Chapter

Anticoagulation

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Abstract

This chapter aims to summarize the most relevant aspects of anticoagulants. Initially, a brief review of the physiology is given in order to understand at which step of coagulation each anticoagulant acts. Later, the main indications and contraindications will be discussed, as well as the considerations that should be taken into account before starting treatment. Finally, the specific characteristics of each type of anticoagulant are developed, starting with vitamin K agonists and continuing with each of the direct oral anticoagulants.

Keywords: coagulation, physiology, anticoagulants, vitamin K agonists, direct oral anticoagulants, indications, contraindications

1. Introduction

Anticoagulation is a crucial treatment that can save lives in various medical conditions. However, it is essential to carefully consider the risks and benefits for each patient. The human body has two main coagulation pathways: intrinsic and extrinsic. These pathways work together to form blood clots, which play a vital role in preventing excessive blood loss and promoting wound healing [1, 2].

The intrinsic pathway is activated when there is damage within a blood vessel and involves factors XII, XI, IX, and VIII. On the other hand, the extrinsic pathway is triggered when damage occurs outside of a blood vessel and involves factor VII. Both pathways converge at the common pathway, where factor X is activated. Factor X then combines with factor V, forming the enzyme prothrombinase. Prothrombinase converts prothrombin into thrombin. Thrombin, in turn, converts soluble fibrinogen into insoluble fibrin, which forms the blood clot [1, 2].

Disruptions in any part of the clotting system, whether it is the extrinsic, intrinsic, or common pathway, can lead to an increased risk of thrombosis or bleeding disorders. Therefore, understanding and managing the coagulation process is essential in maintaining a balanced and healthy clotting system (**Figure 1**).

Anticoagulation is a medical intervention used to prevent the formation or enlargement of blood clots in various conditions such as deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, or heart attack. By disrupting the clotting factors in the blood, anticoagulants hinder the formation of clots. These medications can be administered orally or through injections, depending on the specific medication and

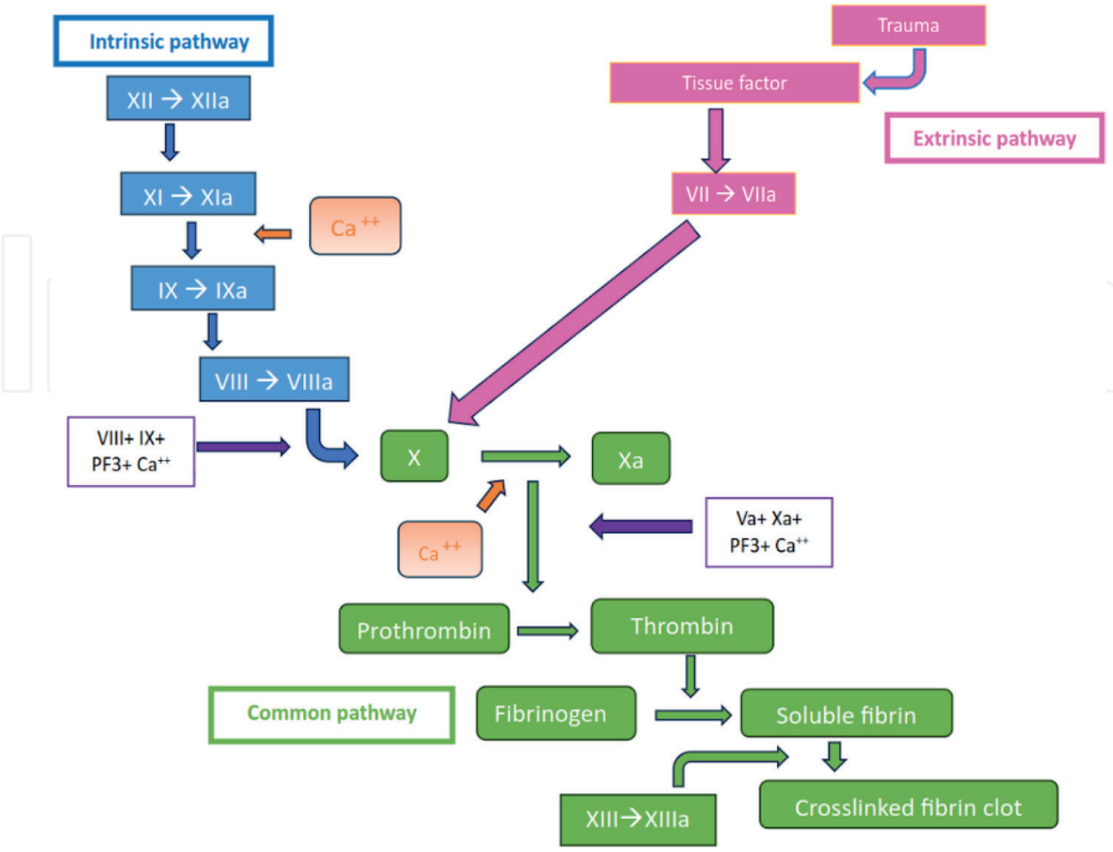

Figure 1.
Coagulation pathways (original creation).

the condition being treated. Commonly used anticoagulants include warfarin, heparin, and novel oral anticoagulants (NOACs) or direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, and apixaban [3–9].

