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REVIEW ON: ANTICOAGULATION THERAPY

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ABSTRACT

Anticoagulation drugs antagonize coagulation and are used to prevent or cure venous thromboembolism (VTE). Drug to prevent clotting have been used for more then a century. Within this review, we aimed to revise the history of the different anticoagulation that are currently prescribe in the clinic. In addition, we compared their pharmacology properties, medical indication and the difficulties in implementing new anticoagulation in vulnerable patient population. Since the introduction of unfractionated heparin in the 1930s, major advance in the mechanistic understanding and medicinal use of anticoagulation have allowed for significant improvement in treating VTE patient. However, a new generation of anticoagulation is currently being tested in clinical trials, with the goal of further optimizing medical care.

KEYWORDS: venous thromboembolism; anticoagulation drugs; heparin; vitamin K antagonist; DOACs; pharmacology; drug-drug interaction; novel anticoagulation.

INTRODUCTION

Medical management of patients on anticoagulation is an integral part of safely performing invasive procedures. Warfarin is the most widely used oral anticoagulation medication, and the indications for its use vary. Heparin and low-molecular-weight heparins are the most common parenteral anticoagulation medications.

Although less common, other anticoagulation formulations exist. Anticoagulants are the drugs used to prevent thrombus extension and embolic complications by reducing the rate of fiber in formation.[1]

They do not dissolve already formed clot but prevent recurrences. Anticoagulants have the ability to prevent devastating medical complications. In a hospital setting anticoagulants are mainly used for the following indications like deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), unstable angina, rheumatic heart disease, vascular surgery, prosthetic heart valve, retinal vessel thrombosis, extra corpuscular circulation, hemodialysis & defibrination.[2]

The introduction of direct oral anticoagulation has transformed clinical practices due to their predictable pharmacokinetics, fewer dietary restriction and reduce need routine laboratory monitoring, with increasing use of anticoagulation in both acute and long term therapy, clinicians must consider factors such as renal function, age and potential drug interaction to optimize outcome.[4]

OVERVIEW

PURPOSE: Anticoagulant therapy uses medications to prevent blood clots from forming, which reduces the risk of heart attacks, strokes, and pulmonary embolisms.[2]

Mechanism: Mechanism include inhibiting thrombin and Factor Xa directly, activating natural anticoagulants like antithrombin, and reducing the liver's Vitamin K-dependent synthesis of essential clotting factors.[4]

TYPES OF ANTICOAGULATION

A. Vitamin K antagonist

EX. Warfarin

B. Direct oral anticoagulation

1. Heparins
2. Factor Xa inhibitor
3. direct thrombin inhibitor
4. Fibrinolytics

A. Vitamin K antagonists

Vitamin K antagonists (VKAs) such as warfarin function by blocking the vitamin K-epoxide reductase, thereby preventing formation of the active form of the vitamin K-dependent clotting factors.[15]

The VKAs have an initial pro-thrombotic effect, by initially blocking proteins C and S, followed by a delayed antithrombotic effect, through the inhibition of coagulation factors II, VII, IX, and X.[15]

EXAMPLE: Warfarin

B. Direct oral anticoagulation

1] Heparins

Unfractionated heparin bind to and increases the activity of antithrombin III by inducing a conformational change to Factor Xa, which ultimately leads to inhibition at Xa and IIa in a 1:1 ratio. Unfractionated heparin also has some inhibition on factors IXa, XIa, XIIa. Low molecular weight heparins (LMWH), which also bind AT3, are smaller and have a higher proportional impact on Xa, versus IIa, in a 3:1 or 2:1 ratio.[5]

Unfractionated heparin (UFH) also has some inhibition on factor IXa, XIa, XIIa. As a result of this inhibition, both the UFH and LMWH ultimately inhibit thrombin activation.[4]

a. Unfractionated Heparin (UFH)

