Antithrombotic: Research and applications in healthcare

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Abstract: Antithrombotic are drugs used to prevent the formation of blood clots, also known as thrombi. These clots can cause serious health problems, such as heart attacks or cerebrovascular disease. This article reviews different types of antithrombotic, such as antiplatelet agents and anticoagulants, and discusses their mechanisms of action. In addition, the benefits and risks associated with the use of antithrombotic are examined. On the one hand, these drugs can reduce the risk of thrombotic events, which may be especially beneficial in patients with high-risk conditions, such as those who have suffered a heart attack or who have atrial fibrillation. On the other hand, the possible side effects of antithrombotic, such as increased risk of bleeding, are also discussed. In addition, guidelines are provided for their safe use in different clinical scenarios. Finally, strategies for monitoring and adjusting the dose of these drugs to ensure their efficacy and safety in patients are addressed.

Key words: Antithrombotic, Antiplatelets, Anticoagulants, Fibrinolysis, Blood coagulation, Cardiovascular events.

Resumen: los antitrombóticos son fármacos que se utilizan para prevenir la formación de coágulos sanguíneos, también conocidos como trombos. Estos coágulos pueden causar graves problemas de salud, como infartos o enfermedades cerebrovasculares. En este artículo se analizan diferentes tipos de antitrombóticos, como los antiplaquetarios y los anticoagulantes, y se discuten sus mecanismos de acción. Además, se examinan los beneficios y los riesgos asociados con el uso de antitrombóticos. Por un lado, estos fármacos pueden reducir el riesgo de eventos trombóticos, lo que puede ser especialmente beneficioso en pacientes con condiciones de alto riesgo, como aquellos que han sufrido un infarto o que tienen fibrilación auricu-

lar. Por otro lado, también se discuten los posibles efectos secundarios de los antitrombóticos, como el aumento del riesgo de sangrado. Además, se proporcionan pautas para su uso seguro en diferentes escenarios clínicos. Finalmente, se abordan las estrategias de monitoreo y ajuste de la dosis de estos medicamentos para garantizar su eficacia y seguridad en los pacientes.

Palabras clave: antitrombóticos, antiagregantes, anticoagulantes, fibrinólisis, coagulación sanguínea, eventos cardiovasculares.

Introduction

Antithrombotic drugs are crucial in healthcare because of their role in the prevention and treatment of thromboembolic disorders. They can be classified into two main categories: antiplatelet agents and anticoagulants. In addition, antithrombotic can have fibrinolytic effects, further preventing the formation of blood clots. These drugs find diverse applications in healthcare, including the prevention and treatment of thromboembolic disorders and perioperative treatment. However, the use of antithrombotic carries potential side effects and adverse reactions, such as bleeding complications, allergic reactions, and drug-drug interactions. Therefore, monitoring and dose adjustments are essential, with laboratory monitoring and dose adjustments in special populations being key considerations. While antithrombotic have important benefits, there are certain contraindications and precautions that must be considered to ensure patient safety. Research and development in this field continues to explore new agents and advances in drug delivery systems.

Definition and purpose

Antithrombotic drugs are medications used to prevent and treat thrombosis, which is the formation of blood clots in the circulatory system. Thrombosis can lead to serious health complications and even death. These drugs work by interfering with the processes involved in clot formation, such as platelet adhesion, activation, and aggregation, as well as fibrin formation. The purpose of antithrombotic drugs is to reduce the risk of thrombotic events, such as heart attacks and cerebrovascular disease (CVD), while balancing the potential risk of bleeding. They are classified into two types: anticoagulant drugs, which target enzymes involved in the clotting process; antiplatelet drugs, which act on platelet receptors. The development of newer antithrombotic drugs aims to improve their efficacy, safety and predictability of effects (1, 2, 3, 4).