It is crucial to note that anticoagulants carry an increased risk of bleeding, and therefore, patients undergoing anticoagulation therapy require close monitoring. While anticoagulation can be a lifesaving treatment, it is essential to consult with a doctor to evaluate the risks and benefits specific to each patient's situation. Anticoagulation is generally recommended for patients at higher risk of developing blood clots or those who have previously experienced clotting events.

The most important thing is to assess whether the patient has an indication for anticoagulation or not. Additionally, we must evaluate the most suitable anticoagulant for our patient's profile. As a general guideline, DOACs preferred over VKAs (vitamin K antagonists) whenever possible. However, we need to consider pharmacological restrictions and the cost of therapy.

2. Indications for anticoagulation

The main indications of anticoagulation are:

1. Deep vein thrombosis: a blood clot is formed in a deep vein in the human body, usually in the lower limbs. The diagnosis involves an approach that includes

clinical assessment, pretest probability, and objective diagnostic testing. Common symptoms of DVT include redness, swelling, pain, and dilated veins. The pretest probability can be determined using a clinical decision. If an "unlikely" DVT is possible, a D-dimer test is recommended. If the D-dimer level is normal, DVT can be ruled out. If increased, a compression ultrasound is necessary to rule out or diagnose DVT. IF "likely" DVT is possible, a compression ultrasound is directly advised. Once DVT is confirmed, anticoagulation is essential to reduce and manage symptoms, prevent the risk of progression, and reduce the risk of complications like postthrombotic syndrome or PE. Anticoagulation treatment options include low molecular weight heparin (LMWH), warfarin, sintrom, or DOACs. DOACs are preferred over warfarin and acenocoumarol due to their comparable effectiveness, improved safety profile, and convenience; however, DOACs should be avoided during pregnancy. Dosage adjustments are required for patients with renal dysfunction. Recent evidence suggests that cancer-related DVT can be treated with edoxaban or rivaroxaban, following the discontinuation of initial heparin or LMWH. However, it should be noted that DOACs carry a higher risk of gastrointestinal bleeding compared to LMWH in patients with gastrointestinal cancer [4, 6, 8].

2. Pulmonary embolism: it occurs when a blood clot travels to the lungs and blocks blood flow. It is a cardiovascular disorder that can be life-threatening. Over time, advancements in understanding the efficient utilization of diagnostic and therapeutic options have transformed the diagnosis, risk assessment, and management of this condition. By employing clinical probability-adjusted or age-adjusted D-dimer interpretation as well as with the DVT, the need for diagnostic imaging to rule out PE has been reduced. Anticoagulation treatment options are similar to the ones for DVT. Moreover, DOAC has opened doors for the safe outpatient management of PE in specific patients. Recent clinical trials have investigated the use of systemic thrombolysis in intermediate to high-risk PE and suggest that this therapy should be reserved for patients experiencing hemodynamic compromise. The effectiveness of low-dose systemic or catheter-directed thrombolysis in other patient subgroups remains uncertain. Despite significant progress in the management of PE, about half of the patients report long-term functional limitations. It is crucial to screen such patients for chronic thromboembolic pulmonary hypertension, although only a small portion of them will have this condition as the underlying cause of their symptoms [2, 6, 17].

3. Atrial fibrillation (AFib): Anticoagulation is often recommended for patients with AFib, which is a type of irregular heartbeat that can increase the risk of blood clots forming in the heart. Diagnosis is made by an electrocardiogram. The decision to initiate anticoagulation in patients with AFib is based on the CHADS2-VASc score. Anticoagulation is recommended for male patients with a CHADS2-VASc score greater than 1 point and female patients with a score greater than 2 points. Non-vitamin K antagonist oral anticoagulants, known as well as NOCs or DOACs, are considered the first choice in nonvalvular AFib. They have an improved efficacy/safety ratio and predictable anticoagulant effects, without the need to perform routine anticoagulation monitoring. The term “nonvalvular” is used to refer to AFib in the absence of a mechanical prosthetic heart valve or moderate to severe mitral stenosis (exclusion criteria in all phase III DOAC vs Warfarin trials in AF).

However, there is no randomized clinical trial (RCT) that indicates less efficacy of these treatments in patients with rheumatic mitral stenosis, nor is there any rational base on which to hypothesize a differential response to DOACs vs. VKA [7].

4. Mechanical heart valves: Anticoagulation is often necessary for patients who have undergone valve replacement surgery, as mechanical valves increase the risk of blood clots forming. In this case only vitamin K antagonists are recommended up to date [10].

3. Contraindications for anticoagulant therapy

Possible contraindications for the use of anticoagulants are:

1. Clinically significant active bleeding (considering the site and degree of bleeding; for example, nasal bleeding and menstruation are generally not contraindications, whereas active intracerebral bleeding is almost always an absolute contraindication).