UFH is indicated for numerous conditions including the treatment and prophylaxis of venous thromboembolisms (VTE), thrombus prophylaxis in atrial fibrillation, and treatment of disseminated intravascular coagulation. Unlike warfarin, UFH is administered parenterally, both subcutaneous for its prophylaxis use and as a continuous intravenous infusion when used therapeutically.[7]

b. Low Molecular Weight Heparin (LMWH)

The LMWH are parenterally administered drugs, and include dalteparin, enoxaparin, and tinzaparin. Compared with UFH, the LMWH have the advantage of a more predictable dose-response curve.17 Consequently, the LMWHs are administered at a fixed dose, based on total body weight, and do not require tight regulation and monitoring as is indicated with warfarin and UFH.17 These drugs have near 100% bioavailability and reach peak levels 2-4 hours after subcutaneous administration.[15]

2] Factor Xa inhibitors

Factor Xa inhibitors are used for prophylaxis and treatment of VTE, as well as for prophylaxis of embolic disease in non-valvular atrial fibrillation, and as an alternative anticoagulant in the setting of HIT. These drugs inhibit factor Xa, the first step in the common pathway, either directly or indirectly.[3]

The inhibition occurs in a dose dependent manner. Apixaban and rivaroxaban, directly bind to the active site of factor Xa, thereby inhibiting both free and clot-associated factor Xa. These drugs also inhibit prothrombinase activity Indirect Xa inhibitors, such as fondaparinux, bind to AT3, resulting in a conformational change, thereby inhibiting factor Xa without having any effect on IIa.[4]

Fondaparinux is primarily eliminated unchanged in the urine. Thus, its use in patients with renal insufficiency is contraindicated as its use in this patient population may increase the risk of hemorrhage. There are no specific laboratory parameters available to monitor the anticoagulant impact of factor Xa inhibitors. A dose-dependent prolongation of aPTT and PT may be seen 1-4 hours after administration of direct Xa inhibitors such as rivaroxaban, matching the peak plasma level; however, this increase is short lived and in general PT, aPTT and bleeding time should not be affected at therapeutic levels of these drugs.[3,4]

3] Direct thrombin inhibitor

As their name implies, the direct thrombin inhibitors (DTIs) inhibit the intrinsic activity of the thrombin. Unlike heparin, which also inhibits thrombin, the DTIs do not require a factor, and can inhibit thrombin directly.[11]

Most direct thrombin inhibitors are administered parenterally, including argatroban, bivalirudin; however, dabigatran is orally administered. These drugs are used for prophylaxis and treatment of VTE and ACS, and for prophylaxis of thrombus formation in non-valvular atrial fibrillation.[11]

They are also used as anticoagulation alternatives in the setting of HIT. Dabigatran, the only orally available DTI, is approved for treatment of VTE in patients treated with concomitant parenteral anticoagulation for at least five days, and for the treatment of thrombus secondary to nonvalvular atrial fibrillation.[18]

4] Fibrinolytics

The antithrombotic effect of fibrinolytics, which include tissue plasminogen activator (tPA) and urokinase, is achieved by inducing the conversion of inactive plasminogen into the active enzyme plasmin, which degrades the fibrin matrix responsible for stabilizing a thrombus. Recombinant forms of tPA and urokinase have been manufactured as fibrinolytics.[18]

They work by acting the body's natural fibrinolytic pathway, primally converting the inactive precursor plasminogen into plasmin. The enzyme responsible for breaking down fibrin, which form the structure framework of a clot. By degrading the fibrin mesh, these agent help restore normal blood flow to ischemic tissue, making them lifesaving in emergency condition.[18]

Common fibrinolytic drug include streptokinase, urokinase, and recombinant tissue plasminogen activator such as alteplase, reteplase, and tenecteplase. Streptokinase indirectly activates plasminogen, while tPA selectively bind to fibrin clot, making them more clot specific and reducing systemic bleeding risk compared to older agents.[18]