Importance in health care

Antithrombotic drugs play a crucial role in medical care by preventing and treating thrombotic complications such as arterial thrombosis, venous thromboembolism and platelet-associated thrombotic complications. These drugs are especially relevant in patients with cardiovascular diseases, such as coronary artery disease, atrial fibrillation and deep vein thrombosis, as they help prevent life-threatening thrombotic events. In addition, antithrombotic play a crucial role in preventing clot formation during medical and surgical procedures, such as cardiac surgeries, joint replacement, and stenting. These drugs help maintain a balance between the procoagulant and anticoagulant systems, which is disrupted in pathological conditions such as thrombosis or pathological bleeding. They are used to prevent blood loss and reduce the risk of morbidity and mortality associated with thromboembolic diseases. They are usually prescribed to modulate hemostasis and prevent both arterial and venous thrombosis. They have been used for decades, and advances in their understanding and use have led to significant improvements in the treatment of thrombotic diseases. However, the use of these drugs also poses challenges, such as the risk of bleeding during invasive procedures, which requires careful perioperative management (3, 5, 6, 7, 8, 9).

Types of antithrombotic drugs

Antithrombotic drugs are divided into two types: antiplatelet agents and anticoagulant drugs. Anticoagulant drugs primarily target enzymes, whereas antiplatelet drugs act on platelet receptors, and fibrinolytic drugs act on fibrinogen. Anticoagulant drugs include enoxaparin, fondaparinux, warfarin, acenocoumarol and phenprocoumon. Direct-acting oral anticoagulants such as apixaban, dabigatran, edoxaban and rivaroxaban are used to prevent stroke and systemic embolism. They have specific indications and are used especially in patients who cannot follow adequate anticoagulant antivitamin K control or who are at considerable risk of bleeding or thrombosis Antiplatelet drugs include clopidogrel, prasugrel and ticagrelor or acetylsalicylic acid and act by preventing platelet aggregation and reducing blood clot formation. They are used to prevent thrombotic events in patients with cardiovascular disease, such as coronary artery disease (1, 2, 10, 11, 12, 12, 13, 14).

