Initiating and Managing Patients with Venous Thromboembolism on Anticoagulant Drugs: A Practical Overview

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Abstract

Several new oral anticoagulants have recently been approved for the treatment of venous thromboembolism (VTE). In this review, we discuss the currently approved drugs and the factors that influence the choice of anticoagulant in a given patient. Once anticoagulation is initiated, periodic monitoring of adequacy of anticoagulation may be necessary depending on the choice of anticoagulant and patient-related factors, such as renal function. Situations that may warrant need for monitoring and the tests available for this purpose are discussed. We review reversal of anticoagulation in urgent/emergent situations as well as perioperative anticoagulation interruption in the elective setting. The data on use of direct oral anticoagulants in patients with compromised renal function, obesity and bariatric surgery, and in the treatment of cancer-associated thrombosis are discussed. The review aims to provide the clinician with the essential information to allow effective and safe use of anticoagulants for the treatment of VTE.

Keywords

- venous thromboembolism
- deep vein thrombosis
- pulmonary embolism
- anticoagulation
- direct oral anticoagulants

Objectives: Upon completion of this article, the reader will be able to identify (1) considerations that determine choice of anticoagulant; (2) advantages and pitfalls of the direct acting oral anticoagulants; and (3) anticoagulation management in special populations, such as those with obesity, cancer, and renal dysfunction.

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) are considered to be aspects of the same disease from the standpoint of etiology and approach to management, and together they are commonly referred to as venous thromboembolism (VTE). The estimated annual incidence of VTE is 300,000 to 600,000 cases in the United States alone.[1] Several new anticoagulant drugs have been approved for the treatment of VTE in recent years. These are all oral agents that specifically target either coagulation factors IIa or Xa, and are referred to as direct acting oral anticoagulants (DOACs), sometimes also termed new oral anticoagulants (NOACs) or target-specific oral anticoagulants (TSOACs).[2] A recent meta-analysis of clinical trials comparing the DOACs to

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vitamin K antagonists (VKAs; e.g., warfarin) found that the DOACs were as efficacious as VKAs, but had a more favorable bleeding risk profile, that is, less fatal, intracranial, major and clinically relevant nonmajor bleeding in patients with VTE.[3,4] This has resulted in the DOACs being recommended over VKAs for the management of non–cancer-associated VTE in recent antithrombotic treatment guidelines.[5,6] This review will focus on the approach to initiation of anticoagulation for the treatment of acute VTE, including laboratory considerations and factors that determine suitability for use of the newer agents. We will also discuss strategies for reversal of anticoagulation in case of major bleeding and the use of DOACs in certain subgroups of patients, such as those with cancer, obesity, and renal impairment where there are limited data to guide their use.

Initiation of Anticoagulation

Currently approved agents for the treatment of VTE are summarized in ►**Table 1**. In general, DOACs are recommended over VKA in patients with VTE,[5,6] but several factors should be considered in determining the appropriate anticoagulant drug for an individual patient. These can be broadly subdivided into patient-specific factors, comorbidities, and disease-specific factors. The patient's preference, convenience of anticoagulant drug and lifestyle/dietary habits also factor into the decision on choice of anticoagulant. These are summarized in ►**Table 2**.

A. *DOACs:* Prior to initiation of DOAC therapy, the following baseline laboratory tests should be obtained:

- Complete blood cell count (CBC) to ensure an adequate platelet count
- Serum creatinine with calculation of glomerular filtration rate (GFR)
- Assessment of liver function. The authors consider an aspartate transaminase (AST), alanine transaminase (ALT), and total bilirubin to be appropriate tests, but it is not clear whether these tests are really needed in patients with no known liver disease.

Once DOAC therapy is initiated, periodic measurement of laboratory tests is not needed if the baseline tests are normal. However, in the patient with comorbid diseases or the elderly, periodic serum creatinine measurements are appropriate. In any patient on long-term anticoagulation, an annual CBC may be appropriate to screen for the development of anemia from overt or occult bleeding.