2. Severe bleeding diathesis (considering the nature, severity, and reversibility of the bleeding diathesis).

3. Severe thrombocytopenia with platelet count <50,000/μl (absolute platelet count, platelet count trend, and platelet function).

4. Major trauma (considering the site, extent of trauma, and time interval since the event; for example, anticoagulation before or after the trauma may be appropriate for a patient with a mechanical heart valve compared to a patient with a minor indication).

5. Invasive procedure or obstetric delivery, whether recent, emergent, or planned (considering the type of procedure and associated bleeding risk, the interval between the procedure and anticoagulation).

6. Previous intracranial hemorrhage (considering the time interval since the hemorrhage and underlying cause; e.g., trauma or uncontrolled hypertension).

7. Intracranial or spinal tumor (considering the location and type of tumor, other comorbidities).

8. Neuraxial anesthesia (considering the time interval since spinal/epidural puncture or catheter removal, other anesthesia alternatives; traumatic procedures are more concerning).

9. Severe uncontrolled hypertension (considering the absolute blood pressure and blood pressure trend).

This list does not replace the clinical judgment regarding the decision to administer an anticoagulant. The clinician will assess the individual patient's risks and benefits on an individual basis [11–14].

4. Considerations prior to initiating anticoagulation

In addition, we must consider the following before initiating anticoagulation:

1. Bleeding risk assessment: Prior to starting treatment, it should be evaluated using the HAS-BLED score. However, a high score on its own is not a reason to withhold anticoagulation. Instead, considering closer monitoring and follow-up is necessary.

2. Baseline hematological profile: Its assessment is recommended as a reference for future follow-up.

3. Frailty, risk of falling, and cognitive decline: These factors alone should not be reasons to withhold anticoagulation, but special considerations must be taken to minimize the risk of falling and ensure proper adherence to treatment.

4. Pregnancy: DOACs are contraindicated in pregnant patients, and reliable contraception should be initiated before considering DOAC therapy in women of childbearing age.

5. Children: DOAC therapy should generally be discouraged in children, but it can be considered in fully grown adolescents with a body weight exceeding 50 kg. It is important to note that specific DOACs, such as rivaroxaban and dabigatran, have shown safe and effective outcomes for children with venous thromboembolism (VTE) under appropriate dosage adjustments.

6. Renal insufficiency: patients with chronic kidney disease are at higher risk for both thromboembolic and bleeding events. Warfarin was previously the preferred option. However, vascular calcifications and worsening of nephropathy have made it necessary to look for other options. All DOACs have renal elimination, so renal dose adjustments, including decreasing dose and decreasing frequency based on renal function, must be considered. It is relevant to highlight that according to FDA-approved prescribing information for apixaban, adjustments are not necessary for renal impairment alone, including end-stage renal disease (ESRD) or hemodialysis. Dose adjustment for this is recommended for this drug if two of the following: ≥80 years, ≤60 kg, or serum creatinine ≥1.5 mg/dl. European guidance on its behalf recommends standard doses for CrCL > 30 ml/min, reduced doses for 30–15 ml/min, and avoiding this treatment for <15 ml/min.

7. Hepatic impairment: these patients also have an increased risk of bleeding or thrombotic events. Their severity must be valued according to the Child-Pugh score. If severe hepatic disease, warfarin is the only recommended anticoagulant. In moderate cases, apixaban, edoxaban, and dabigatran can be used, not needing dose adjustment.

8. Crushed form administration: Most DOACs can be administered in crushed form via nasogastric tube without altering their bioavailability. However, it is crucial not to open Dabigatran capsules, as this can lead to a substantial increase in drug bioavailability.

9. Food: Rivaroxaban should be taken with food, as it significantly increases its plasma concentration (area under the curve, AUC) by 39% with almost 100% bioavailability. The other DOACs do not have significant food interactions.

10. Co-administration with dual antiplatelet drugs: When DOACs are used in combination with dual antiplatelet drugs, active measures must be taken to prevent bleeding.

11. Interaction with proton-pump inhibitors (PPIs) and H2-blockers: PPIs and H2-blockers can decrease the bioavailability of dabigatran but do not affect its clinical efficacy. No relevant interactions have been described with other DOACs [11–14].

5. Options for anticoagulation

From this point in the chapter, we will begin discussing each type of anticoagulant, their characteristics, how they are used, and their initiation and discontinuation, if necessary, due to surgery or any side effects.

