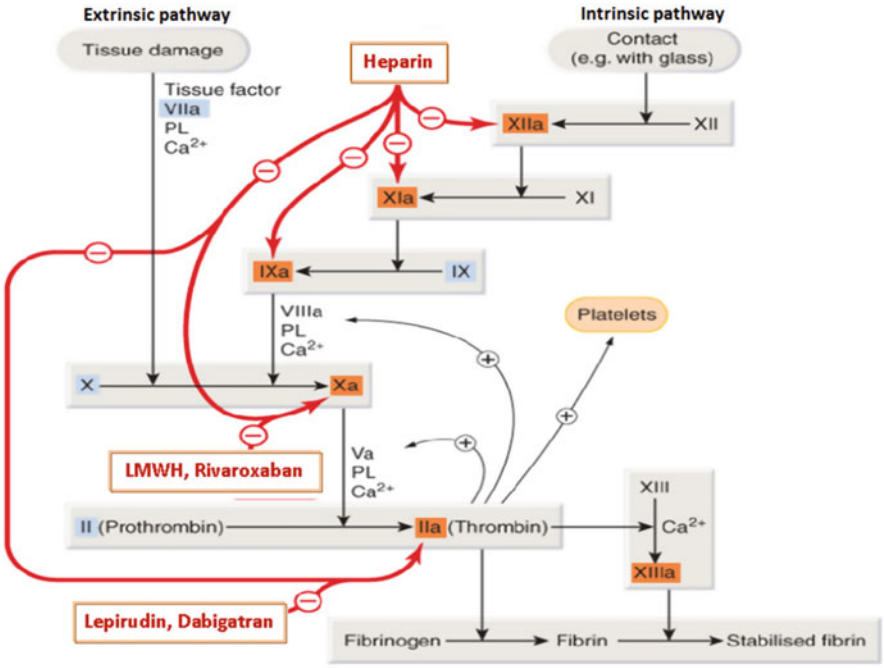

Fig. 18.1 Coagulation cascade depicting the site of action of various anticoagulants (Ritter et al. 2019)

18.2 Classification of Anticoagulants

1. Parenteral anticoagulants
   (a) Heparin and its derivatives
      - Unfractionated heparin (UFH)
      - Low-molecular-weight heparin (LMWH)
      - Fondaparinux
   (b) Other parenteral anticoagulants
   Direct thrombin inhibitors (DTIs)
      - Lepirudin
      - Desirudin
      - Bivalirudin
      - Argatroban
2. Oral anticoagulants
   (a) Coumarin derivatives, e.g., warfarin
   (b) Direct oral anticoagulants (DOACs)
      - Direct thrombin inhibitors
        – Dabigatran
      - Direct factor Xa inhibitors
        – Rivaroxaban
        – Apixaban
        – Edoxaban

18.3 Anticoagulant Drugs

18.3.1 Heparins

Heparin is present in the secretory granules of mast cells. On getting released from mast cells, it gets ingested and destroyed by macrophages and cannot be detected in plasma under normal circumstances. Unfractionated heparin (UFH) chains have a mean molecular weight of 15,000 (range 5000–30,000). Low-molecular-weight heparin (LMWH) is prepared from UFH and consists of smaller fragments of heparin and has a mean molecular weight of about 5000 (range 2000–8000). Fondaparinux is a synthetic heparin derivative and congener of the pentasaccharide sequence in heparin with a molecular weight of 1728 (Hogg and Weitz 2018).

18.3.1.1 Mechanism of Action

The anticoagulant effect of heparin is mediated by an endogenous component of plasma—antithrombin. Antithrombin is an endogenous anticoagulant and a plasma protease inhibitor, synthesized in the liver. It is a suicide substrate for the target enzymes. Antithrombin neutralizes the clotting factor proteases, particularly thrombin and factor Xa, by forming stable complexes with them. Heparin acts by