Table 1 Approved anticoagulant drugs for treatment of VTE

Drug	Treatment dose	Dose adjustment for renal function
Unfractionated heparin	*Continuous IV:* 80 U/kg bolus followed by infusion at 18 U/kg/h; infusion rate adjusted to maintain aPTT 1.5–2× baseline *SQ*: 333 U/kg followed by 250 U/kg BID	None recommended
Enoxaparin (Lovenox)	1 mg/kg SQ BID (or) 1.5 mg/kg SQ once daily	For CrCl < 30 mL/min
Dalteparin (Fragmin)	Month 1: 200 IU/kg SQ once daily *Month 2 onward*: 150 IU/kg SQ once daily Total daily dose not to exceed 18,000 IU	For CrCl < 30 mL/min, adjust dose to maintain anti-Xa level 0.5–1.5 IU/mL
Tinzaparin (Innohep)	175 IU/kg SQ once daily	Use with caution for CrCl < 30 mL/min; avoid in patients 90 years or older with CrCl < 60 mL/min
Fondaparinux (Arixtra)	Weight <50 kg: 5 mg SQ once daily Weight 50–100 kg: 7.5 mg SQ once daily Weight >100 kg: 10 mg SQ once daily	Use with caution for CrCl 30–50 mL/min, avoid if CrCl <30 mL/min
Vitamin K antagonists (Warfarin) (Coumadin, Jantoven)	Dose titration to therapeutic INR between 2 and 3	None recommended
Dabigatran (Pradaxa)	150 mg PO BID after 5–10 days of parenteral anticoagulation	Avoid if CrCl <30 mL/min
Rivaroxaban (Xarelto)	*First 3 wk*: 15 mg PO BID *After 3 wk*: 20 mg PO once daily	Avoid if CrCl <30 mL/min
Apixaban (Eliquis)	*First week*: 10 mg PO BID *After first week*: 5 mg PO BID *After "at least 6 mo"*: 2.5 mg PO BID	None recommended
Edoxaban (Savaysa)	60 mg PO once daily after 5–10 days of parenteral anticoagulation	For CrCl <15–50 mL/min; avoid if CrCl <15 mL/min

Abbreviations: SQ: subcutaneously; PO: by mouth; BID: twice daily; CrCl: creatinine clearance.

Table 2 Factors influencing choice of anticoagulant drug

	Comments
Patient-related factors	
• Patient preference • Weight • Poor adherence to therapy	Preferred may be a once daily drug or agent with an approved antidote; one without dietary restrictions; a drug that does not require routine monitoring; and one with fewer drug–drug interactions Insufficient data exit for the use of DOACs in patients <50 kg and >120 kg (or a body mass index >40 kg/m^2); thus, VKA may be a better choice. An easily monitored agent may be a better choice
Patient comorbidities	
• Renal insufficiency • Liver disease • H/o GI bleeding • H/o gastric bypass/resection or small bowel/colon resection	Agents with elimination that is not dependent or minimally dependent on renal or liver function would be preferred VKAs or apixaban would be preferred based on data from the atrial fibrillation trials DOACS are not good options because of unpredictability of absorption; VKA strongly preferred
Disease-related factors	
• Cancer-associated VTE • Splanchnic vein thromboses • Antiphospholipid syndrome	LMWHs preferred. DOACs or VKAs reasonable; limited data on the use of both DOACs or VKAs reasonable; data on DOAC use limited to case series; VKAs have a high failure rate

Abbreviations: DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

B. *VKAs:* Prior to the initiation of low-molecular-weight heparin (LMWH)/VKA treatment, a CBC, serum creatinine, and prothrombin time (PT) should be obtained.