There are two main types of anticoagulation (**Figure 2**), which are:

1. Vitamin K antagonists (AVK): Warfarin and acenocoumarol [13].

2. DOACs that can be classified into different categories [12, 15, 16]:

1. Factor Xa inhibitors:

   - Apixaban
   - Edoxaban
   - Rivaroxaban

2. Direct thrombin inhibitor:

   - Dabigatran

3. Factor XIa inhibitors:

   - Asundexian (under investigation)

Each type of anticoagulant is preferred for different patient profiles. Although the vast majority of anticoagulants can be used for all indications of anticoagulation, we must be aware of exceptions. Xa inhibitors are not recommended for the following patient profiles:

1. Mechanical heart valve.

2. ESRD or those on dialysis due to a lack of clinical trial evidence.

3. Severe hepatic impairment.

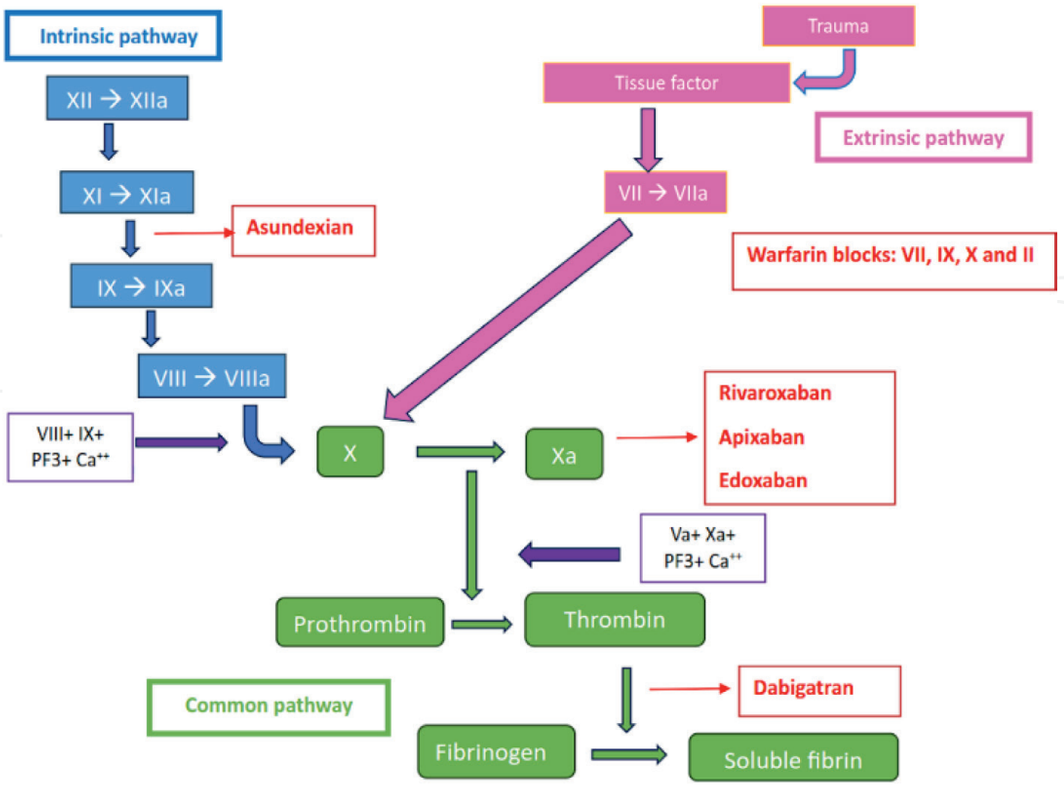

Figure 2.
Anticoagulants and how they affect the coagulation pathways (original creation).

4. Seizures, as there may be possible interactions between seizure treatments and the serum concentration of these anticoagulant medications (especially with phenytoin, fosphenytoin, carbamazepine).

5. HIV on protease inhibitor-based antiretroviral therapy.

6. BMI (body mass index) greater than 40 or a weight exceeding 120 kg [11–14].

6. Warfarin and acenocoumarol

Warfarin and other vitamin K antagonists, known as coumarins, the best-known acenocoumarol, are of great use in multiple clinical settings. Their use is challenging because they have a narrow therapeutic range, and the dose is affected by multiple factors, such as genetic variations, drug interactions and diet; being interesting to highlight the influence of excessive amounts of alcohol in short periods of time (with a single meal, for example). They also need annual monitoring of basal hemoglobin (every 6 months if low hemoglobin is detected). Being outside the therapeutic range increases the risk of bleeding and/or thromboembolic complications that VKAs try to prevent. However, there is extensive clinical experience and high efficacy in reducing the risk of arterial and VTE in many settings [10, 13, 14].

VKAs have advantages and disadvantages compared to other anticoagulants, and the choice of agent depends on the clinical environment and patient characteristics [10, 13, 14].

Disadvantages include the following:

- Higher rates of thromboembolic and hemorrhagic complications compared to DOACs in patients with AFib.
- High costs and burdens of frequent supervision required.
- Dosage is affected by diseases, changes in diet, and numerous drug interactions [10, 13, 14].

The advantages include:

- Extensive clinical experience (including long-term use) and medical familiarity with its use.
- Greater efficacy than other oral anticoagulants in patients with cardiac valve prostheses.
- Low cost and wide availability.
- High experience in reversing the anticoagulant effect if necessary (e.g., in severe bleeding) using vitamin K, fresh frozen plasma (FFP), or complex prothrombin concentrates (PCC) [10, 13, 14].