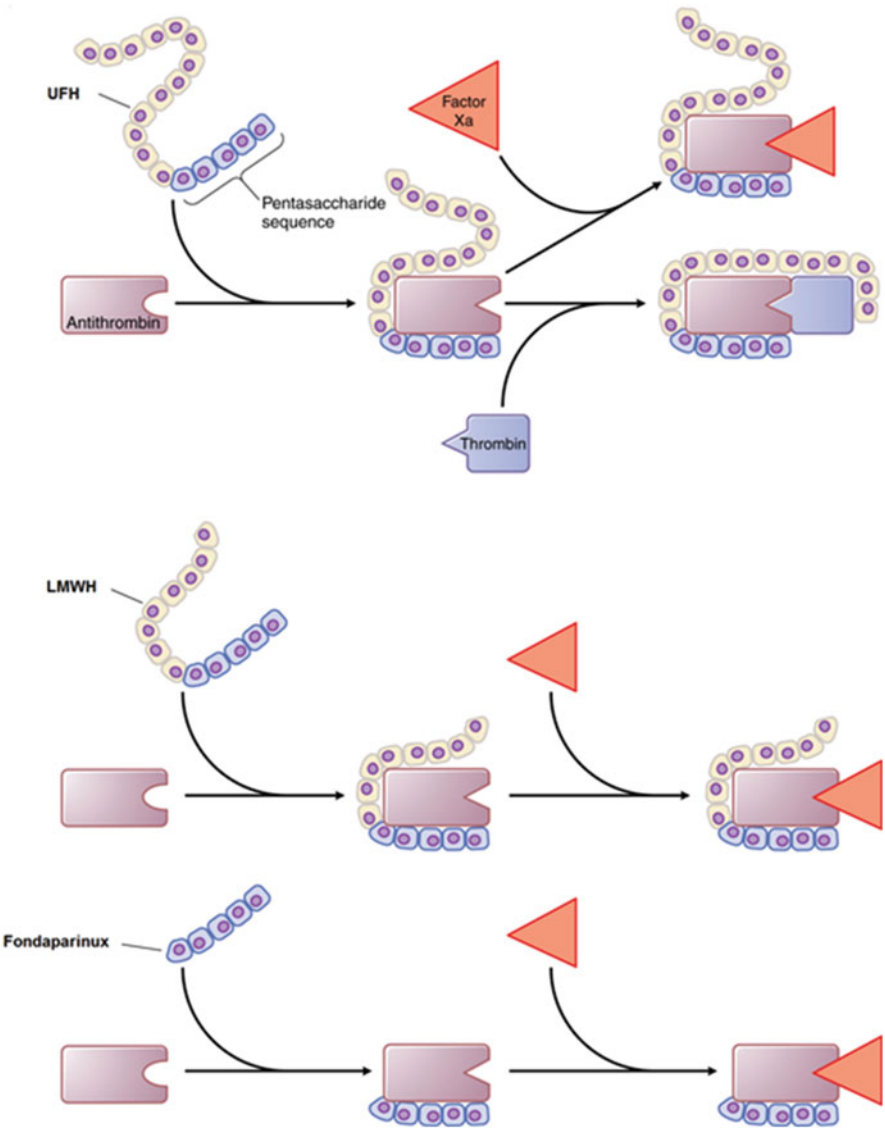

Fig. 18.2 Mechanism of action of UFH, LMWH, and fondaparinux

increasing the rate of these, or otherwise through slow reactions by about 1000-fold. It binds to antithrombin through its unique pentasaccharide sequence, thus inducing a conformational change that accelerates the interaction of antithrombin with factor Xa. Heparin should simultaneously bind to both antithrombin and thrombin to potentiate thrombin inhibition as shown in Fig. 18.2. This bridging can be achieved only by unfractionated heparin which has at least 18 saccharide units with a

molecular weight of 5400 (Hogg and Weitz 2018). Almost all chains of UFH have the capacity to inhibit thrombin. Thus, UFH has equal capacity to enhance the inhibition of both thrombin and factor Xa.

LMWH exerts its anticoagulant activity by selectively inhibiting factor Xa with little effect on thrombin. With less than 18 saccharide units, LMWHs are of insufficient length to catalyze the inhibition of thrombin. However, these are able to accelerate factor Xa inhibition by antithrombin as it is mainly because of the conformational change in antithrombin brought about by binding of the pentasaccharide sequence. Thus, LMWH has its anticoagulant effect largely because of factor Xa inhibition (Fig. 18.2).

Fondaparinux accelerates only factor Xa inhibition by antithrombin, by inducing conformational change, as the pentasaccharide sequence is short and cannot bind antithrombin and thrombin together (Fig. 18.2).