	Dose Reduction in Renal Failure	Laboratory Monitoring	Adverse Events	Potential Reversal Agents
Vitamin K Antagonist				
Warfarin	None	PT, INR	Hemorrhage Purple Toe Skin Necrosis Teratogen	Vitamin K: PO vs IV FFP PCC: 3 vs 4 factor rVIIa
Heparins				
Unfractionated Heparin	None	aPTT	Hemorrhage HIT	Protamine Sulfate: 1mg per 100U of UFH given over previous 4 hrs
Enoxaparin	Yes	Anti-factor Xa	Hemorrhage HIT	Protamine Sulfate: 1mg per 1mg of enoxaparin
Daltaparin	Yes	Anti-factor Xa	Hemorrhage HIT	Protamine Sulfate: 1mg per 100U of factor Xa inhibition
Tinzaparin	Yes	Anti-factor Xa	Hemorrhage HIT	Protamine Sulfate: 1mg per 100U of factor Xa inhibition
Factor Xa Inhibitor				
Fondaparinux	Yes	Anti-factor Xa	Hemorrhage	Possibly four-complex PCC
Rivaroxiban	Yes	Anti-factor Xa	Hemorrhage	Possibly four-complex PCC
Apixaban	Unknown	Anti-factor Xa	Hemorrhage	Possibly four-complex PCC
Direct Thrombin Inhibitor				
Dabigatran	Yes	Thrombin time Ecarin Clotting Time	Hemorrhage	Possibly four-complex PCC
Bivalirudin	Yes	Thrombin time Ecarin clotting time	Hemorrhage	Possibly four-complex PCC
Argatroban	None	Thrombin time Ecarin clotting time	Hemorrhage	Possibly four-complex PCC
Fibrinolytics				
Alteplase	None	PT, aPTT, fibrinogen	Hemorrhage	Aminocaproic acid Tranexamic acid
Reteplase	None	PT, aPTT, fibrinogen	Hemorrhage	Aminocaproic acid Tranexamic acid
Tenecteplase	None	PT, aPTT, fibrinogen	Hemorrhage	Aminocaproic acid Tranexamic acid
Urokinase	None	PT, aPTT, fibrinogen	Hemorrhage	Aminocaproic acid Tranexamic acid

Figure 3. Comparison table for anticoagulants.[9,19,25,38]

Fig. No.1: Comparison table for anticoagulation.

CLINICAL APPLICATIONS

Anticoagulants have a wide range of applications in disease conditions, many of which require long-term administration. In addition to their use in postoperative thromboembolic prophylaxis (after orthopedic, general, and vascular surgery), anticoagulants are also used in the treatment of existing thromboembolism and in the prevention of its recurrence.[17]

Other applications include preventing venous thromboembolism in hospitalized medical patients, in patients with cancer and in pregnancy, and in the prevention of systemic embolic events in patients with nonvalvular atrial fibrillation (AF), valvular heart disease, prosthetic heart valves, acute myocardiat infarction, ischemic stroke and unstable infarction.[17]

1. Venous thromboembolism treatment and secondary prevention

Typically, treatment of venous thromboembolism involves co administration of UFH (IV) or LMWH and warfarin or other coumarins (oral) until therapeutic levels of anticoagulation by warfarin are achieved, at which time heparin treatment is discontinued. Warfarin treatment is then continued for 3 to 6 months.[20]

For a VIT event provoked by a transient risk factor (e.g., surgery, trauma): 3 month of anticoagulation often sufficient. For a unprovoked VIT with persistent risk factor: consider long duration For secondary prevention, reduced dose anticoagulation may be considered in appropriate patients once acute phase is over, to lower bleeding risk while still protecting against recurrence.[21]

2. Medical and cancer patients

Hospitalized patients with general medical conditions such a as congestive heart failure, chronic obstructive pulmonary disease, or injections are also at moderate risk for the development of venous thromboembolism, and a higher risk is associated with the need for critical care.