Its aim is to decrease the tendency to clotting the blood, not prevent clotting completely, so the dose is adjusted based on the results of periodic blood tests, keeping the clotting time within a target range. In most cases, the goal of international normalized ratio (INR) should be between 2 and 3, which increases to 2.5–3.5 in patients with mechanical heart valves. The initial warfarin dose is usually 4–6 mg daily, while acenocoumarol is usually 1–3 mg/day. However, loading doses should be avoided, and lower starting doses should be considered in elderly or weakened patients. Heparin should be administered simultaneously to the VKAs in the first few days until two measurements with adequate INR are separated by 24 hours [10, 13, 14].

The frequency of INR measurement depends primarily on dose response and current clinical information and varies over time:

- Check INR one to two times per week at the beginning of therapy until you achieve therapeutic range and keep it for two consecutive tests.
- The peak effect of warfarin may not be seen for 3–4 days; it takes up to 10–14 days to stabilize.
- INR checks every 2–3 weeks are usually required for the next several weeks.
- For patients who have achieved stable therapeutic levels, INR monitoring can be spaced up to 6–12 weeks, unless specified by a referral provider, although the standard is 4 weeks.

- Instead of making frequent adjustments to warfarin doses, caution should be exercised to get slightly out-of-range results, repeating the INR within a week before making changes [10, 13, 14].

For dose modifications, percentage changes are based on the total dose of the previous 7 days (mg warfarin/week). In addition, dose increases/decreases should be distributed as evenly as possible over the next seven days, avoiding large variations from day to day. In certain patients, INR testing at the point of care of the patient at home and self-adjustment of the dose of VKA (patient self management or PSM) over any other type of management are recommended. Bridge anticoagulation in patients with warfarin may be appropriate if there is a very high thromboembolic risk and there is a prolonged interruption of the anticoagulant for any reason. On the other hand, it is not necessary for simple dental procedures, cataract removal, or minor dermatological surgery [10, 13, 14].

Conditions to consider bridge anticoagulant therapy:

- Embolic stroke or systemic embolic event within the previous 12 weeks.
- Mechanical mitral valve.
- Mechanical aortic valve and additional stroke risk factors.
- AFib and very high risk of stroke (e.g., CHADS-VASc score of 5 or more, stroke systemic embolism within the previous 12 weeks).
- VTE within the previous 12 weeks.
- Previous Thromboembolism during interruption of chronic anticoagulation [10, 13, 14].

There are several options for reversing AVKs for surgery or urgent procedure:

First, try to give vitamin K (2.5–5 mg) intravenously. If a more urgent reversal is required, you can choose FFP or other prothrombin concentrate in addition to vitamin K (2.5–5 mg). If a more urgent reversal is required, you can choose FFP or other prothrombin concentrate in addition to vitamin K (2.5–5 mg). In critical settings, patients receiving acetylsalicylic acid, clopidogrel, or both, who have undergone surgery, with excessive or life-threatening perioperative bleeding, may need platelet transfusions or other prohemostatic agents [10, 13, 14].

Special caution is necessary in all patients with anticoagulation who undergo epidural or spinal anesthesia or puncture. Bruising has occurred that can lead to long-term or permanent paralysis (**Figure 3**).

7. Dabigatran

Dabigatran (brand name, Pradaxa) is an oral prodrug that is converted in the liver to dabigatran, an active direct thrombin inhibitor. It is recommended for preventing and treating VTE, stroke prevention in patients with AFib, and ischemic heart disease. Its half-life is in the range of 12–17 hours [7, 11–13, 15].