Among the DOACs, factors such as renal function, comorbidities, and patient preference help determine which agent is best suited for an individual patient. Some real-life scenarios to illustrate this are listed below:

- In general, a DOAC that can be initiated without need for initial LMWH bridge (i.e., rivaroxaban and apixaban) and is dosed once daily (i.e., Rivaroxaban) is preferred by patients and providers.
- In the setting of renal insufficiency, a DOAC that is least dependent on renal function for elimination (apixaban—only ~25% cleared by kidneys) or an agent that is not dependent on renal function at all (VKAs) would be preferred.
- In patients at high risk for bleeding, a DOAC with an approved, specific reversal agent (i.e., dabigatran) or VKAs would be preferred over an anticoagulant that does not have one.
- In a patient with impaired intestinal absorption, that is, one who had small bowel resection or bariatric surgery, a drug whose anticoagulant effect can be monitored (VKAs) is preferred over one that cannot be easily monitored (i.e., a DOAC).
- Cost of the anticoagulant drug and, in the case of VKAs, the cost associated with monitoring need to be considered. A patient's copay for the drug cost needs to be assessed. All companies making DOACs have patient support programs through which many patients can get a DOAC for a low copay.
- In a patient with concern for nonadherence to therapy, an anticoagulant that can be monitored is preferred (VKA), but even then significant management problems remain.

Monitoring of Anticoagulation

The need for ongoing monitoring of anticoagulation is determined primarily based on the type of anticoagulant used. Traditional anticoagulants such as unfractionated heparin (UFH) and VKAs require scheduled monitoring as dose adjustments are likely to be required periodically.

LMWHs: Routine monitoring for adequacy of anticoagulation is not required for LMWHs. The PT and activated partial thromboplastin time (aPTT) are not sensitive for monitoring LMWHs. If necessary, the level of anticoagulation with LMWHs can be evaluated by measurement of the anti-Xa activity. This test is available at most tertiary centers and can also be ordered as a "send-out" test to a referral test center if not offered at the local laboratory. It is important to notify the laboratory which specific LMWH the patient is on, as this influences the calibrator which the laboratory uses with the anti-Xa assay. The blood sample should be obtained 3 to 4 hours after the SQ injection of LMWH, that is, the time when the peak level is reached. The target therapeutic range varies based on once or twice daily dosing: for twice daily dosing, it is 0.6 to 1.0 U/mL; for once daily dosing, it is 1.0 to 2.0 U/mL.

DOACs: Similar to LMWHs, routine monitoring of anticoagulant activity is not required or recommended for the DOACs, that is, the direct thrombin inhibitor (dabigatran) and the Xa inhibitors (apixaban, edoxaban, and rivaroxaban). These agents do not prolong the PT or aPTT reliably enough that these tests would be useful for monitoring.

More specialized coagulation tests to assess the DOAC's anticoagulant activity have been evaluated and correlate in a linear fashion with concentrations of the DOACs. Mass spectrometry drug testing for the DOACs is also offered by some commercial laboratories and provide reliable drug levels. These tests can, therefore, be used for DOAC monitoring purposes. However, they are as yet not widely available.

Dabigatran: The thrombin time (TT) is highly sensitive to dabigatran and is, thus, a sensitive screen for the presence of any dabigatran concentration in the plasma. However, at therapeutic drug levels, the TT is invariably unmeasurably prolonged and, therefore, not a useful test to quantify therapeutic or supratherapeutic levels. The dilute thrombin time (dTT) and the Ecarin time—either as a clotting or as a chromogenic assay—are good tests to quantify subtherapeutic, therapeutic, and supratherapeutic levels. Similarly, mass spectrometry drug level testing can be used for this purpose.

Apixaban, edoxaban, and rivaroxaban: The anticoagulant effect of these agents can be reliably measured using anti-Xa activity assays if the assay is calibrated with drug-specific standards. They can also be tested via mass spectrometry. However, these tests are also not easily available at this point. While they can be obtained through commercial referral laboratories, the turnaround time is often 3 to 7 days, and the results may be reported without therapeutic ranges provided. The latter is because there are no recommended "therapeutic" levels for these drugs. When drug levels are measured, it is generally to evaluate whether the result is within expected ranges for peak or trough levels for the given drug.[7] However, therapeutic ranges are wide and the correlation between levels and efficacy and safety has only been established for some, but not all of the DOACs.[8,9] Dose adjustments of DOACs based on measured drug levels should not be undertaken, as this practice lacks clinical evaluation. Situations when a clinician may consider testing are listed in ►**Table 3**.