Venous thromboembolism is also a common complication in patients with cancer, due to a hypercoagulable state attributable the malignancy or to chemotherapy, radiotherapy, or central venous lines.[19]

Medications such as low molecular weight heparins and direct oral anticoagulants help prevent clot formation while allowing continuation of cancer care. However, cancer patients also face a higher risk of bleeding, making individualized drug selection and close monitoring

essential. Effective anticoagulation reduces morbidity and mortality, improves quality of life, and supports better overall outcomes in oncology patients.[18]

3. Pregnancy and thrombophilia

Maternal deep vein the risk is escalated in pregnant women who also have thrombophilia due to congenital deficiencies: for example, in those with antithrombin, protein C or protein S deficiencies, and in those with factor V Leiden gene mutations. Because there are safety concerns with the use of warfarin in pregnancy, heparin or LMWH is most commonly used, but both are inconvenient, expensive, and associated with risks of bleeding, osteoporosis, and HIT.[18]

Thrombophilia significantly increases the risk of venous thromboembolism and placental complication during pregnancy, making anticoagulation therapy a crucial part pf management.[6]

4. Atrial fibrillation

Prevention of thromboembolic stroke in patients with nonvalvular atrial fibrillation (AF) is a major indication for long-term anticoagulation with warfarin.

Cerebral embolism is the pathogenic mechanism behind 16 to 20% of all ischemic strokes and is most commonly associated with AF. Atrial fibrillation becomes an increasingly important risk factor for stroke with advancing age, with an attributable risk of 23.5% in the 80-’to 89-year-old age group.[1]

Atrial fibrillation can occur due to structural heart diseases like hypertension, coronary artery disease, valvular abnormalities, heart failure, or due to metabolic and lifestyle factors including thyroid disorders, obesity, diabetes, alcohol consumption, and aging. Clinically, patients may present with palpitations, fatigue, breathlessness, dizziness, or may remain asymptomatic, making detection challenging.[4]

Management of atrial fibrillation primarily focuses on three goals: control of ventricular rate, restoration and maintenance of normal sinus rhythm when appropriate, and prevention of stroke through anticoagulation therapy.

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PATIENT RISK OFF ANTICOAGULATION THERAPY

Stopping or reversing anticoagulation therapy is not without risk and there may be transient rebound hypercoagulability from the cessation and subsequent resumption of anticoagulation therapy.

Therefore, the risk of anticoagulation therapy cessation also needs stratification. This is based on the indication for anticoagulation therapy, and can be categorized into low or high risk based on indication and length of therapy.[21]

Common indications for anticoagulation therapy are addressedhere; however, it should be noted that iterations of indications and confounding factors are infinite.[22]

Patients with anticoagulation therapy of less than one-month duration and unknown atrial thrombus status should be considered high risk for cessation of anticoagulation. If the procedure cannot Pulmonary embolism and venous thromboembolic disease are other common indications for anticoagulation therapy.[22]

Another important risk is non-adherence or incorrect dosing, especially in long-term therapy. If anticoagulant levels drop too low, patients become susceptible to clot formation, defeating the purpose of treatment. Conversely, excessive dosing increases hemorrhage risk. Patients may also face complications when undergoing emergency surgery or invasive procedures because the blood's inability to clot can result in uncontrolled bleeding, requiring timely use of reversal agents.

In recent years, Direct Oral Anticoagulants (DOACs) have reduced some of these concerns by offering more predictable pharmacokinetics and fewer interactions. However, they still require careful patient selection particularly in those with kidney dysfunction and the risk of bleeding persists.