Figure 1. Types of anticoagulants

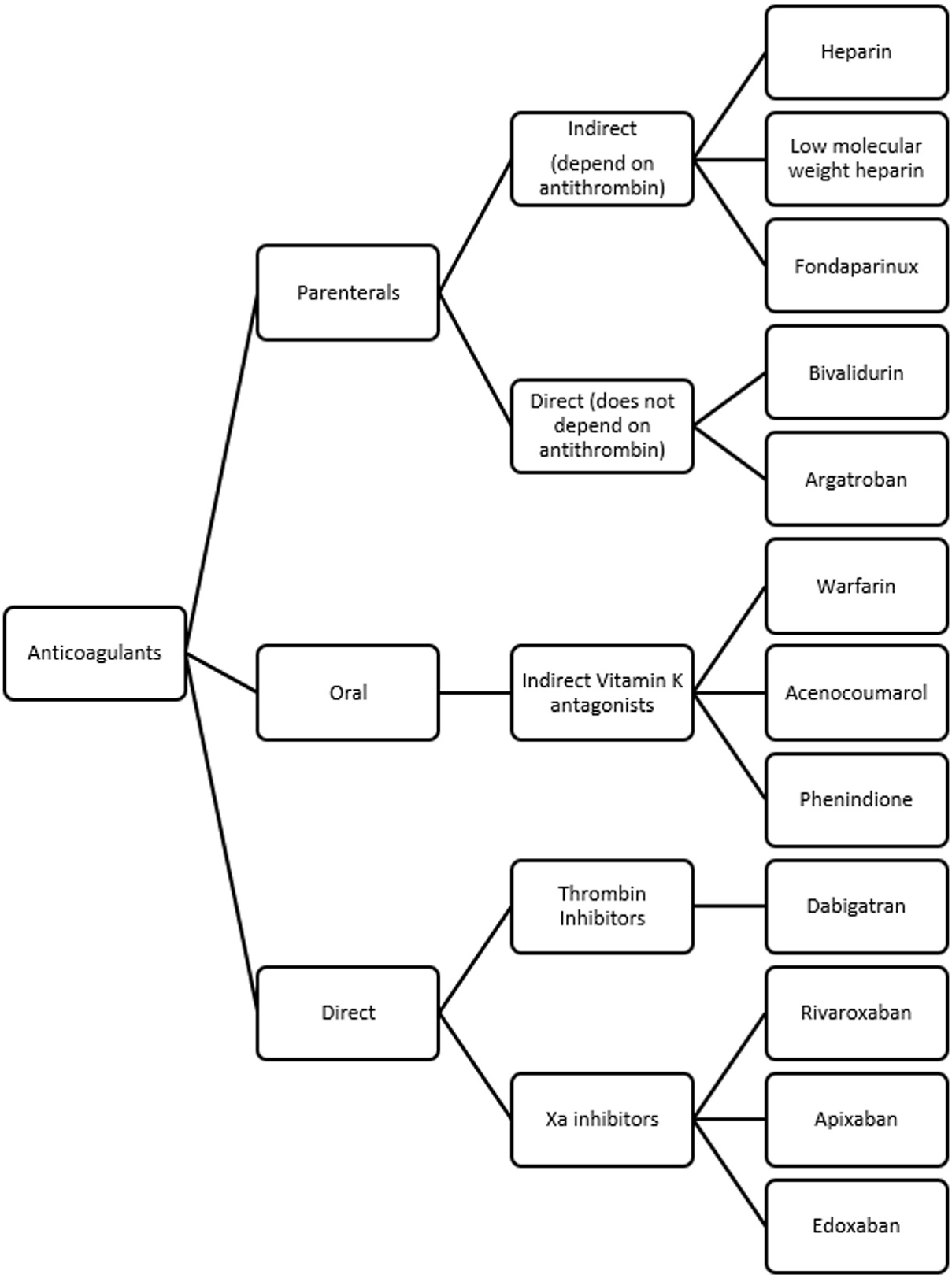

Table 1. Types of antiplatelet drugs

Antiplatelets
Cyclooxygenase-1 (COX-1) Inhibitors
Acetylsalicylic acid
P2Y12 receptor antagonists
Thienopyridines: Clopidogrel, Prasugrel
Non-Thienopyridine: Ticagrelor
Glycoprotein IIb/IIIa inhibitors
Abciximab, Eptifibatide, Tirofiban

Table 2. Fibrinolytic Table

Fibrinolytics	
1st generation	Streptokinase Urokinase
2nd generation	Tissue Plasminogen Activator rt-PA SK-Plasminogen activator complex (APSAC) Prourokinase
3rd generation	Reteplasa TNK

Antiplatelet agents

Antiplatelet agents are drugs that prevent the formation and growth of blood clots by inhibiting platelet aggregation. They are crucial in the treatment and prevention of cardiovascular disease. These agents target different phases of thrombogenesis, including platelet adhesion, activation and aggregation. Currently available antiplatelet agents include acetylsalicylic acid, thienopyridine-based P2Y12 inhibitors, and glycoprotein (GP) IIB/IIIa antagonists. Aspirin and P2Y12 inhibitors inhibit platelet activation, whereas GP IIB/IIIa antagonists inhibit platelet aggregation. However, GP IIB/IIIa antagonists are associated with an increased risk of bleeding. These agents target various platelet surface receptors and intracellular signaling pathways involved in platelet activation and thrombosis. The development

of new antiplatelet agents aims to reduce the risk of bleeding while maintaining optimal efficacy (8, 10, 15, 16, 16, 17, 18)

Anticoagulants

Anticoagulants are chemicals that prevent clotting or prolong clotting time by suppressing the functions or synthesis of clotting factors in the blood. It is used to prevent or cure venous thromboembolism (VTE). Anticoagulants disrupt coagulation by interfering at various points in the coagulation cascade. They decrease the activity of vitamin K-dependent clotting factors and anticoagulant proteins. Anticoagulants do not lyse existing clots but prevent thrombus formation and slow the extension of an existing clot. They are prescribed to treat both arterial and venous thromboembolic diseases. The balance between the procoagulant and anticoagulant systems is disturbed under pathological conditions, and anticoagulants are used to restore this balance (2, 14, 19).

Action Mechanisms

Inhibition of coagulation factors

Different types of anticoagulants exist with diverse mechanisms of action and pharmacological properties. Unfractionated heparin, introduced in the 1930s, was the first major advance in anticoagulant therapy. Its anticoagulant activity is attributed to its interaction with antithrombin, enhancing its inhibitory action on coagulation factors. This interaction occurs through conformational changes induced by heparin binding, leading to the exposure of exosites on antithrombin that bind directly to target enzymes. Heparin also exhibits non-anticoagulant activities, including anti-inflammatory, antiviral and antitumor effects. The mechanisms underlying these non-anticoagulant activities are not yet fully understood (1, 13, 20).