Reversal of Anticoagulation

Immediate reversal of anticoagulation may be needed in the setting of major bleeding or need for urgent/emergent surgery. Only urgent reversal will be discussed in this section. The approach to perioperative interruption of anticoagulation in the setting of elective procedures is discussed separately. Several anticoagulants have approved drug-specific antidotes. These are summarized in ►**Table 4**.

Table 3 Situations where monitoring of DOACs should be considered

• Obesity (BMI >40 kg/m^2; weight >120 kg)
• Underweight (<50 kg)
• Concern over interfering medications
• Fragile, elderly patients
• Borderline renal function
• Recurrent thrombosis on DOAC therapy
• Major bleeding on DOAC therapy
• Assessing persistent DOAC plasma levels prior to surgery
• Assessing patient adherence to anticoagulant therapy

Abbreviations: BMI, body mass index; DOACs, direct oral anticoagulants.

At the University of North Carolina at Chapel Hill, we have developed institutional guidelines for urgent reversal for all anticoagulant drugs. This resource for healthcare providers is available at https://www.med.unc.edu/emergmed/files/emergent-anticoagulation-reversal-guideline-unc-healthcare.

Dabigatran reversal: A target-specific antidote has been developed for reversal of dabigatran. Idarucizumab (Praxbind) is a monoclonal antibody fragment that binds to dabigatran with an affinity that is 350-fold greater than the affinity of dabigatran for thrombin. Idarucizumab, therefore, binds both free and thrombin-bound dabigatran effectively.[10] The reversal dose is 5 g administered as an intravenous bolus. The reversal effect after one bolus dose lasts for at least 24 hours, so that there is no need for continued or repeated antidote dosing. A prospective, multicenter, cohort study to evaluate the efficacy and safety of idarucizumab for the reversal of anticoagulation in patients with life-threatening bleeding or need for urgent/emergent surgical procedures is ongoing (RE-VERSE AD trial). The target for enrollment is 300 patients and data on the initial 90 patients enrolled in this trial were recently published.[11] Idarucizumab administration resulted in rapid and complete reversal of anticoagulation in 88 to 98% of patients who had elevated clotting times prior to reversal.[11] Furthermore, of the patients in whom anticoagulation was reversed for surgery, 92% underwent surgery successfully and without problems achieving hemostasis. There were no major bleeding complications. Idarucizumab was approved by the U.S. Food and Drug Administration (FDA) in October 2015 and by the European Medicines Agency in November 2015.

Anti-Xa drug reversal: The subset of anticoagulant drugs without approved drug-specific antidotes is the oral anti-Xa agents. Potential approaches to restore hemostatic potential with the use of these agents include administration of a single dose of the following: four-factor prothrombin complex concentrate (PCC; KCentra; 50 U/kg intravenously) or activated prothrombin complex concentrate (aPCC; FEIBA; 80 U/kg). It is our preference to use the four-factor PCC in this setting, given that it has less of a risk of thrombosis than aPCC.

Andexanet alfa is a target-specific antidote with efficacy against all anticoagulants that target factor Xa. It is not FDA approved as of September 2016. Andexanet alfa is a recombinant modified factor Xa protein that retains capability to bind anti-Xa drugs but is not biologically functional (no catalytic or membrane-binding activity). The interim report on the first 67 patients treated in the ongoing multicenter, prospective, open-label clinical trial (ANNEXA-4) on the use of Andexanet for reversal of anticoagulation associated with four anti-Xa agents (rivaroxaban, apixaban, edoxaban, and enoxaparin) was recently published.[12] Andexanet was administered as an intravenous bolus followed by a 2-hour infusion. Andexanet was effective in decreasing anti-Xa activity by more than 80% by the end of the infusion and excellent or good hemostatic activity was achieved in 79% of the patients. This study is ongoing and the targeted enrollment is 162 and 230 patients for efficacy and safety outcomes, respectively. The FDA did not