Overall, patient risk during anticoagulation therapy depends on individual clinical factors, comorbidities, drug selection, treatment duration, and the quality of monitoring and patient education.[21]

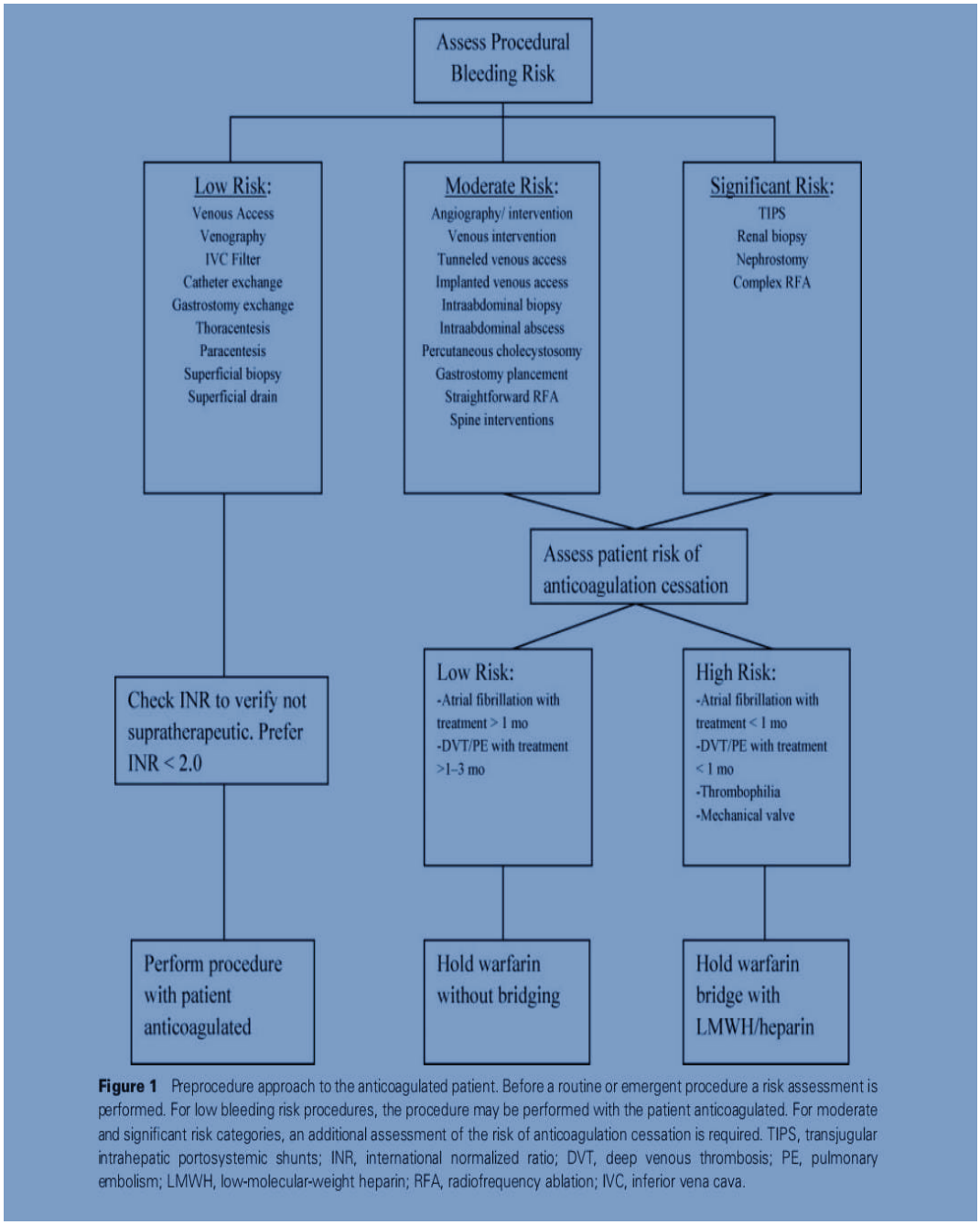

Figure 1 Preprocedure approach to the anticoagulated patient. Before a routine or emergent procedure a risk assessment is performed. For low bleeding risk procedures, the procedure may be performed with the patient anticoagulated. For moderate and significant risk categories, an additional assessment of the risk of anticoagulation cessation is required. TIPS, transjugular intrahepatic portosystemic shunts; INR, international normalized ratio; DVT, deep venous thrombosis; PE, pulmonary embolism; LMWH, low-molecular-weight heparin; RFA, radiofrequency ablation; IVC, inferior vena cava.