Warfarin is a compound of organic coumarin derivatives, and it is used as an anticoagulant. It works by inhibiting the synthesis of vitamin K in the liver, which blocks the synthesis of vitamin K-dependent blood clotting factors (2, 19, 20).

Newer oral anticoagulants, also known as direct oral anticoagulants (DOACs), act by directly inhibiting specific factors involved in the coagulation cascade, blocking specific proteins, either thrombin or factor Xa, resulting in anticoagulant effects. Dabigatran is a direct inhibitor of thrombin (Factor IIa), while rivaroxaban, apixaban and edoxaban directly inhibit activated Factor X (FXa). They have a relatively short half-life, rapid onset of action, and do not require routine laboratory monitoring. The pharma-

cology of these new drugs is not homogeneous, and there are differences between direct anti-Xa and anti-IIa agents. They are eliminated through renal or biliary-fecal routes. They have limited pharmacological interactions, with P-glycoprotein and/or cytochrome P3A4. Unlike vitamin K antagonists, DOACs have a lower propensity for food-drug interactions. They have been shown to be at least as effective as vitamin K antagonists for the prevention and treatment of thrombosis, with a lower risk of life-threatening hemorrhage (see Table 3) (2, 5, 12, 13, 14, 19, 22).

Table 3. Behavior of coagulation factors

Group/Drug	Molecular target	Route of administration	Monitoring	Drug half-life	Elimination	Antidote
Unfractionated heparin	Antithrombin	IV/SC	PTT	1-15	Reticuloendothelial + renal system	Protamine Sulfate
Low molecular weight heparin	Antithrombin	IV/SC	Xa Factor	5	Renal	Dialyzable Protamine Sulfate
Fondaparinux	Antithrombin	IV/SC	Xa Factor	17-21	Renal	Dialyzable
Vitamin K antagonists (Ex. Warfarin)	II, VII, IX, X Factor	PO	INR	20-60	Hepatic	Vitamin K
Direct thrombin inhibitor (Bivalidurin)	Thrombin	IV	PTT, ACT	1-15	Renal + Proteolytic	N/A
Direct factor IIa inhibitor	IIa Factor	PO	N/A	12-17	Renal + glucuronidation	Idarucizumab
Direct factor Xa inhibitor	Xa Factor	PO	N/A	5-9	Renal + metabolic + Digestive	Andexanet alfa, concentrated Prothrombin complexes

Inhibition of platelet activation

Platelets play a key role in hemostasis and their activation can lead to thrombus formation. Antithrombotic drugs that target platelet activation inhibit platelet aggregation and adhesion, thereby reducing the risk of clot formation. These drugs can target various receptors and signaling pathways involved in platelet activation, such as the P2Y12 receptor, glycoprotein IIb/IIIa receptor, and thromboxane A2 production. Another approach is the use of IL-37, which directly attenuates platelet activation and thrombus formation through the IL-1R8 receptor. IL-37 inhibits platelet aggregation, ATP release in dense granules, P-selectin exposure, αIIbβ3 integrin activation, platelet spreading, and clot retraction. Another potential target for inhibiting platelet activation is SIRT6, which regulates platelet function and thrombosis. Deletion of SIRT6 increases platelet aggregation, dense particle release, αIIbβ3 integrin activation, and thrombosis, whereas activation of SIRT6 suppresses these effects. By interfering with these pathways, they effectively decrease platelet activation and help maintain normal blood flow, reducing the risk of

thromboembolic events. Some commonly used antiplatelet agents include acetylsalicylic acid, clopidogrel and ticagrelor (1,8,10,15,16,18,23,24).