Table 4 Urgent reversal of anticoagulation with specific antidotes

Anticoagulant drug	Reversal agent (dose)	Comments
UFH	Protamine (1 mg/100 U of heparin)	Consider only amount of heparin administered in the 3 h prior to protamine for dose calculation. Risk for allergic/hypersensitivity reactions in patients with fish allergy or previous protamine exposure Cap protamine at 50 mg/dose. Reversal effect in 5–10 min, monitor aPTT Repeat doses may be necessary
LMWH	Protamine (1 mg/mg of LMWH if anticoagulant given <8 h prior to protamine) (0.5 mg/mg of LMWH if anticoagulant given 8–12 h prior to protamine)	Protamine does not completely reverse LMWH (~60% of LMWH anti-Xa activity). Risk for allergic/hypersensitivity reactions in patients with fish allergy or previous protamine exposure. Repeat dose at 0.5 mg/mg LMWH if bleeding persists or elevated anti-Xa activity after 4 h
VKAs	PCC (KCentra; 25–50 U/kg infusion depending on INR)	Also administer vitamin K 5–10 mg IV/PO. PT/INR check 10–30 min after PCC dose to assess efficacy Repeat PT/INR Q6 h × 4 given short half-life of PCCs
Dabigatran	Idarucizumab (Praxbind; 5 g IV)	Monoclonal antibody fragment that binds dabigatran with high affinity In the setting of acute renal failure, hemodialysis may be considered to facilitate drug elimination
Anti-Xa agents	Andexanet (AndexXa in the United States, IndexXa in Europe)	Clinical trial ongoing; not FDA approved as of September 8, 2016

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; PCC, prothrombin complex concentrate; PT, prothrombin time; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

approve Andexanet in a decision on August 18, 2016, and has apparently requested more information from the manufacturer, specifically information related to manufacturing of the drug, and additional data to support inclusion of edoxaban and enoxaparin in the label. The FDA also intends to finalize its review of the manufacturer's proposals for post-marketing data collection on the performance of Andexanet. A new FDA decision is expected sometime in 2017.

VKA reversal: The approach to reversal of VKA anticoagulation is to restore sufficient activity of the vitamin K–dependent coagulation factors (factors II, VII, IX, X, protein C, protein S, and protein Z). Traditionally, this was achieved by concomitantly administered vitamin K (intravenously or orally) and infusing fresh frozen plasma (FFP). This approach had certain drawbacks: (1) multiple units of FFP are necessary in patients with a supratherapeutic PT/INR (international normalized ratio) with the risk of volume overload in patients with compromised cardiac function; (2) FFP contains a lot more than just the vitamin K–dependent clotting factors and patients are obligated to be exposed to them; (3) ABO typing is necessary for FFP and the units also need to be thawed/prepared prior to administration and there tends to be longer than a 60-minute delay from the time the product was requested to the time of infusion. Finally, it takes 12 to 24 hours for the vitamin K to impact hemostatic ability in any meaningful way.

PCCs are plasma-derived, pooled, clotting factor concentrates that contain only the vitamin K–dependent factors without extraneous proteins, so that only the clotting factors affected by VKAs are replaced. Volume overload is seldom an issue with these agents. PCCs are available as "four-factor concentrates" and "three-factor concentrates." The difference is primarily that the four-factor concentrates (e.g., KCentra) have factors II, VII, IX, and X, while the three-factor concentrates (Bebulin, Profilnine) do not contain significant amounts of factor VII. A prospective clinical trial evaluating four-factor PCC versus FFP showed that four-factor PCC was noninferior to FFP for hemostatic efficacy.[13] Further, four-factor PCC resulted in rapid INR reduction and increased plasma levels of the vitamin K–dependent coagulation factors (>60% activity) compared with FFP—30 minutes for four-factor PCC versus approximately 6 hours for FFP to achieve comparable levels.[13] For these reasons, and given the significantly smaller volume and ability to administer the drug quickly in the urgent/emergent setting (no thawing or ABO typing needed), four-factor PCCs are the preferred agents for urgent reversal of VKA anticoagulation. KCentra was approved by FDA in 2013 for reversal of VKA anticoagulation in the setting of major bleeding or urgent reversal for other reasons.[13,14] In cases where PCCs are not available, patients should receive FFP and vitamin K for reversal.