18.3.1.2 Pharmacology

UFH, LMWH, and fondaparinux are administered by parenteral routes of administration as these cannot be absorbed by the GI mucosa. UFH is given by continuous or intermittent intravenous infusion (IV) or subcutaneous (SC) injection. When heparin is given IV it has immediate onset of action but subcutaneous injection has a delayed onset of about 1–2 h and variable bioavailability. UFH has dose-dependent clearance and half-life. At low doses, heparin has a short half-life as it binds to the endothelium. The half-life increases with increasing doses as the endothelium becomes saturated and clearance of heparin is reduced. Intravenous heparin in doses of 100, 400, or 800 units/kg has a half-life of about 1, 2.5, and 5 h, respectively. Also, certain heparin-binding proteins in the plasma reduce the anticoagulant activity of heparin. The levels of plasma proteins vary from patient to patient, thus resulting in a variable anticoagulant activity of heparin. These proteins also include certain acute-phase reactants in ill patients and platelet factor 4 released from activated platelets. Consequently, heparin therapy requires monitoring to achieve optimal therapeutic response. This can be done by monitoring the activated partial thromboplastin time (aPTT) or by anti-factor Xa level. A two- to threefold rise in aPTT usually denotes adequate therapeutic levels of heparin.

LMWH is usually given subcutaneously. Because of shorter chains, LMWHs bind weakly to the endothelium, macrophages, and heparin-binding proteins. Therefore, it has dose-independent half-life and clearance. The plasma half-life of LMWH is nearly 4 h. The bioavailability on subcutaneous injection is about 90% with a predictable dose response. It can be administered once or twice daily and does not require any monitoring. This makes it a suitable anticoagulant for nonhospitalized patients. In case monitoring is required it can be done using anti-factor Xa levels. LMWH gets excreted mainly by kidneys and can get accumulated in renal insufficiency. Such patients may require monitoring with anti-factor Xa levels. Monitoring of LMWH should also be done in obese patients, pregnancy, infants, children, and patients with mechanical heart valves.

Fondaparinux is administered by subcutaneous route, once a day. Monitoring is not required. It does not bind to the endothelial cells or plasma proteins. The plasma

half-life is 17 h and the clearance is dose dependent. However, it is excreted unchanged in urine. It is recommended that LMWH or fondaparinux should not be given to patients with creatinine clearance <30 mL/min (Hogg and Weitz 2018; Leavitt and Minichiello 2019).

18.3.1.3 Administration and Dosage

Prophylactic dose of **UFH** is 5000 units subcutaneously, twice or thrice a day. This dose does not require monitoring. For therapeutic purpose, weight-based heparin nomograms are utilized to standardize the dose of heparin and to achieve therapeutic aPTT in a short time. An initial bolus dose of 5000 units or 70 units/kg of heparin is administered followed by an infusion of 12–15 units/kg/h.

LMWH doses for prophylactic or therapeutic purpose vary depending upon the LMWH preparation. For prophylaxis, usually a dose of 4000–5000 units subcutaneously is administered once a day or 2500–3000 units subcutaneously twice a day. For therapeutic purpose, dose of LMWH in venous thromboembolism (VTE) is 150–200 units/kg, given once daily.

Fondaparinux is given at a dose of 2.5 mg once a day for prevention of VTE. For established VTE, the dose is 7.5 mg once daily (Weitz 2018).

Adverse Effects

1. Bleeding: This is a major complication with these drugs, although UFH carries the highest risk. Risk increases with increasing doses of heparin and any underlying cause, e.g., recent surgery, trauma, peptic ulceration, underlying hemostatic defects, and antiplatelet or fibrinolytic drugs. Elderly women and patients with renal dysfunction are more prone. Mild bleeding can usually be controlled by discontinuing the drug but life-threatening hemorrhage may require administration of heparin antagonist protamine sulfate, through slow intravenous infusion. For every 100 U of heparin remaining in the patient, 1 mg of protamine sulfate at a rate not exceeding 50 mg in 10 min can be used. Excess amount of protamine should be avoided as it has anticoagulant effect of its own. Also, slow infusion is recommended to reduce the risk of anaphylactoid reaction. Protamine is less effective as an antidote for LMWH and not effective at all against fondaparinux as it can bind only to longer heparin chains.
2. Thrombocytopenia: Heparin-induced thrombocytopenia (HIT) is seen in 1–4% of patients treated with UFH for at least 7 days. It is a hypercoagulable state in which the platelet count is <1,50,000/mL or <50% from pretreatment value. This is an antibody-mediated process resulting in platelet activation and generation of platelet microparticles and thus promotes thrombin generation. There is generation of immunoglobulin G antibodies formed in response to the heparin-platelet factor 4 complexes. LMWH has much lower risk of thrombocytopenia as it binds weakly to platelets, thus causing less platelet factor 4 releases. Fondaparinux does not cause HIT as it does not bind to these proteins. HIT requires discontinuation of heparin and replacement with direct thrombin inhibitors or fondaparinux (Thachil et al. 2020). LMWH should not be used for replacing UFH for HIT in view of the cross-reactivity shown by the antibodies (Zehnder 2018).