Fibrinolytic effects

Fibrinolytic effects are a crucial aspect of antithrombotic therapy. Fibrinolysis, the process of breaking down blood clots, is achieved by activation of plasminogen into plasmin. This can be facilitated by several drugs, such as tissue plasminogen activators (tPA) and streptokinase. These agents enhance the conversion of plasminogen to plasmin, leading to fibrin dissolution. Fibrinolytic effects are particularly useful in the treatment of acute thrombotic events, such as myocardial infarction and cerebrovascular disease of ischemic origin, where rapid clot dissolution is essential to restore blood flow and prevent tissue damage. In addition, fibrinolytics can be used in the treatment of deep vein thrombosis and pulmonary embolism, aiding in the resolution of these life-threatening conditions. Drugs with fibrinolytic effect include: Tissue plasminogen activator (tPA): is a drug used to dissolve blood clots in cases of stroke, myocardial infarction and pulmonary thromboembolism; Streptokinase: is another fibrinolytic drug used to dissolve blood clots in cases of myocardial infarction and pulmonary thromboembolism; Anistreplase: is a fibrinolytic drug used to dissolve blood clots in cases of myocardial infarction; Urokinase: is a fibrinolytic drug used to dissolve blood clots in cases of myocardial infarction (3, 9, 12, 15).

Indications and dosage

Anticoagulants are commonly prescribed to prevent or treat venous thromboembolism. These are used for the prevention of CVEs in patients with nonvalvular atrial fibrillation, thromboprophylaxis after mechanical cardiac procedures, and in patients with severely dilated left ventricle and spontaneous echo contrast who have had a previous ischemic CVE. Also, they are the mainstay of therapy for the prevention and treatment of arterial and venous thrombosis. The newer anticoagulants, the DOACs, have demonstrated superior safety and efficacy in certain conditions, such as nonvalvular atrial fibrillation and venous thromboembolism. However, the use of anticoagulants in patients with mechanical heart valves and left ventricular assist devices is contraindicated due to potential harm (5, 6, 11, 12, 12, 16, 18). For dosage consultation see Table 4:

Table 4. Dosage of antithrombotic drugs

Low Molecular Weight Heparins	
Enoxaparin	1mg/Kg every 12 hours
Tinzaparin	175 IU/Kg daily
Bemiparin	115 IU/Kg daily
Vitamin K Antagonists	
Warfarin	1-5mg daily adjusted to INR
Acenocoumarin	2-4mg daily adjusted to INR
Direct Oral Anticoagulants	
Rivaroxaban	20mg daily
Apixaban	5mg every 12 hours
Dabigatran	150mg every 12 hours
Edoxaban	60mg daily
Antiplatelet Agents	
Acetylsalicylic acid	75-100mg daily
Clopidogrel	75mg daily
Prasugrel	5-10mg daily
Ticagrelor	90mg every 12 hours

Perioperative management

Perioperative treatment involves careful consideration of the benefits and risks associated with its use in surgical patients. The primary goal is to prevent thromboembolic events during and after surgery, while minimizing the risk of excessive bleeding. Several factors need to be taken into account, including the type of surgery, the patient's underlying medical conditions, and the specific antithrombotic agent used. Strategies for perioperative management of antithrombotic include temporary discontinuation or adjustment of the drug dose, bridging therapy with alternative antithrombotic, and the use of local hemostatic measures. Close monitoring of coagulation parameters and clinical signs of bleeding is crucial to ensure optimal perioperative outcomes. Effective perioperative management of antithrombotic requires a multidisciplinary approach involving surgeons, anesthesiologists, and hematologists, with a focus on individualized patient care (2, 7, 26). Table 5 describes perioperative management:

Table 5. Perioperative management

DOAC	Risk	Pre-procedure Interruption						Surgery – Day 0	Post-procedure resumption			
		Day -6	Day -5	Day -4	Day -3	Day -2	Day -1		Day +1	Day +2	Day +3	Day +4
Apixaban	High											
	Moderate/ Low											
Dabigatran ClCr≥50ml/min	High											
	Moderate/ Low											
Dabigatran ClCr<50ml/min	High											
	Moderate/ Low											
Edoxaban	High											
	Moderate/ Low											
Rivaroxaban	High											
	Moderate/ Low											

Do not administer DOAC in this interval

Side effects and adverse reactions

Side effects and adverse reactions of antithrombotic include several potential complications. A common problem is bleeding, which can range from minor bruising to severe hemorrhage. Allergic reactions are also possible, with symptoms ranging from a mild rash to life-threatening anaphylaxis. In addition, antithrombotic may interact with other drugs, reducing efficacy or increasing the risk of side effects. It is important to consider contraindications and precautions when prescribing antithrombotic therapy, as certain conditions or patient populations may be more prone to adverse effects.