Fig. No. 2: Assess procedural bleeding risk.

ANTICOAGULATION TREATMENT

The current mainstays of anticoagulation treatment off thromboembolic disorders are heparins, which exert their effects via the indirect inhibition of thrombin, and coumarins (also known as vitamin K antagonists).[18]

Warfarin, the most commonly used coumarin derivative, achieves its anticoagulant effect by modulating the synthesis of vitamin K-dependent proteins, resulting in the synthesis of detective coagulation factors without any coagulant activities.[18]

Warfarin is administered orally, with a bioavailability of almost 100%; however, more than 98% is plasma protein bound. In addition, as a result of interactions with dietary vitamin K, concomitant medications, and cytochrome P450-dependent metabolism, there is high variability among individual responses to warfarin treatment. Consequently, individual dosing regimens must be tailored to the needs of each patient, with the added requisite of frequent monitoring to ensure that an adequate of anticoagulation is maintained.[20]

Consequently, individual dosing regimens must be tailored to the needs of each patient, with the added requisite of frequent monitoring to ensure that an adequate of anticoagulation is maintained.[20]

In contrast, Direct Oral Anticoagulants (DOACs), including factor Xa and thrombin inhibitors, offer more stable pharmacological profiles with fixed dosing and fewer monitoring requirements, making them increasingly preferred in clinical practice.[18]

Dose adjustments, patient education, and regular follow-ups are crucial to maintaining therapeutic safety and effectiveness. Reversal agents for warfarin and newer specific antidotes for DOACs have improved emergency management of bleeding episodes, contributing to safer long-term therapy. Ultimately, the goal of anticoagulation treatment is to achieve a careful balance between preventing thrombosis and minimizing hemorrhagic complications through optimal drug selection and tailored clinical care. [21]

DISCUSSION

The current study showed that the anticoagulants are very commonly used for treatment and for prophylaxis. The pattern of use was based more on clinician's judgment and experience, and in few situations the usage pattern deviated from American College of Chest Physicians (ACCP) guidelines based on patient's requirements.

Over one year of study on patients ranging from age 18 to 80 years, it was observed that there were 10 (11.6%) of wrong prescription of anticoagulants where patients were prescribed anticoagulant therapy without any indication. This brings in an added cost burden to the patient including cost of monitoring along with unwanted pain and longer duration of hospital

stay oral anticoagulant was acenocaumarol followed by warfarin which is same on discharge also. Warfarin was used only for prophylaxis and closer monitoring of patients was recommended by the clinical pharmacist.

The future of anticoagulation therapy is focused on achieving an optimal balance between preventing thrombosis and minimizing bleeding risk a challenge that continues to drive innovation. Emerging research is directed toward the development of next-generation anticoagulants that target upstream factors of the coagulation cascade, particularly Factor XI and Factor XII inhibitors, which are believed to reduce clot formation without significantly impairing physiological hemostasis.

Early clinical trials have shown promising outcomes with reduced bleeding complications, indicating a potential paradigm shift from current therapies that pose higher hemorrhagic risk.

CONCLUSION

Anticoagulation therapy plays a crucial role in preventing and managing thromboembolic disorder such as deep vein thrombosis, pulmonary embolism, and atrial fibrillation.

Over the year, advancement in anticoagulation drug especially the introduction of direct oral anticoagulation (DOACs) have improved treatment safety, and effectiveness compared to the traditional agent like warfarin.

However, successful therapy depends on individualized patient assessment, regular monitoring, and patient education to balance the benefits of clot prevention with the risks of bleeding.

Therefore, maintaining a balance between efficacy and safety remains the key to successful anticoagulation therapy.

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