3. Osteoporosis: Bone density is reduced with heparin therapy given for a duration of over 1 month. Prolonged therapy has been found to be associated with spontaneous fractures. Heparin reduces the bone formation as well as increases bone resorption. Osteoporosis risk is lesser with LMWH.
4. Enhanced level of transaminases: Mild and reversible elevation in serum transaminase levels without a concomitant rise in serum bilirubin may be seen with heparin therapy (Weitz 2018).

Comparison of Pharmacological Effects of UFH and LMWH

- Given subcutaneously, LMWH has better bioavailability and longer half-life than UFH.
- UFH has dose-dependent half-life and clearance and thus requires frequent dosage adjustments, in contrast to LMWH.
- UFH has less predictable anticoagulant response and therefore requires regular monitoring with aPTT or anti-factor Xa level. LMWH need not be monitored for its anticoagulant activity.
- LMWH has lesser adverse effects including thrombocytopenia and osteoporosis, so it is safer than UFH especially for long-term use.

18.3.2 Parenteral Direct Thrombin Inhibitors

Lepirudin and desirudin are recombinant forms of hirudin. They are eliminated by the kidneys; the half-life is about 2 h after subcutaneous administration and about 10 min after IV infusion. Desirudin is used for thromboprophylaxis in patients undergoing hip replacement surgery. Both of these are also used for the treatment of thrombosis in patients with HIT (Kelton et al. 2013). Lepirudin can be given by IV infusion if rapid anticoagulation is desired; otherwise it is given by subcutaneous route. Caution should be exercised in patients with impaired renal function. Daily monitoring of serum creatinine and aPTT needs to be done.

Bivalirudin is administered intravenously. It is the shortest acting parenteral DTI with a plasma half-life of 25 min. It is partially excreted via kidneys; dosage reductions are recommended for patients with renal impairment. aPTT can be used to evaluate its activity. Bivalirudin is approved as an alternative to heparin for patients who undergo percutaneous coronary intervention (PCI). It has also been found to be useful in HIT patients who require PCI or cardiac bypass surgery (Barria Perez et al. 2016).

Argatroban is administered intravenously with a half-life of 40–50 min. It undergoes hepatic metabolism and is excreted in bile. Therefore, it is safe in patients with renal impairment, but dose needs to be reduced in patients with hepatic dysfunction. It is approved both for prophylaxis and treatment of patients who have or are at risk of developing HIT (Grouzi 2014). The anticoagulant effect is monitored using aPTT.

18.3.3 Direct Oral Anticoagulants (DOACs)

For a long time, vitamin K antagonists such as warfarin were the only option available as oral anticoagulant. However, the scenario changed with the arrival of direct oral anticoagulants, which include dabigatran, rivaroxaban, apixaban, and edoxaban. DOACs have consistently shown equivalent antithrombotic efficacy and lower bleeding rates when compared with conventional warfarin therapy. However, one should be cautious that owing to their short half-life, patient noncompliance will quickly lead to loss of anticoagulant effect and risk of thromboembolism.

18.3.3.1 Advantages of DOACs Over Conventional Oral Anticoagulants

The new direct oral anticoagulants represent a significant advance in the prevention and therapy of thrombotic disease. Their advantages include

- Predictable pharmacokinetic parameters (including bioavailability) which permit fixed dosing and also predictable anticoagulant response which makes routine coagulation monitoring unnecessary
- The quick onset of action of these agents which allows for immediate anticoagulation
- Fewer drug and dietary interactions in comparison with warfarin, which is known to have multiple drug-drug and drug-food interactions
- Convenience of once- or twice-daily oral dosing

18.3.3.2 Direct Thrombin Inhibitor

Dabigatran is the only oral direct thrombin inhibitor approved by the FDA.

Mechanism of Action: It acts by the blockade of the active site of free as well as clot-bound thrombin in a competitive and reversible manner. This further blocks thrombin-mediated conversion of fibrinogen to fibrin and hence feedback activation of coagulation cascade.

Pharmacology: The maximum effect occurs in 2 h with a half-life of 12–14 h. The oral bioavailability is 3–7%. Dabigatran is 35% bound to plasma proteins. Renal impairment leads to prolonged drug clearance. Hence, dose reduction is needed in the presence of severe renal insufficiency (creatinine clearance 15–30 mL/min) (Hogg and Weitz 2018).