Hemorrhagic complications

Hemorrhagic complications are the most common adverse reaction associated with the use of antithrombotic medications. It is important for healthcare providers to closely monitor patients receiving antithrombotic for any signs or symptoms of bleeding, such as hemoptysis, blood in stool, hematuria, disseminated ecchymosis, to intracranial hemorrhage. In addition, patients should be educated about the potential risks and advised to seek immediate medical attention if they experience any unusual bleeding. Despite the risk of bleeding complications, the benefits of antithrombotic therapy often outweigh the potential harms in patients at risk for thromboembolic disorders. (2,10,12,13,19,21,22)

Allergic reactions

Allergic reactions are a possible side effect. These reactions can range in severity from mild rash and pruritus to life-threatening anaphylaxis. Common symptoms of allergic reactions include hives, edema, dyspnea, and hypotension. In cases of severe allergic reactions, immediate medical intervention is necessary, and the drug should be discontinued. Patients with known allergy to a specific antithrombotic agent should be prescribed an alternative treatment to prevent risks (2, 13, 21).

Interactions with other drugs

Antithrombotic drugs may interact with other drugs, leading to possible drug-drug interactions (DDI). For example, antithrombotic used in the treatment of hepatitis C virus can have significant DDIs with antiviral drugs. Nonsteroidal anti-inflammatory drugs used concomitantly with antithrombotic may increase the risk of bleeding and thromboembolism. Herbal antithrombotic drugs, such as Danshen-Chuanxiong, may interact with Western cardiovascular drugs, affecting antithrombotic pathways. Coumarin derivatives and warfarin are highly interactive with other drugs, resulting in hypoprothrombinemia: antibiotics have been associated with bleeding events in patients on warfarin, particularly in older adults and those who underwent valve replacement surgery. The use of fluoropyrimidine anticancer drugs, such as 5-fluorouracil (5-FU) and capecitabine, may enhance their efficacy, leading to prolonged prothrombin time and activated partial thromboplastin time. Herbal medicines also have the potential to interact with warfarin, with 84% of them increasing its effect and the risk of bleeding. Additionally, drugs that modify cytochrome 2C9, 3A4, or both, as well as p-glycoprotein modifiers, may interact with warfarin and other direct oral anticoagulants. In the management of cancer-associated thrombosis, DOACs may have significant pharmacokinetic DDIs with anticancer therapies, requiring careful consideration. Concomitant use with Rifampicin, Cholestyramine, Cyclosporin A, Calcium Polystyrene Sulfonate or Phenytoin, tends to decrease their effect (2, 5, 10, 16, 20, 21, 27, 28, 29).

Monitoring and dose adjustments

Monitoring and dose adjustments are essential for the safe and effective use of antithrombotic. Laboratory monitoring helps to assess drug efficacy and ensure that therapeutic levels are maintained. This is particularly important for anticoagulants, as it allows doses to be adjusted to achieve the desired anticoagulant effect and minimize the risk of bleeding. Special

populations, such as elderly patients or those with renal insufficiency, may require dose adjustments to account for differences in drug metabolism or elimination. Close monitoring is also necessary during transitions between different antithrombotic therapies to avoid overlap or insufficient anticoagulation. By periodically monitoring patients and making appropriate dose adjustments, health care providers can maximize the benefits of antithrombotic therapy while minimizing the risk of adverse events.

For vitamin K antagonists such as warfarin, the Fiix prothrombin time (Fiix-PT) has been introduced as a modified PT that is not affected by variations in factor VII, leading to improved time in range and reduced thromboembolism. In the responsible treatment of chronic diseases, dose adjustment of drugs can be done using mathematical models and control theory, taking into account individual sensitivity and external influences. DOACs may not require laboratory testing for dose adjustment, but there are cases where laboratory measurement of the anticoagulant effect of the drug may be useful, such as before initiation of treatment or in cases of hemorrhagic or thrombotic events. In the case of pharmacological thromboprophylaxis, unadjusted dosing based on mass index and total body weight is prevalent, especially in critically ill patients (2, 10, 11, 12, 14, 16, 20, 21, 22).