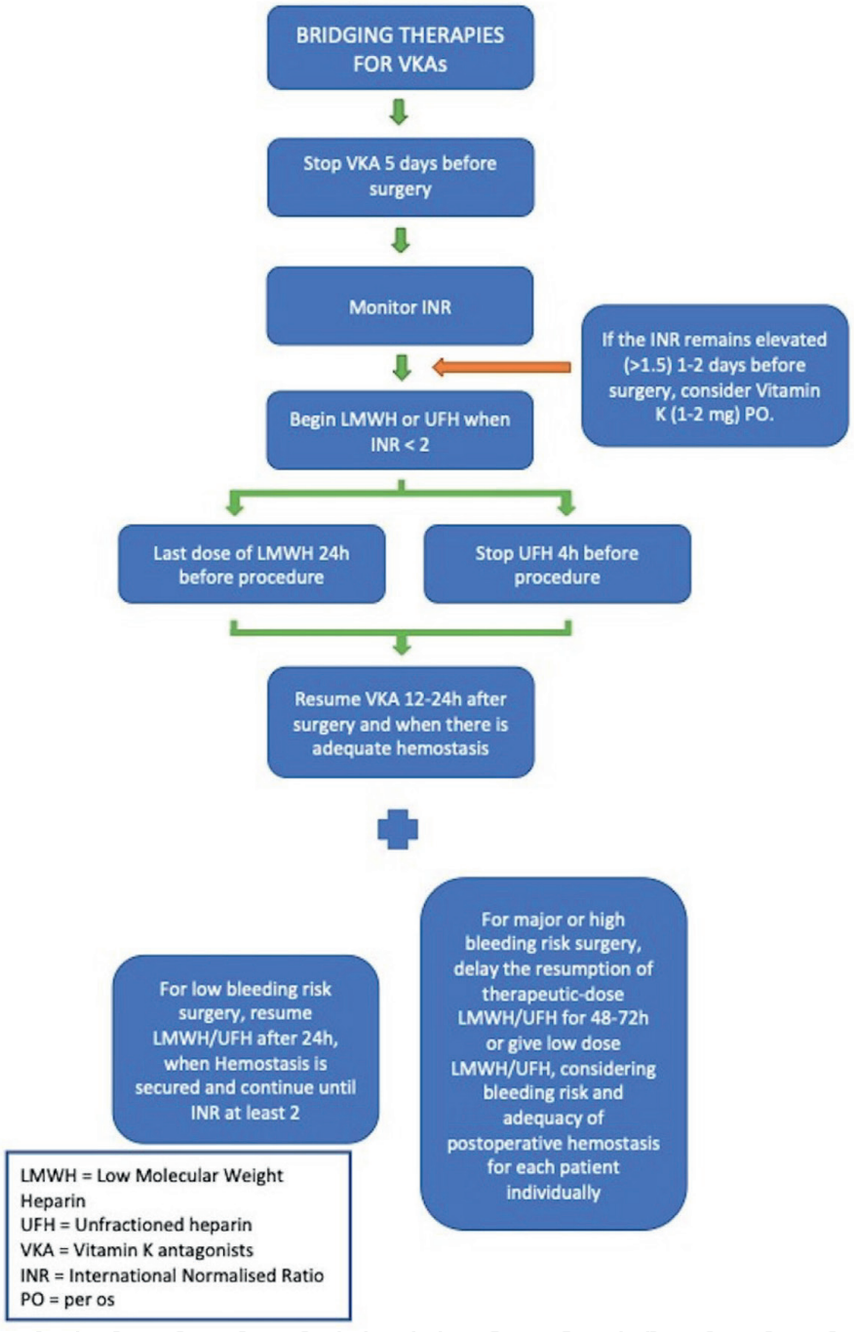

Figure 3.
How to stop warfarin before surgery (original creation).

It is not recommended in patients with mechanical prosthetic heart valves or during pregnancy [7, 11–13, 15].

Generally, it is given at a fixed dose (150 mg twice daily), and food does not affect its absorption. As a curious fact, it should be dispensed and stored in its original bottle (with desiccant) or blister package. Sometimes, the dose is needed to be reduced from 150 mg twice daily to 75 mg twice daily, for example, in case of kidney failure with CrCl between 15 and 30 ml/min, patients older than 75 years, patients who are treated with inhibitors of P-glycoprotein and have kidney failure, since it may increase the anticoagulant effect of dabigatran, and patients who are treated with inducers of P-glycoprotein, since it may reduce the anticoagulant effect of dabigatran.

Before starting anticoagulation treatment with dabigatran a blood test is needed, which should include platelet count, aPTT, and prothrombin time (PT). But then, routine monitoring of coagulation times is not required [7, 11–13, 15].

The kidney excretes it, so we also must test kidney function, and it should not be used in patients with CrCl <30 ml/min [7, 11–13, 15].

8. Rivaroxaban

Rivaroxaban (brand name, Xarelto) is a direct oral inhibitor of factor Xa with a half-life of 5 to 9 hours, but it may be longer in older individuals [7, 11–13, 15].

It is used to prevent and treat VTE disease, stroke prevention in patients with AFib, and ischemic heart disease. Rivaroxaban should not be used in individuals with mechanical prosthetic heart valves or during pregnancy [7, 11–13, 15].

It is generally given at a fixed dose without monitoring. The 15 and 20 mg tablets used in adults must be taken with food. The dosing differs according to the clinical indication and the patient's kidney function. For VTE prophylaxis in surgical patients: 10 mg tablets are used daily; duration between 12 and 35 days, depending on the type of surgery. Treatment and secondary prevention of VTE: 15 mg twice daily for 21 days, followed by 20 mg once daily. Adequate treatment for VTE is full-dose anticoagulation for 3–6 months. If secondary prevention is considered after full-dose treatment, the dose can be reduced to 10 mg once daily for selected individuals. However, for those with an increased risk for VTE beyond six months of anticoagulation (e.g., two or more episodes of VTE), the 20 mg once-daily dose should be used. For stroke prevention in AF: 20 mg once daily with the evening meal (creatinine clearance [CrCl] > 50 ml/min); or 15 mg once daily with the evening meal (CrCl ≤ 50 ml/min). Secondary prevention in individuals with stable cardiovascular disease—2.5 mg twice daily in combination with aspirin [7, 11–13, 15].

Rivaroxaban is not recommended for VTE prophylaxis, treatment, or secondary prevention in individuals with a CrCl < 30 ml/min. The drug should not be used in individuals with a CrCl <15 ml/min, as well as in those with significant hepatic impairment (Child-Pugh Class B and C with coagulopathy) [7, 11–13, 15].