18.3.3.3 Direct Factor Xa Inhibitors

Mechanism of Action: Rivaroxaban, apixaban, and edoxaban inhibit factor Xa in the final common pathway of clotting leading to reduction in generation of thrombin. Hence, this leads to suppression of platelet aggregation and formation of fibrin.

Pharmacology: Bioavailability of rivaroxaban is 80% with maximum effect seen in 3 h. Its half-life is 7–11 h. If given with meals, its absorption is enhanced. It is 95% plasma protein bound. Dose reduction is required in patients with renal impairment or severe hepatic dysfunction as levels are increased in such patients.

Apixaban has oral bioavailability of 50% with peak onset of action 1–3 h after ingestion. Its absorption is not affected by the presence of food.

Edoxaban has oral bioavailability of 62% and peak levels are observed 1–2 h after ingestion. Food has no effect on its absorption. The drug does not undergo hepatic metabolism, and hence can be used safely in patients with liver disease. The plasma level is increased in the presence of renal dysfunction and low body weight. Therefore, the dose should be reduced in patients with a creatinine clearance between 15 and 50 mL/min, in those with a body weight of 60 kg or less (Hogg and Weitz 2018).

Indications for DOACs

1. To prevent stroke in patients who have nonvalvular atrial fibrillation: For this indication, they have been compared with warfarin in four randomized trials that enrolled 71,683 patients. The results demonstrated that DOACs have a better benefit-to-risk ratio compared with warfarin, and have comparable relative efficacy and safety among a broad spectrum of patients with atrial fibrillation (Zehnder 2018).
2. DOACs were compared with conventional anticoagulants in patients with acute venous thromboembolism in a large group of patients. The results showed that DOACs are non-inferior to well-managed warfarin for the treatment of VTE, but are linked with significantly less bleeding episodes. Parenteral anticoagulant therapy has to be given for a minimum period of 5 days before starting dabigatran. But edoxaban, rivaroxaban, and apixaban can be administered as an all-oral regime starting with a higher dose for 21 days and 7 days, respectively (Weitz 2018).
3. In some countries, lower dose regime of once-daily dabigatran is approved for thromboprophylaxis after knee or hip arthroplasty. Rivaroxaban and apixaban are also licensed for the same indication (Weitz 2018).

Adverse Effects and Contraindications of DOACs

1. As with any anticoagulant drug, bleeding is the major adverse effect. In elderly patients with atrial fibrillation, the risk of major bleed with DOACs is comparable to that with warfarin. Nevertheless, the risk of intracranial bleed is markedly lower as compared with warfarin. The only exception is GIT; incidence of GI bleed with dabigatran, rivaroxaban, and edoxaban, but not apixaban, is higher than with warfarin. This might be due to the ability of unabsorbed drug in the GIT to promote bleed from preexisting lesions (Zehnder 2018). The risk of bleeding is higher if patient is also taking antiplatelet or nonsteroidal anti-inflammatory agents.
2. Dyspepsia is observed in up to 10% of patients on dabigatran but taking the drug with food reduces the incidence. Dyspepsia is not common with rivaroxaban, apixaban, and edoxaban.
3. DOACs are contraindicated for prevention of stroke in patients with mechanical heart valves.
4. All DOACs, being small molecules, can easily pass through placenta. Hence, they are contraindicated in the setting of pregnancy, and if used by women of childbearing potential, appropriate contraceptive methods should be employed.

They should be avoided in lactating mothers and their safety in children is yet to be established.

18.3.3.4 Drug Interactions of DOACs

All DOACs are substrates for P-glycoprotein efflux pump; so drugs that inhibit P-glycoprotein like verapamil, dronedarone, quinidine, ketoconazole, and clarithromycin may increase their plasma levels whereas concomitant administration of rifampicin which induces P-glycoprotein may decrease their plasma levels. Rivaroxaban and apixaban are metabolized by CYP3A4 enzymes, whereas edoxaban undergoes only minimal CYP3A4-mediated metabolism. Therefore, serum levels of rivaroxaban and apixaban may be altered by concomitant administration of CYP3A4 inducers such as carbamazepine and phenytoin or inhibitors like erythromycin and ketoconazole (Preston 2019; Anderson and Smith 2019).