Laboratory monitoring

It involves periodic testing of blood parameters to assess the efficacy and safety of these drugs. The most commonly monitored parameter is the international normalized ratio (INR), which measures the blood's ability to clot. For patients taking anticoagulants, maintaining the INR within a therapeutic range is essential to prevent both bleeding and clotting events. A range between 1-2 indicates risk of thrombosis, stroke or embolism; a range between 2-3 indicates a controlled anticoagulated patient, which is the goal for Atrial Fibrillation, Biological Valvular Prosthesis, Mechanical Aortic Valvular Prosthesis and Venous Thromboembolism; finally, values between 2.5-3.5 are useful in cases of mechanical Mitral or Tricuspid Prosthesis, or in multiple prostheses; higher values are of high risk of hemorrhage. Other tests, such as platelet count and coagulation factor levels, can also be monitored to ensure adequate antithrombotic therapy. Regular laboratory monitoring allows health care providers to adjust doses and tailor treatment plans according to individual patient needs, optimizing the benefits of antithrombotic drugs and minimizing the risk of adverse effects (4, 10, 11, 11, 14).

Dose adjustments in special populations.

These populations include individuals with renal impairment, hepatic impairment, and elderly or low body weight individuals. It is recommended that dosing regimens be adjusted in these populations based on pharmacokinetic and pharmacodynamic considerations. It also highlights the importance of individualized dosing to optimize therapeutic efficacy while minimizing the risk of adverse events. In addition, dosing considerations should be taken during pregnancy and lactation, emphasizing the need for careful risk-benefit assessment and close monitoring (2, 16, 21).

Contraindications and Precautions

Absolute contraindications are situations in which the administration of antithrombotic is prohibited because of the possibility of serious adverse effects. On the other hand, relative contraindications recognize that, while the use of antithrombotic may be possible, caution and careful evaluation of risks and benefits are necessary. In addition, special precautions and considerations should be taken into account when prescribing antithrombotic, such as specific patient populations or situations that may require modified dosing or close monitoring. Understanding these contraindications and precautions is essential for health care professionals to make informed decisions and ensure patient safety (2, 30, 31, 32).

Absolute Contraindications

Some common absolute contraindications include active bleeding, known hypersensitivity to the antithrombotic agent, severe uncontrolled hypertension, recent intracranial hemorrhage, and major active bleeding disorders. In addition, the use of antithrombotic should be avoided in patients with active peptic ulcer, current or recent (within the last three months) ischemic CVE, or recent major surgery. Strict adherence to these contraindications is essential to prevent life-threatening complications.

Relative contraindications

Conditions like uncontrolled hypertension, recent active bleeding, and hepatic or renal dysfunction are included in this category. Other relative contraindications may include recent surgery or alcoholism, where the potential benefits and risks should be carefully considered before initiating antithrombotic therapy. It is critical that health care professionals evaluate these factors individually and weigh the potential benefits against the potential risks.

Special precautions and considerations

Special considerations include the use of antithrombotic in pregnant and lactating women, as well as in patients with renal or hepatic insufficiency. In cases of advanced liver cirrhosis requiring concomitant use of anticoagulants, the Child-Pugh scale indication should be taken: in the case of Warfarin, it does not require adjustment at any stage, while DOACs do not require adjustment in stage A; adjust their dose in stage B and contraindicated in stage C. Elderly patients also require additional attention due to age-related changes in drug metabolism. Other precautions involve drug-drug interactions, particularly with nonsteroidal anti-inflammatory drugs and other anticoagulants. In addition, patients with a history of allergies or hypersensitivity reactions require careful monitoring when initiating antithrombotic therapy (Table 6 and 7).

Table 6. Anticoagulants according to patient profile (33)

Patient Profile	Oral Anticoagulant
Atrial fibrillation Mechanical valve Antiphospholipid Antibody Syndrome Extreme weight extremes	Warfarin o Acenocoumarin
Over 75 years of age	Apixaban o Edoxaban
Severe obesity (BMI 40-49Kg/m2)	Apixaban, Edoxaban o Rivaroxaban
Low body weight: 40-60Kg	Apixaban o Edoxaban
Chronic Kidney Disease GFR 15-49ml/min)	Apixabán, Edoxaban o Rivaroxaban
Advanced Cirrhosis	Dabigatran o Apixaban
High risk of gastrointestinal bleeding	Apixaban, Dabigatran o Edoxabán
Dyspepsia or gastroesophageal reflux	Apixaban, Edoxaban o Rivaroxaban
Atrial fibrillation with high bleeding risk (HASBLED ≥3)	Apixaban, Dabigatran o Edoxaban
Atrial fibrillation with high thrombotic risk and low bleeding risk	Dabigatran
Adherence problems	Edoxabán o Rivaroxabán