Perioperative Management of Anticoagulation

Brief interruption of anticoagulation for elective procedures or surgeries is a relatively common occurrence. We will divide this section into pre- and postoperative periods for ease of discussion. We will discuss patients with intact renal function in this section, whereas management in patients with renal insufficiency is discussed later.

Preoperative period: The decision on how soon before the procedure anticoagulation must be withheld depends on the half-life of the anticoagulant drug and the risk of bleeding associated with the procedure (low, moderate, or high as outlined in the Society for Interventional Radiology (SVIR) consensus guidelines[15]).

In hospitalized patients on therapeutic anticoagulation with an UFH infusion, the infusion should be held 4 hours prior to the procedure, given the short half-life of UFH. In the case of therapeutic LMWH dosing, the time of drug discontinuation depends on whether LMWH is being given once or twice daily. In general, the last LMWH dose should have been given 24 hours before the procedure. This translates to holding the dose of twice daily enoxaparin the evening (12 hours) and the morning before the procedure or the dose of once daily dalteparin, enoxaparin, or fondaparinux the morning (24 hours) before the planned procedure.

In patients on VKAs with a therapeutic INR, anticoagulation is held 5 days prior to the procedure to allow the PT/INR to drift down to normal. In individuals who had their episode of acute VTE within the last 3 months, bridging with LMWH once the INR has drifted below 2 and until the morning 1 day (i.e., 24 hours) before the procedure is recommended, given the increased risk for VTE recurrence in such individuals. On the other hand, in patients with a remote history of VTE ($>$ 3 months before procedure), pre-procedure LMWH bridging following discontinuation of VKA is not needed.

Until recently, the vast majority of patients requiring interruption of anticoagulation were on VKAs. Since the advent of DOACs, there is some degree of uncertainty on how to safely interrupt anticoagulation in patients on DOACs. An ongoing clinical study is investigating the effectiveness and safety of a proposed DOAC interruption scheme (PAUSE study, ClinicalTrials.gov Identifier: NCT02228798). Until we learn the best management from the results of that study, DOACs should be withheld 24 to 36 hours prior to procedure if the bleeding risk is low or moderate, and 2 to 4 days prior to procedure if the bleeding risk associated with the procedure is high (e.g., transjugular intrahepatic portosystemic shunt (TIPS), renal biopsy).[16,17] However, renal function is important to consider, as renal impairment leads to prolonged DOAC half-life and the need to discontinue the DOAC even earlier before the procedure. There is no need for LMWH bridging when the DOACs are held pre-procedure.

Postoperative period: Therapeutic anticoagulation is generally resumed 8 to 24 hours postprocedure, but the timing depends on the bleeding risk associated with the procedure. In the case of hospitalized patients on UFH, the heparin infusion should be resumed without a bolus and at the pre-procedure UFH infusion rate to decrease risk for bleeding. LMWH can similarly be resumed at the preprocedure dose. Patients on VKAs will require postprocedure bridging with LMWH for at least 5 days and until the INR is in the therapeutic range, which typically takes 5 days. Patients on DOACs can resume the drug at preprocedure dose and no LMWH bridging is needed. The timing of resumption of anticoagulation and/or the dose of the anticoagulant may need to be modified based on patient- and procedure-specific factors. In situations where oral intake is delayed (e.g., abdominal surgery), patients can be managed with LMWH and transitioned to the DOAC when clinically appropriate.