18.3.3.5 Administration and Dosage

For stroke prophylaxis in patients with nonvalvular atrial fibrillation, dabigatran is given 150 mg twice a day with a dose reduction to 75 mg twice a day if creatinine clearance is between 15 and 30 mL/min; rivaroxaban is administered 20 mg once a day with a dose reduction to 15 mg once a day in patients with a creatinine clearance of 15–49 mL/min; apixaban is given 5 mg twice a day with dose reduction to 2.5 mg twice a day in patients with at least two of the following criteria: age 80 years or more, body weight of 60 kg or less, and serum creatinine >1.5 g/dL; and edoxaban is administered 60 mg once a day with a dose reduction to 30 mg once a day for patients with a creatinine clearance between 15 and 50 mL/min and body weight of 60 kg or less, or receiving concomitant potent P-glycoprotein inhibitors.

For treatment of VTE, dabigatran is administered 150 mg twice daily after a minimum duration of a 5-day course of heparin or LMWH; rivaroxaban is given 15 mg twice a day for 21 days, and then the dose is reduced to 20 mg once a day; apixaban is started 10 mg twice a day for 7 days and then for next 6 months, dose is reduced to 5 mg twice a day after which the dose can be further reduced to 2.5 mg twice a day; and edoxaban is administered at a dose of 60 mg once a day after a minimum duration of a 5-day course of heparin or LMWH. The dose of edoxaban is reduced to 30 mg once daily for patients with a creatinine clearance of 15–50 mL/min and body weight of 60 kg or less, or receiving concomitant potent P-glycoprotein inhibitors.

For thromboprophylaxis after hip or knee replacement surgery, rivaroxaban is administered 10 mg once a day while apixaban is given 2.5 mg twice a day. The drugs are usually given for 14 days after knee arthroplasty and for 35 days' duration after hip arthroplasty (Weitz 2018).

The major characteristic features of various DOACs are highlighted in Table 18.1.

18.3.3.6 Assessment and Reversal of DOACs' Effects

For qualitative assessment of anticoagulant activity, prothrombin time can be utilized for factor Xa inhibitors and aPTT for dabigatran. Rivaroxaban and edoxaban

Table 18.1 Comparison of the features of DOACs

Feature	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prodrug	Yes	No	No	No
Bioavailability (%)	3–7	80	50	62
Half-life (h)	12–14	7–11		
Renal excretion (%)	80	33	25	35
Drug interactions	P-gp	CYP 3A4/P-gp	CYP 3A4/P-gp	P-gp
Dosing regimen	Twice a day	Once a day	Twice a day	Once a day
Antidote	Idarucizumab	Andexanet	Andexanet	Andexanet

Abbreviations: *P-gp* P-glycoprotein, *CYP* cytochrome p450

prolong the prothrombin time more than apixaban. Reversal of anticoagulant effect should be considered in patients with life-threatening bleeding, like intracranial bleeding, if bleeding continues despite supportive measures or urgent surgery is required. Idarucizumab, a humanized monoclonal antibody, is a specific reversal agent for dabigatran. The recommended dose is 5 g as an intravenous bolus injection. If bleeding recurs, a second dose may be given. Andexanet alfa is a reversal agent for various oral Xa inhibitors. By sequestering circulating factor Xa inhibitors, it quickly reverses the anti-factor Xa activity and restores thrombin generation. It is administered as an IV bolus followed by a 2-h infusion. Higher doses are required to reverse rivaroxaban or edoxaban than apixaban. Ciraparantag, a potential reversal agent for all DOACs, is at an early stage of development (Hogg and Weitz 2018). Until these reversal agents are available, prothrombin complex concentrate can be considered for reversal of the oral factor Xa inhibitors in patients with life-threatening or ongoing bleeding.

18.4 Anticoagulant Therapy in COVID-19 Patients: The Present Scenario

There are more than ten international guidelines and guidance statements that emphasize the role of anticoagulants in COVID-19. The major ones include the 2020 CHEST COVID-19 Guidelines (COVID-19 Guidelines 2020), the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) COVID-19 clinical guidance, the American Society of Hematology (ASH) 2021 guidelines, the Anticoagulation (AC) Forum interim clinical guidance, and the American College of Cardiology (ACC) clinical guidance.