Table 7. Recommended doses according to renal function (34)

	CrCl >95ml/min	CrCl 51-94 ml/min	ClCr 31-49 ml/min	ClCr 15-30 ml/min	CrCl <15 ml/min or on dialysis
Apixaban	5mg/12 hours	5 or 2,5mg/12 hours*	5 or 2,5mg/12 hours*	5 or 2,5mg/12 hours*	5 or 2,5mg/12 hours*
Dabigatran	150mg/12 hours	150mg/12 hours	150mg/12 hours	75mg/12 hours	Contraindicate
Edoxaban	60mg/ day	60mg/ day	30mg/ day	30mg/ day	Contraindicate
Rivaroxaban	20mg/ day	20mg/ day	20mg/ day	15mg/day	15mg/day**

CrCl: Creatinine Clearance.
*2,5 mg twice daily if: serum creatinine ≥1,5mg/dl, age ≥80 years or body weight ≤60Kg.
** Rivaroxaban is not recommended for use in these patients, although it is not mentioned in the update guidelines.

Future development and research

Future developments and research in the field of antithrombotic hold great promise for improving patient outcomes and expanding treatment options. One area of interest is the development of new antithrombotic agents, which aim to provide more targeted and effective therapies with reduced side effects. These new agents may include (ACODs) that have shown promising results in clinical trials. In addition, advances in drug delivery systems are being explored to improve the pharmacokinetics and bioavailability of antithrombotic drugs. This includes the use of nanoparticles, micelles, and other innovative approaches to improve drug stability, release, and targeting (8, 13, 19, 35, 36).

New antithrombotic agents

Recent studies have focused on the development of new antithrombotic agents. These include newly developed (novel) antithrombotic agents for pregnant and postpartum patients, inhibitors of factor XI or XII as potentially safer anticoagulants, and antithrombotic agents that act on well-established targets such as factor Xa and thrombin. Additionally, studies are underway on the safety and efficacy profiles of the most important antithrombotic agents in development, including Non-Vitamin K Oral Anticoagulants (NOACs). The search for an anticoagulant that combines optimal efficacy with minimal hemorrhagic diathesis is still underway.

Advances in drug delivery systems

Advances in drug delivery systems have become an important area of development in antithrombotic. These systems aim to improve drug efficacy,

safety, and patient comfort. One such advance is the use of targeted drug delivery systems, which allow site-specific drug release and minimize systemic side effects. In addition, the development of nanotechnology-based drug delivery systems has shown promising results in improving drug solubility and bioavailability. The incorporation of smart drug delivery systems, such as stimuli-responsive nanocarriers, enables the controlled release of drugs in response to specific physiological signals. Advances in transdermal drug delivery systems offer a convenient and noninvasive route of administration for antithrombotic drugs. These advances in drug delivery systems have great potential to optimize the therapeutic outcomes of antithrombotic treatments, leading to better patient outcomes and improved healthcare.

Conclusion

Antithrombotic play a crucial role in the prevention and treatment of thromboembolic events. Antiplatelet and anticoagulant agents are the two main types of antithrombotic and target different aspects of the coagulation process. These drugs act by inhibiting platelet activation, clotting factors, and promoting fibrinolysis. They are used in a variety of situations, including prevention of thromboembolic events, treatment of thromboembolic disorders and perioperative management. However, it is important to be aware of the potential side effects and adverse reactions of antithrombotic, such as bleeding complications, allergic reactions, and drug-drug interactions. Regular monitoring and dose adjustments may be necessary, especially in special populations. While there are certain contraindications and precautions associated with these drugs, ongoing research is focused on the development of new antithrombotic agents and advances in drug delivery systems. In general, antithrombotic play a crucial role in maintaining cardiovascular health and preventing life-threatening complications associated with abnormal coagulation.

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