Rivaroxaban interacts with drugs that are potent dual inhibitors of CYP-3A4 and P-glycoprotein (e.g., systemic ketoconazole, itraconazole, posaconazole, or ritonavir), and concurrent use is contraindicated. Drugs that inhibit CYP-3A4 but do not also inhibit P-glycoprotein (e.g., diltiazem, fluconazole, and voriconazole) may also increase rivaroxaban effect, but to a lesser extent than dual inhibitors. Potent inducers of CYP-3A4 (e.g., rifamycins, carbamazepine, St. John's wort) may reduce rivaroxaban's effects [7, 11–13, 15].

Laboratory testing prior to initiating rivaroxaban should include platelet count, PT, and activated partial thromboplastin time (aPTT), to assess and document coagulation status before anticoagulation; and measurement of serum creatinine and liver function tests, as a baseline and for potential dose adjustment in the event of impaired kidney or liver function [7, 11–13, 15].

Routine monitoring of coagulation times is not required for patients taking rivaroxaban because drug levels are relatively predictable for a given dose, and there is no established therapeutic range. If there is a concern that drug levels are abnormally low or abnormally high, it may be appropriate to test for the presence of the drug [7, 11–13, 15].

Cases of liver injury following rivaroxaban administration have been reported, although this was not seen in larger trials. The incidence of this complication is unknown. As with all anticoagulants, rivaroxaban increases bleeding risk and is administered in the setting of increased thrombotic risk. Product labeling for rivaroxaban has Boxed Warnings regarding the risk of spinal/epidural hematoma in patients undergoing neuraxial anesthesia or spinal puncture and the risk of thrombotic events following premature discontinuation [7, 11–13, 15].

9. Apixaban

Apixaban (brand name, Eliquis) is a direct oral inhibitor of factor Xa. It is recommended to prevent and treat VTE and stroke prevention in AFib. It appears to have greater efficacy and safety in individuals with VTE of all direct factor Xa inhibitors. Its half-life is approximately 12 hours [7, 11–13, 15].

It is not recommended in patients with mechanical prosthetic heart valves or during pregnancy [7, 11–13, 15].

Generally, it is given at a fixed dose (depending on the pathology), and food does not affect its absorption. Patients treated for VTE are given 10 mg twice daily for 7 days, followed by 5 mg twice daily. For secondary prevention, the dose is reduced to 2.5 mg twice daily. For patients being treated for stroke prevention in AFib, a typical dose is 5 mg twice daily, but sometimes we must reduce it to 2.5 mg twice daily for those with any two of the following: patients older than 80 years, body weight below or equal to 60 kg, serum creatinine 1.5 mg/dl or patients who are treated with strong dual inhibitors of CYP-3A4 and P-glycoprotein [7, 11–13, 15].

A blood test is needed before starting anticoagulation treatment with apixaban, which should include platelet count, aPTT, and PT. But then, routine monitoring of coagulation times is not required [7, 11–13, 15].

Although serum creatinine and liver function test measurements are also needed, apixaban has the least dependence on clearance by the kidney. It is not recommended in patients with CrCl < 15 ml/min [7, 11–13, 15].

10. Edoxaban

Edoxaban (brand name, Lixiana) is a direct oral inhibitor of factor Xa. It is recommended for preventing and treating VTE and stroke prevention in AFib. Its half-life is in the range of 10–14 hours [7, 11–13, 15].

It is not recommended in patients with mechanical prosthetic heart valves or during pregnancy [7, 11–13, 15].

Generally, it is given at a fixed dose (60 mg once daily), and food does not affect its absorption. As a curious fact, it is lactose-free. Sometimes, the dose is needed to be reduced from 60 to 30 mg once daily; for example, in case of kidney failure with CrCl between 15 and 50 ml/min, weight below or equal to 60 kg, patients who are treated with potent inhibitors of P-glycoprotein (because it is a substrate for this protein) and concomitant use of dronedarone, ketoconazole, ciclosporin or erythromycin [7, 11–13, 15].

Before starting anticoagulation treatment with edoxaban, a blood test is needed, which should include platelet count, aPTT, and PT. But then, routine monitoring of coagulation times is not required [7, 11–13, 15].

The kidney excretes it, so we also have to test kidney function, and it should not be used in patients with CrCl > 95 ml/min or <15 ml/min [7, 11–13, 15].

11. Betrixaban

Betrixaban (brand name, Bevyxxa) was a direct oral inhibitor of factor Xa with a half-life of 19–27 hours. It was discontinued in the United States in 2020 (for business reasons) and was not marketed in other countries [11].

12. Asudeixan

Currently, it is a new anticoagulant under study, on a phase two clinical trial. The only published information about this new anticoagulant is available from two articles based on two studies.