The ISTH-SSC guidance in hospitalized patients with COVID-19 suggests that both critically ill patients (who develop respiratory or cardiovascular failure normally requiring advanced clinical support in the ICU or CCU) and acutely ill patients (who require hospital admission without advanced clinical support) should receive standard prophylactic doses of LMWH or UFH, although intermediate-intensity LMWH may be considered for patients at high VTE risk. The convenient dosage schedule of once-daily administration of LMWH gives it an edge over UFH which

has to be injected twice or thrice daily and has a higher incidence of heparin-induced thrombocytopenia (Zhai et al. 2020). The ISTH-SSC suggests that therapeutic-intensity anticoagulation should not be used until clear-cut scientific evidence is available in its favor. Although certain DOACs are approved for prophylaxis in hospitalized patients, they should be used cautiously in COVID-19 patients in whom co-administration of immunosuppressant, antiviral, and other experimental drugs may interfere with their action. The guidelines also suggest the duration for which thromboprophylaxis should be given in hospitalized COVID-19 patients. In high-VTE-risk medically ill patients, as in pneumonia or sepsis, this risk may extend up to 6 weeks posthospital discharge. Based on the recent data, it is recommended that extended-duration thromboprophylaxis for nearly 4 weeks with prophylactic dose LMWH (e.g., enoxaparin, dalteparin) or a DOAC (e.g., rivaroxaban) should be given. For confirmed VTE in hospitalized COVID-19 patients, LMWH should be preferred in patients when they are hospitalized followed by DOACs at the time of discharge (Spyropoulos et al. 2020).

The American Society of Hematology (ASH) 2021 panel has recommended using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19-related acute illness and critical illness without a suspected or confirmed VTE. Pertaining to the choice of a specific agent, not enough clinical trials have been conducted comparing different anticoagulants. The drug (for example low-molecular-weight heparin, UFH) may be chosen based upon its availability, cost, facilities, familiarity, and effort to minimize PPE usage or reduce the exposure of hospital staff to COVID-19-infected patients. Various patient-specific factors for example renal function, history of HIT, and issues regarding GIT absorption should also be taken into consideration (Cuker et al. 2021).

The anticoagulant regimens have been classified on the basis of intensity as prophylactic, intermediate, and therapeutic intensity as shown in Table 18.2.

Similar to the views expressed in other guidelines (Singhania et al. 2020), the expert panel report from CHEST also recommends the use of anticoagulant thromboprophylaxis in both acutely ill and critically ill patients. These guidelines favor LMWH or fondaparinux over UFH and these drugs over DOACs in acutely ill patients. In critically ill patients, order of preference for thromboprophylaxis is LMWH followed by UFH and then fondaparinux or DOACS. LMWH has the advantage of limited staff exposure as compared to UFH. The panel cautions against the use of DOACs especially in critically ill patients because of hemodynamic instability, chances of possible drug interactions with other adjunctive therapies, and high risk of acute kidney injury. Moreover, the use of DOACs carries a high risk of rapid clinical deterioration and gastrointestinal disturbances. The other issues of concern with DOAC use are cost implications and/or lack of reversal agents in some hospitals (Bikdeli et al. 2020). As per the guidelines, inpatient thromboprophylaxis only is recommended over extended thromboprophylaxis after hospital discharge (Moores et al. 2020).

The AC Forum document also includes suggestions on thromboprophylaxis in pregnant women and monitoring strategies for parenteral anticoagulation therapy (Barnes et al. 2020).

Table 18.2 Classification of anticoagulant regimens by intensity (Cuker et al. 2021)