DOAC Use in Special Circumstances

Renal Insufficiency/Failure

There are considerable differences between the DOACs in terms of dependence on renal function for drug elimination. Dabigatran is most dependent on renal function, as 80% of the drug is cleared by the kidneys. Edoxaban's and rivaroxaban's clearance is approximately 35% dependent on the kidney. Apixaban has the most favorable profile in this setting, as only approximately 25% of the drug's clearance is dependent on renal function.

The dosing guidelines recommend avoiding use of dabigatran and rivaroxaban in patients with creatinine clearance $<$30 mL/min (►**Table 1**). Similarly, dosing guidelines recommend avoiding use of edoxaban in patients with creatinine clearance $<$15 mL/min and dose reduction for creatinine clearance between 15 and 50 mL/min (►**Table 1**). The prescribing guidelines for apixaban do not recommend any dose adjustment for renal insufficiency/failure. However, patients with creatinine clearance $<$15 mL/min were not studied in the efficacy and safety trials. Apixaban has been evaluated in patients with renal failure undergoing hemodialysis or with various degrees of renal impairment, albeit in small numbers and after a single dose of drug.[18,19] These studies concluded that renal failure has limited impact on apixaban levels in patients with renal impairment, renal failure, or on regular hemodialysis.

We recommend VKAs as the first choice in patients with renal insufficiency/failure. It is our practice and recommendation that dabigatran and rivaroxaban be avoided in patients with renal insufficiency and creatinine clearance $<$40 mL/min. Apixaban could be considered in patients with renal insufficiency as a second-line option to VKAs, but we do not recommend its use in patients with renal failure until more evidence is available to support the safety of this practice.

Cancer-Associated Thrombosis

Data on the use of DOACs in patients with cancer are limited. There are retrospective case series that suggest that these agents are effective in patients with cancer-associated thrombosis. A meta-analysis of cancer patients who participated in the DOAC clinical trials found DOACs were as effective and safe as VKAs.[20] Three large prospective clinical trials

comparing LMWHs to DOACs for the treatment of cancer-associated VTE are ongoing.

Current guidelines recommend LMWHs as the preferred agents for the treatment of cancer-associated VTE.[5,21] In patients in whom LMWHs are not an option (cost, patient preference, etc.) DOACs can be considered. DOACs are more convenient than warfarin in cancer patients, as their quick onset of action and their shorter half-life allow better anticoagulant management at times of thrombocytopenia compared with VKAs. However, DOACs and VKAs also share several disadvantages when it comes to cancer patients: a patient's poor oral intake and gastrointestinal problems (nausea and vomiting) and the DOACs' interactions with chemotherapeutic agents may limit their use/efficacy in this population.

Obesity

The phase III trials of the DOACs included patients who were obese (defined as a body mass index [BMI] >30 kg/m^2), but the numbers of patients with extreme body weights ($>$ 120 kg or BMI $>$ 40 kg/m^2) were limited. There is uncertainty regarding the efficacy of DOACs in extremely obese patients, as the limited pharmacokinetic/pharmacodynamic data available raise concern over decreased peak concentrations and half-lives in patients with BMI >40 kg/m^2. The use of DOACs in obese patients was specifically addressed in a recent guidance document from the International Society on Thrombosis and Hemostasis (ISTH).[22] Our practice regarding the use of DOACs in obese patients is in keeping with the ISTH guidance, which recommends the following: (1) avoiding DOACs in patients with BMI >40 kg/m^2 or weight >120 kg and (2) if DOACs are used in these patients, monitoring drug levels to ensure the levels are within the expected peak and trough range for the given drug.

Bariatric Surgery

All orally taken anticoagulants are absorbed in the small intestine (duodenum, jejunum), some also partially in the distal stomach. However, limited data on the exact location of absorption exist for the DOACs. The anatomic changes after bariatric surgeries (i.e., gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion) not only affect the area available for drug absorption but also the amount of food intake, gastric and small intestinal transit time, and gastric and duodenal acidity. Al these factors lead to an unpredictable absorption of DOACs after bariatric surgery. Therefore, our practice in patients who have undergone bariatric surgery and who require anticoagulation is to use VKAs which can easily be monitored with the INR rather than to use a DOAC.

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