The first study aimed to determine the optimal dose of asundexian and compare its bleeding incidence with that of apixaban in patients with AFib. The trial involved 862 patients across 93 sites in 14 countries. Participants were randomly assigned to receive either asundexian 20 or 50 mg once daily or apixaban 5 mg twice daily. The primary endpoint was the occurrence of major or clinically relevant nonmajor bleeding. The results showed that both doses of asundexian resulted in lower bleeding rates compared to standard dosing of apixaban. Asundexian 20 mg demonstrated 81% inhibition of activated coagulation factor XIa (FXIa) activity at trough concentrations and 90% inhibition at peak concentrations. Asundexian 50 mg achieved 92% inhibition at trough concentrations and 94% inhibition at peak concentrations. The adverse event rates were similar among the three treatment groups.

Overall, the findings suggest that asundexian, with its near-complete in vivo FXIa inhibition, may offer a potential alternative for stroke prevention in AFib patients, reducing bleeding concerns associated with traditional anticoagulants [16].

The second study, which is a phase 2b dose-finding trial called PACIFIC-Stroke, aimed to investigate the efficacy and safety of asundexian for the secondary prevention of recurrent stroke. The study included patients with acute noncardioembolic ischemic stroke and aimed to determine the optimal dose of asundexian while assessing its effects on brain infarcts and recurrent stroke. A total of 1808 participants from 23 countries were randomly assigned to receive once-daily oral doses of asundexian (10, 20, or 50 mg) or placebo in addition to standard antiplatelet therapy. The primary efficacy outcome was the effect on the composite of covert brain infarcts and symptomatic recurrent ischemic stroke at or before 26 weeks after randomization. The primary safety outcome was major or clinically relevant nonmajor bleeding [17].

The results showed that FXIa inhibition with asundexian did not reduce the composite of covert brain infarction or ischemic stroke compared to placebo. Furthermore, there was no significant increase in the composite of major or clinically relevant nonmajor bleeding with asundexian compared to placebo. The study concluded that asundexian did not demonstrate efficacy for secondary prevention of recurrent stroke and did not increase bleeding risk in patients with acute noncardioembolic ischemic stroke [17].

Overall, these findings suggest that asundexian, as an FXIa inhibitor, did not provide significant stroke prevention benefits in this patient population [17].

When comparing both studies, it becomes apparent that asundexian's effects may vary depending on the indication. While it showed promise in reducing bleeding rates compared to apixaban for stroke prevention in AFib (first study), it did not provide significant benefits for secondary prevention of recurrent stroke compared to placebo (second study). These findings highlight the importance of assessing the balance between efficacy and bleeding risk when evaluating anticoagulant therapies. Further research is needed to understand better the potential benefits and limitations of asundexian in different patient populations and indications [16, 17].

13. Transition between anticoagulant treatments

1. *VKA to DOAC*

If INR is below or equal to 2, DOAC can be initiated immediately, while if INR is between 2 and 2.5, initiation of DOAC can be started immediately as well or delayed for the next day. However, if INR is above 2.5, special caution must be taken. In this manner, the half-life of the actual VKA must be considered (8–24 hours for acenocoumarol, 36–48 hours for warfarin). After the indicated time has passed, a new INR measurement must be performed. According to the summary of product characteristics, rivaroxaban can be initiated once INR is below 3, edoxaban when below 2.5 and apixaban and dabigatran when below 2 [7, 10–15].

2. *DOAC to VKA*

First of all, it must be considered that achieving adequate INR levels can take between 5 and 10 days, with large individual variations, the reason why it will be necessary to overlap both treatments temporarily (similarly to when VKA is initiated first and heparin overlapping is necessary). As indicated previously, loading doses are not advised in any case. DOACs can influence INR values; this value should be measured before the next intake and 2–3 days after concluding this treatment. INR control should be performed similarly to previously explained for VKA initiation alone. If concomitant DOAC administration is inappropriate, this treatment can be switched to heparin while transitioning to VKA [7, 11–13, 15].

3. *From one DOAC to another*

The second DOAC can be started when the next dose of the first DOAC is indicated, procuring not to overlap. An exception for this would be a situation where higher than therapeutic plasma concentrations of the first DOAC are expected, a condition where a longer interval between DOACs can be convenient. DOAC to heparin or heparin to DOAC parenteral or subcutaneous anticoagulants can be initiated when corresponding to the next dose of DOAC. On the other hand, DOACs can be initiated when the next dose of LMWH is indicated or 2–4 hours after concluding treatment with unfractionated heparin (UFH) [7, 10–15].

14. Conclusion

Anticoagulants are medications aimed to prevent and treat the formation of blood clots by acting on different phases of the coagulation pathways, either direct, indirect,

common, or a combination of the previous. Vitamin K antagonists are the most antique oral anticoagulants and are traditionally the most employed. However, over the last decades, new anticoagulants, known as DOACs, offer a series of advantages over the previous, principally concerning safety and lack of need for monitoring. Nonetheless, they also count their own limitations and disadvantages, mainly concerning the contraindication for their use on patients with mechanical heart valves and a less accessible and more complicated option for reversion of their action. Moreover, we must always remember that each type of anticoagulant has a prototype of the optimal patient and certain considerations that must be considered. However, it is also interesting to consider that changes between one and another anticoagulant are possible. Overall, what cannot be lost in translation is that these are lifesaving treatments when applied adequately.

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