Prophylactic intensity
Apixaban 2.5 mg, orally, twice a day
Dabigatran 220 mg, orally, once a day
Dalteparin 5000 Unit, subcutaneously, once a day
Enoxaparin 40 mg (4000 Unit), subcutaneously, once a day
Fondaparinux 2.5 mg, subcutaneously, once a day
Unfractionated heparin 5000 Unit, subcutaneously, twice a day
Unfractionated heparin 5000 Unit, subcutaneously, thrice a day
Rivaroxaban 10 mg, orally, once a day
Intermediate intensity
Enoxaparin 0.5 mg/kg (50 U/kg), subcutaneously, twice a day (if CrCl >30 mL/min)
Enoxaparin 0.5 mg/kg (50 U/kg), subcutaneously, once a day (if CrCl <30 mL/min)
Unfractionated heparin 7500 Unit, subcutaneously, thrice a day
Dalteparin 5000 Unit, subcutaneously, twice a day
Therapeutic Intensity
Apixaban 5 mg, orally, twice a day
Apixaban 10 mg, orally, twice a day
Argatroban, intravenous to target aPTT therapeutic range as per institutional guidelines
Bivalirudin, intravenous to target aPTT therapeutic range as per institutional guidelines
Dabigatran 75 mg, orally, twice a day (if CrCl 15–30 mL/min)
Dabigatran 150 mg, orally, twice a day (if CrCl >30 mL/min)
Dalteparin 100 Unit/kg, subcutaneously, twice a day
Dalteparin 150 Unit/kg, subcutaneously, once a day
Edoxaban 30 mg, orally, once a day (≤60 kg, CrCl 15–50 mL/min)
Edoxaban 60 mg, orally, once a day (weight ≥60 kg and CrCl >50 mL/min)
Enoxaparin 1 mg/kg (100 Unit/kg), subcutaneously, twice a day (for CrCl >30 mL/min)
Enoxaparin 1.5 mg/kg (150 Unit/kg), subcutaneously once a day (for CrCl >30 mL/min)
Enoxaparin 1 mg/kg (100 Unit/kg), subcutaneously, once a day (for CrCl <30 mL/min)
Fondaparinux 5 mg, subcutaneously, once a day (if weight <50 kg and CrCl >50 mL/min
Fondaparinux 5 mg, subcutaneously, once a day (if weight 50–100 kg and CrCl 30–50 mL/min)
Fondaparinux 7.5 mg, subcutaneously, once a day (if weight 50–100 kg and CrCl >50 mL/min)
Fondaparinux 7.5 mg, subcutaneously, once a day (if weight >100 kg and CrCl 30–50 mL/min)
Fondaparinux 10 mg, subcutaneously, once a day (if weight >100 kg and CrCl >30 mL/min)
Unfractionated heparin 250 Unit/kg, subcutaneously every 12 hourly
Rivaroxaban 15 mg, orally, twice a day
Rivaroxaban 15 mg, orally, once a day (for GFR 15–50 in AF patients)
Rivaroxaban 20 mg, orally, once a day

Abbreviations: *AF* Atrial fibrillation, *aPTT* Activated partial thromboplastin time, *CrCl* Creatinine clearance, *GFR* Glomerular filtration rate

Heparin, in addition to anticoagulant effects, has been found to be especially useful in COVID-19 patients by virtue of its additional anti-inflammatory (Young 2008) and antiviral properties (Mukhopadhyay et al. 2010; Ghezzi et al. 2017). Inhaled forms of heparin have also been tried as COVID-19 ARDS is known to

cause significant pulmonary injury in the form of diffuse alveolar damage with extensive pulmonary coagulation activation (Thachil et al. 2020). UFH prevents SARS-CoV-2 from binding with ACE-2 and thus infecting cells. Also, as an antiviral, if administered via inhalational route, it may prevent disease progression (Van Haren et al. 2020).

Although none of the societies recommend routine use of DOACs for anticoagulant thromboprophylaxis (Flaczyk et al. 2020; Schulman et al. 2020) there are very few published studies which favor the use of DOACs for thromboprophylaxis. A retrospective, observational cohort study was conducted by Wenzler et al. (2020) to describe the safety and efficacy outcomes of the use of therapeutic dose of apixaban in critically ill ICU patients with severe COVID-19. The results indicated that apixaban appeared safe and efficacious in this high-risk population. None of the participants had any major bleeding event or any other serious adverse effect in spite of the patient cohort suffering from high incidence of renal dysfunction and severe respiratory illness leading to ARDS. Hence, apixaban may be considered as a safe and effective alternative to UFH or LMWH in hospitalized patients with COVID-19, including those with severe disease. The major advantages of apixaban are that it can be given twice a day and requires less frequent monitoring. Also, the exposure of hospital staff and PPE use is minimized. Further, apixaban has an additional anti-inflammatory property similar to that of UFH and LMWH through inhibition of plasma-evoked superoxide generation (Ishibashi et al. 2014).

18.5 Conclusion

Ever since the onset of the pandemic, a lot of clinical trials are being conducted on various strata of population based on different set of criteria. Consequently, a plethora of scientific literature addressing varied issues (including coagulopathies) related to COVID-19 has been emerging over time. Anticoagulants, by acting on various steps of coagulation cascade, have been found to be extremely useful for prophylaxis and treatment of thromboembolism. Various internationally recognized societies have issued guidelines regarding management of COVID-19-associated coagulopathies. These guidelines have significant similarities as well as differences but they all unanimously agree that thromboprophylaxis should be given in all hospitalized patients with COVID-19 infection. There are a number of issues including choice of anticoagulant, dose and duration of thromboprophylaxis, and postdischarge treatment, for which studies are ongoing and the scientific literature is being updated continuously. The clinicians need to keep themselves apprised of the latest guidelines for optimal management and benefit of patients.

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